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Contents

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META-ANALYSIS

1 Preoperative colonic stents *vs* emergency surgery for acute left-sided malignant colonic obstruction: Meta-analysis with systematic review of the literature

De Simone B, Catena F, Coccolini F, Di Saverio S, Sartelli M, Heyer A, De Angelis N, De Angelis GL, Ansaloni L

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Volume 5 Number 1 February 26, 2017

Contents

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META-ANALYSIS

Preoperative colonic stents *vs* emergency surgery for acute left-sided malignant colonic obstruction: Meta-analysis with systematic review of the literature

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Author contributions: De Simone B and Catena F designed the study; De Simone B collected the data and wrote the manuscript; De Simone B and Catena F statistically analyzed the data for meta-analysis; Catena F reviewed the manuscript; De Simone B revised the data and reviewed the final version of the manuscript; all the authors read and approved the manuscript.

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Abstract

AIM

To investigate by meta-analytic study and systematic review, advantages of colonic stent placement in comparison with emergency surgery.

METHODS

We conducted an extensive literature search by PubMed, Google Scholar, Embase and the Cochrane Libraries. We searched for all the papers in English published till February 2016, by applying combinations of the following terms: Obstructive colon cancer, colon cancer in emergency, colorectal stenting, emergency surgery for colorectal cancer, guidelines for obstructive colorectal cancer, stenting *vs* emergency surgery in the treatment of obstructive colorectal cancer, self-expanding metallic stents, stenting as bridge to surgery. The study was designed following the Prisma

Statement. By our search, we identified 452 studies, and 57 potentially relevant studies in full-text were reviewed by 2 investigators; ultimately, 9 randomized controlled trials were considered for meta-analysis and all the others were considered for systematic review.

RESULTS

In the meta-analysis, by comparing colonic stenting (CS) as bridge to surgery and emergency surgery, the pooled analysis showed no significant difference between the two techniques in terms of mortality [odds ratio (OR) = 0.91], morbidity (OR = 2.38) or permanent stoma rate (OR = 1.67); primary anastomosis was more frequent in the stent group (OR = 0.45; *P* = 0.004) and stoma creation was more frequent in the emergency surgery group (OR = 2.36; *P* = 0.002). No statistical difference was found in disease-free survival and overall survival. The pooled analysis showed a significant difference between the colonic stent and emergency surgery groups (OR = 0.37), with a significantly higher 1-year recurrence rate in the stent group (*P* = 0.007).

CONCLUSION

CS improves primary anastomosis rate with significantly high 1-year follow-up recurrence and no statistical difference in terms of disease-free survival and overall survival.

Key words: Colonic stent; Self-expandable metallic stent; Obstructive left colon cancer; Emergency surgery; Endo-laparoscopic approach; Oncological outcome

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Core tip: The management of patients presenting with acute large bowel obstruction caused by left-sided colorectal cancer is still debated. Recently published conflicting results regarding colonic stenting and its oncological outcome, not allowing the emergency surgeon to consider this therapeutic option, with the aim to convert an urgent situation into an elective one and to decrease the stoma creation rate. We decided to carry out a meta-analysis of all the available randomized controlled trials comparing colonic stenting *vs* surgical decompression to investigate the real advantage of self-expandable metallic stent placement and its oncological safety.

De Simone B, Catena F, Coccolini F, Di Saverio S, Sartelli M, Heyer A, De Angelis N, De Angelis GL, Ansaloni L. Preoperative colonic stents *vs* emergency surgery for acute left-sided malignant colonic obstruction: Meta-analysis with systematic review of the literature. *World J Meta-Anal* 2017; 5(1): 1-13 Available from: URL: http://www.wjgnet.com/2308-3840/full/v5/i1/1.htm DOI: http://dx.doi.org/10.13105/wjma.v5.i1.1

INTRODUCTION

Colorectal cancer (CRC) is a common malignant condition in Western countries; approximately 10%-30% of patients affected present with acute large bowel obstruction (ALBO) requiring urgent decompression. CRC presenting with obstruction is associated with increasing age, lower socioeconomic status, more advanced disease and considerably increased hospital morbidity and mortality[1]. Treatment options include resection of the obstructing tumor with primary anastomosis, proximal diversion, or insertion of a self-expandable metal stent (SEMS).

Emergency surgery (ES) for acute colonic obstruction is associated with a significant risk of mortality and morbidity and with a high percentage of stoma creation[2].

About 70% of all large bowel obstructions occur in left-sided lesions and there is still no consensus about the emergency management of the obstructed left colon cancer. Colonic stenting (CS) has been suggested as an alternative to surgery, as a bridge to surgery (BTS), as allowing time for a preoperative evaluation, as a means to improve the patient's medical condition, and as a means to facilitate bowel decompression; it also has a palliative purpose in patients considered non-operable because of advanced neoplastic disease.

Since Dohmoto *et al*[3] described the use of SEMS in patients with non-resectable or metastatic rectal cancer and Tejero *et al*[4] published their experience of metallic stent placement in 2 patients with colonic obstruction as BTS, several studies have demonstrated that endoscopic stenting, followed by elective surgery with optimal timing (within 5-7 d)[5,6], increases the primary anastomosis rate in patients with obstructive left-sided lesion. Lately, many studies have reported conflicting results from comparison of SEMS as BTS and ES, in terms of safety, morbidity, disease-free survival (DFS), overall survival (OS), and medium- and long-term oncological outcomes.

According to the current literature, colon perforation after SEMS placement occurs in 3.8% to 6.9% of patients treated[7], resulting in seeding of neoplastic cells in the abdominal cavity; colonic perforation after stent can be classified as: (1) immediate or delayed (technical problems are frequently responsible for immediate perforation; stent quality is an important factor affecting delayed perforation; patients in whom a SEMS was placed at the recto-sigmoid junction are at high risk of delayed perforation); (2) free, associated with fecal peritonitis, or silent (microperforation)[8].

Almost 70% of colon perforations occur in the first week after stenting and they could have a negative effect on long term survival, especially in patients whose disease is potentially curable. Maruthachalam *et al*[9] first reported that endoscopic insertion of colonic stents results in increased levels of CK20 mRNA in the peripheral circulation. Malgras *et al*[10] showed an increased metastatic process and shorter survival time in a mouse model of colonic cancer treated with SEMS.

We decided to comprehensively review the current literature and to carry out a meta-analysis of the last

randomized controlled trials (RCT) published, with the aim to evaluate the efficacy and safety of CS as BTS *vs* ES.

MATERIALS AND METHODS

Literature search

We conducted an extensive literature search of the PubMed, Google Scholar, Embase and the Cochrane Library databases. We searched for all the papers in English published till February 2016 by applying combinations of the following terms: Obstructive colon cancer, colon cancer in emergency, colorectal stenting, ES for colorectal cancer, guidelines for obstructive colorectal cancer, stenting *vs* ES in the treatment of obstructive colorectal cancer, SEMS, stenting as BTS.

We considered for our analysis all systematic reviews, RCT, large case series, original case reports, meta-analyses, retrospective and prospective comparative studies.

The study was designed following the Prisma Statement[11].

Study selection

All the collected studies, as full manuscripts, were reviewed and selected applying the following inclusion criteria: (1) RCT; (2) retrospective studies; (3) prospective studies; and (4) case matched studies, comparing CS as BTS *vs* ES in the treatment of the left colon obstruction caused by adenocarcinoma.

Exclusion criteria

We excluded from analysis, studies evaluating stenting for benign stenosis and for right colon cancer, primary and secondary stenting in patients with advanced neoplastic disease and/or for patients who received chemotherapy with palliative treatment, and colon stenting for extrinsic tumor compression.

Data extraction

Two investigators, following selection criteria established before the literature search was initiated, extracted the following data from the RCT included in the meta-analysis: First name author and year of publication, country of origin, study design, whether it was a single or multicenter study, total number of patients included and number of subjects in each group (colonic stent and ES group), sex and age of patients. Clinical variables were: Tumor site, type of stent used and modality of insertion, type of surgery after stent insertion, type of surgery in emergency, data on technical and clinical success (defined as successful stent placement across the stricture and its deployment and adequate bowel decompression (within 48-72 h) from stent insertion without need for re-intervention), stenting-related complications (bleeding, stent obstruction, stent migration, bowel perforation) and elective surgery-related complications.

Primary outcomes reported for the two techniques were: Short term morbidity, in-hospital mortality, permanent stoma creation, primary anastomosis and stoma creation rate, 1-year recurrence rate, OS and DFS.

Quality evaluation

Study quality was assessed by evaluating randomization, generation of allocation sequence and allocation concealment, blinding, description of follow-up, definition of outcome measures, adequate power for clinically significant effect size, intention-to-treat analysis and baseline assessment of treatment group characteristics, according to the quality criteria suggested for RCT by Jüni *et al*[12].

Statistical analysis

Data analysis was performed with RevMan 5.3 software (Cochrane collaboration). The outcomes of meta-analysis were morbidity and mortality rates, permanent stoma rate, primary anastomosis and temporary stoma creation rates, 1-year recurrence rate, DFS and OS rates. The Odds ratio (OR) was used to compare the different outcomes for ES and endoscopic stenting in the groups analyzed. The *P* values and 95%CI were provided for all outcomes. Forest plots for all the outcomes were constructed. A P value < 0.05 was considered significant.

RESULTS

Literature search results

By our search, we identified 452 studies, including 57 potentially relevant studies in full-text that were reviewed by 2 investigators. Eight RCT (Table 1) were considered for meta-analysis. Eight meta-analyses and systematic reviews, 4 reviews of the literature, 17 retrospective comparative studies, 11 prospective comparative studies, 1 experimental study and 5 international guidelines were included in our comprehensive review of the literature (Figure 1).

Four RCT were published between January 2012 and February 2016: (1) Cheung *et al*[13] carried out a randomized multicenter (12 university Korean hospitals involved) prospective study on 123 patients with malignant colonic obstruction treated by stenting, 58 of them with palliative intent and 65 as BTS, to determine and compare the clinical outcome and safety of the Taewoong D-type uncovered stent (Taewoong Medical Co., Gimpo, South Korea) and the Boston Scientific WallFlex stent (Boston Scientific Corp., Natick, MA, United States); (2) Sloothaak *et al*[14] reported oncological data of the Dutch Stent-In 2 RCT[15,16] stopped prematurely in March 2010 because the clinical stent or procedure-related perforation rate was 13% and occult perforations were revealed in a further 10% of the resected specimens; follow-up time for this study was mean 45 mo for the ES group (32 patients) and 41 mo for the colonic stent as BTS (26 patients); (3) Tung *et al*[17] reported long-term follow-up (32 mo for the open

Table 1 Characteristics of included studies

Ref.	Format	Country	Type of study	CS/ES	Etiology of obstruction	Site of obstruction	Colonic stent	Emergency surgery	Elective surgical treatment
van Hooft *et al*[16], 2008	FT	Netherlands	MLC	11/10	OLCC	RS: 16 DC: 6	Endoscopic-fluoroscopic placement of Boston Scientific WallFlex	Open or laparoscopic palliative resection or fecal diversion	None
Cheung *et al*[18], 2009	FT	China	MNC	24/24	OLCC	Between the splenic flexure and the RSJ	Endoscopic-fluoroscopic placement of Boston Scientific Wallstent	Hartmann's procedure; primary anastomosis after subtotal or total colectomy or segmental colectomy with on-table lavage according to the operators' judgment	Elective laparoscopic-assisted colectomy
Alcántara *et al*[22], 2011	FT	Spain	MNC	15/13	OLCC	SF: 6 DC: 3 Sigma: 15 RSJ: 3 Rectum sup: 1	NA	Retrowash (Intermark Medical Interventions Ltd, Bromley, Kent, United Kingdom), a retrograde variation of the traditional anterograde lavage	Colectomy with PA: 14 HP: 1
Pirlet *et al*[20], 2011	FT	France	MLC	35/32	OLCC: 60 benign Stenosis: 3 NA: 7	RSJ: 15 Sigma: 33 DC: 8 SF: 3 NA: 1 (10 drop-out)	Endoscopic-fluoroscopic placement of Bard nitinol uncovered self-expanding stents (Voisins le Bretonneux, France)	One-stage procedure: 14 Two-stage surgery: 8 Three-stage surgery: 2	Colectomy with PA
van Hooft et al[15,16], 2011	FT	Netherlands	MLC	47/51	NA	NA	Endoscopic-fluoroscopic placement of Wallstent and WallFlex colonic stents (Boston Scientific, Natick, MA, United States)	Treatment according to conventional standards	NA
Cheung *et al*[13], 2012	FT	South Korea	MLC	58/62	OLCC	Ascending colon: 10 Transverse: 9 DC: 14 Sigma: 65 Rectum: 25	Taewoong D-type uncovered stent; Boston scientific WallFlex stent fluoroscopy placement with through the scope or over the wire method		Palliative intent: 58 BTS: 65
Ghazal *et al*[19], 2012	FT	Egypt	MNC	30/30	OLCC	RSJ: 12-10 Sigma: 14-17 DC: 4-3	Endoscopic placement under fluoroscopic guidance	Total abdominal colectomy and ileorectal anastomosis by laparotomy	Left hemicolectomy or anterior resection
Tung *et al*[17], 2012	FT	China	MNC	24/24	OLCC	NA	Endoscopic-fluoroscopic placement of Boston Scientific Wallstent	NA	LR

BTS: Bridge to surgery; DC: Distending colon; FT: Full-text; HP: Hartmann's procedure; LR: Laparoscopic resection; MLC: Multi-center study; MNC: Mono-centric study; NA: Not available; OLCC: Obstructive left-sided colon cancer; PA: Primary anastomosis; RSJ: Rectosigmoid junction; SF: Splenic flexure.

surgery group and 65 mo for the endo-laparoscopic group) data of the RCT conducted by Cheung *et al*[18] with the aim to compare the endo-laparoscopic approach and open surgery in the treatment of obstructing left-sided colon cancer[17]; and (4) Ghazal *et al*[19] conducted a RCT to compare the procedures of endoscopic stenting followed by elective colectomy *vs* total abdominal colectomy and ileorectal anastomosis in the management of acute obstructed carcinoma of the left colon[19].

Data from 8 RCT[15-22] were analyzed with a total of 361 patients: 182 who received CS as BTS and 179 who underwent surgery in emergency. The location of the tumor was well indicated in all the RCT (transverse colon; splenic flexure, descending colon, sigmoid colon,

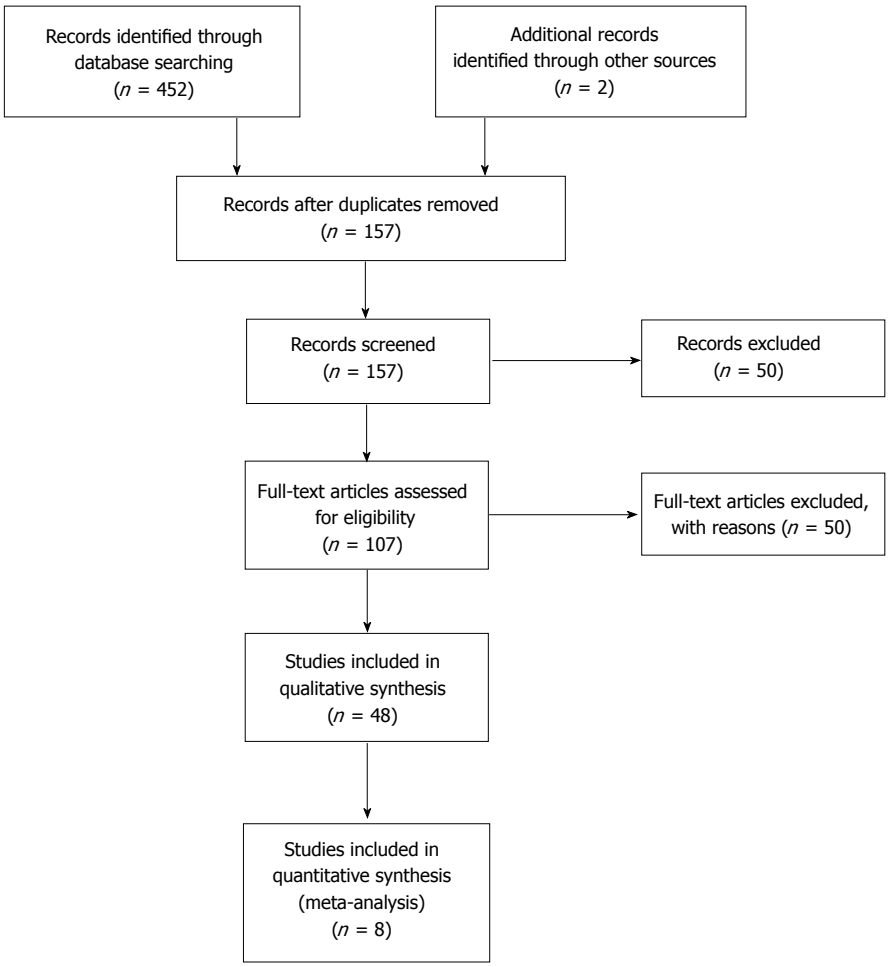


Figure 1 PRISMA 2009 flow diagram.

rectosigmoid).

Different colonic stents were used across the studies: Van Hooft *et al*[15,16] used both the Boston Scientific WallFlex and Wallstent; Cheung *et al*[18] used the Boston Scientific Wallstent; Pirlet *et al*[20] used the Bard nitinol uncovered stent; Ho *et al*[21] used the Boston Scientific WallFlex, while Alcántara *et al*[22] and Ghazal *et al*[19] did not indicate the type of stent used.

The stent placement was performed by an experienced endoscopist and/or radiologist in the studies of Cheung *et al*[13], van Hooft *et al*[15], Pirlet *et al*[20] and Alcántara *et al*[22]. Ho *et al*[21] reported that the stent was inserted by an endoscopist or endoscopist-surgeon. Ghazal *et al*[19] did not reported this information.

The colonic stent group was surgically treated by elective colic resection with 1-stage technique, by laparoscopic approach[17,18], laparotomy or Hartmann's procedures. In the ES group, the surgical technique employed was decided by the surgeon, case by case. All the patients in the ES group of the Ghazal *et al*[19] study had undergone total abdominal colectomy and ileorectal anastomosis.

Meta-analysis

A sensitivity analysis using random *vs* fixed-effect models for all the outcomes showed a limited difference between the OR and the corresponding 95%CI. Statistical tests confirmed the presence of between-study heterogeneity; therefore, a random-effects model was utilized for the statistical analysis.

Morbidity and mortality

All studies provided data on mortality[14-22]. There were 14/179 (7.82%) deaths in the surgery group and 15/182 (8.2%) deaths in the stent group; the pooled analysis showed no significant differences between the two strategies (OR = 0.91; 95%CI: 0.29-2.79) (Figure 2). All the studies considered reported medical and surgical complications in the two groups of patients. The morbidity rate was 37.36% (68/182) in the stent group and 53.07% (95/179) in the surgical group and, also for this parameter, the pooled analysis showed no significant differences between the two strategies (OR = 2.38; 95%CI: 0.80-7.06) (Figure 3).

Permanent stoma

Only 5 studies were considered for this parameter (16-20). The permanent stoma rate was 37/126 (29.36%) in the stent group and 52/136 (38.23%) in the surgical group; the pooled analysis showed no signifi-

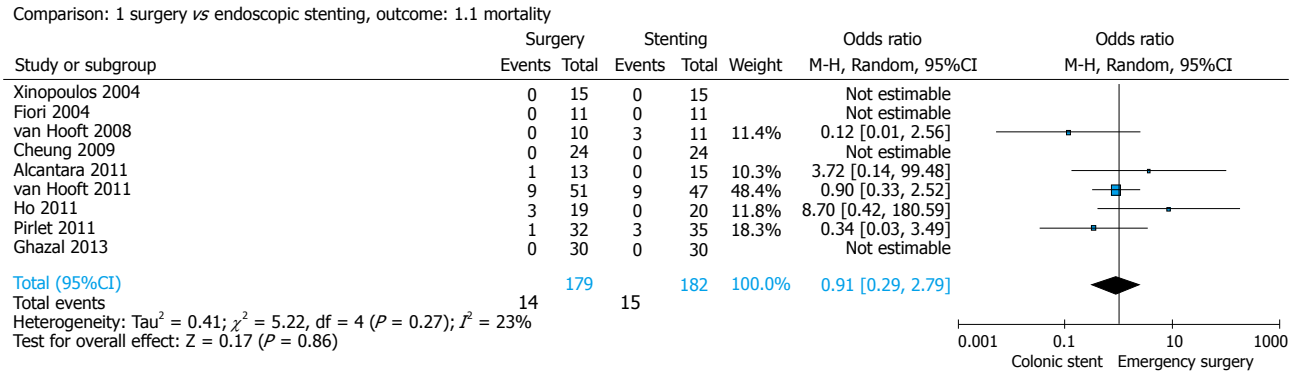


Figure 2 Mortality rate. No statistically significant difference was found between the colic stenting and emergency surgery groups.

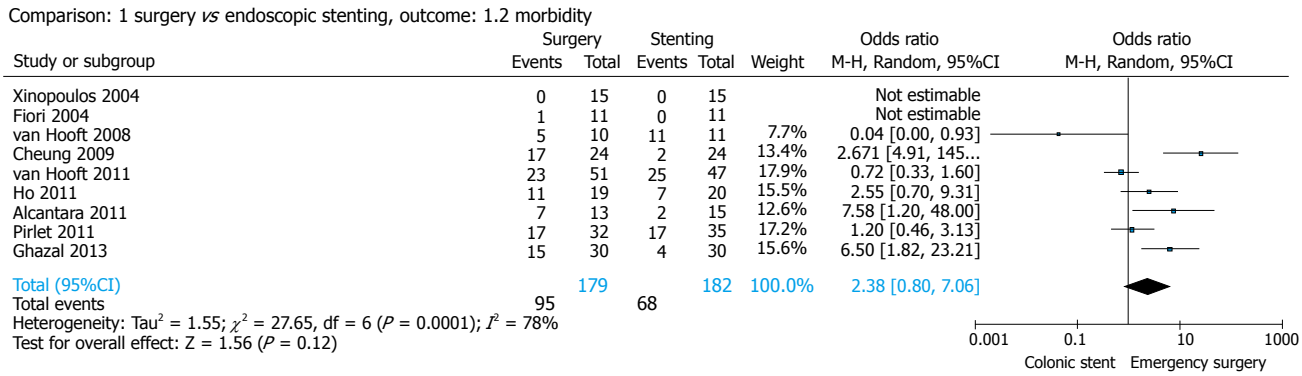


Figure 3 Morbidity rate. No statistically significant difference was found between the colon stenting and emergency surgery groups.

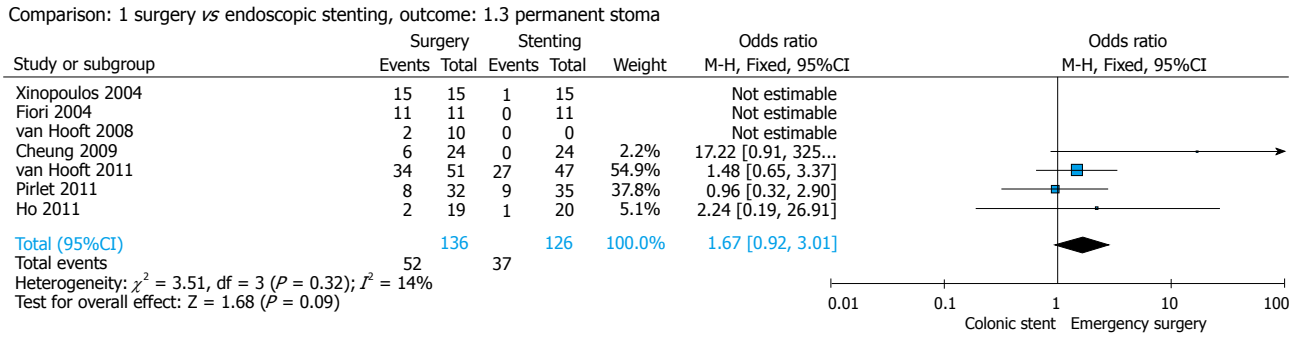


Figure 4 Permanent stoma rate. No significant difference was found between the colon stenting and emergency surgery groups.

cant differences between the two groups (P = 0.09) (Figure 4), with an OR of 1.67 (95%CI: 0.92-3.01).

Primary anastomosis and stoma creation

By comparing ES and CS in studies that analyzed the use of stenting as a BTS procedure[14,16,17,19,20,22], the pooled analysis showed that primary anastomosis was significantly frequent in the stent group (121/171, 70.76%) as compared to the surgical group (95/169, 56.21%; Figure 5), with an OR of 0.45 (95%CI: 0.26-0.77; P = 0.004), and that the stoma creation was more frequent in the surgical group (77/169, 45.56%) as compared to the stent group (52/170, 30.58%; Figure 6), with an OR of 2.36 (95%CI: 1.37-4.07; P = 0.002).

One-year recurrence rate

Only 3 studies were considered[16,20,22] for this parameter. One-year recurrence rate was 18.60% (16/86) in the surgery group and 36.70% (29/79) in the stent group, with an OR of 0.37 (95%CI: 0.18-0.76). The pooled analysis showed a significant difference between the two groups with a significant higher 1-year recurrence rate in the stent group (P = 0.007) (Figure 7).

DFS

Two studies reported data about DFS[20,21]; the statistical analysis showed a higher DFS in the surgery group (26/56, 46.42%) as compared to the stent group (22/56, 39.28%) with no significant difference in the pooled analysis (P = 0.45) and an OR of 1.34 (95%CI:

0.63-2.83) (Figure 8).

OS

Cheung *et al*[18] and van Hooft *et al*[16] reported data about OS; the pooled analysis showed no significant difference between the two groups (ES group: 25/56, 44.64% *vs* stent group: 24/50, 48%; $P = 0.65$) and an OR of 0.84 (95%CI: 0.39-1.81) (Figure 9).

DISCUSSION

ALBO presents a challenge to any surgeon. Distended unprepared bowel, patient dehydration, advanced disease and frequent need for surgery out of hours, often at night, are all factors that predispose the patient to complications. Its surgical management is still debated and includes: (1) primary resection and anastomosis (1-stage procedure), which prevents the confection of a loop colostomy but presents the risk of anastomotic leakage; (2) Hartmann's procedure, which prevents anastomotic leakage but needs a second operation to reverse the colostomy; (3) the 3-stage procedure (decompressive colostomy-colic resection-colostomy closure); (4) subtotal or total colectomy with/without primary anastomosis, which is indicated in diastatic colon perforation or synchronous right colonic cancer; and (5) temporary or definitive loop colostomy/ileostomy, in case of important bowel dilatation proximal to obstruction, advanced neoplastic disease or peritoneal carcinomatosis[1,2].

Many available studies reported the increasing number of surgical procedures involving the creation of a diverting or permanent stoma and this seems to increase with age, decreasing the quality of life of patients[23,24].

The "ideal" operation is the elective one. The immediate colic resection with primary anastomosis represents the gold standard in patients with low risk. A temporary de-functioning colostomy or ileostomy could be proposed to patients with an intermediate anesthetic risk. In high-risk cases, advanced obstruction, simultaneous colonic perforation, metastatic or locally advanced disease, Hartmann's operation should be preferred. Colonic stents represent the best option when skills are available[2].

CS as BTS seems to provide a good alternative therapeutic option to convert an emergency clinical situation into a more elective one.

SEMS insertion and complications

SEMS placement can be associated with complications, such as perforation, migration, tumor in-growth, stool impaction, bleeding and pain.

The perforation rate ranged from 0% to 83% and the overall risk of perforation was about 5%, which is a relatively low risk, but the mortality rate of patients with perforations was 16%[8].

Van Hooft *et al*[15,16] reported 6/47 stent-related perforations and Pirlet *et al*[20] reported 2 stent perforations and 8 silent perforations in 30 patients randomized to CS as BTS.

The endoscopist's experience, the type of colic obstruction (partial or complete), the type of stent and the insertion technique are fundamental to reach CS technical and clinical success[25].

CS is more likely to be successful in shorter, malignant strictures with less angulation, distal to the obstruction[26].

Geraghty *et al*[27] reported that technical success and good outcome for the emergency management of malignant left colon obstruction (MLBO) by SEMS insertion is higher for experienced operators who had performed more than 10 procedures, using the through-the-scope endoscopy technique.

Gianotti *et al*[28], evaluating prospectively short- and long-term results from CS as BTS, showed a benefit for the CS group compared to ES group and concluded that this results from the experience of the endoscopist and the relatively low rate of complete colonic obstructions included in the study.

Mehmood *et al*[29] reported that CS can be performed by an endoscopist without radiologist support if adequately trained, with good outcomes, highlighting the central role of the endoscopist.

SEMS can be divided into two types: Uncovered and (fully and partially) covered. Tumor in-growth occurs often with uncovered SEMS, and migration occurs often with covered SEMS[30].

Selection of the appropriate stent is very important for outcomes, considering material, design, diameter, length, radial force, flexibility, foreshortening ratio and delivery system, but there is no evidence to indicate which stent type is superior.

Cheung *et al*[13] recently conducted a multi-center, randomized, prospective, comparative study aimed to compare the efficacy and complication rates of the D-type colonic stent with those of the WallFlex stent; both stents were uncovered, with different radial and axial force, to reduce the excessive pressure on the ends, which could result in contact with the normal mucosa of the colon, increasing risk of perforation. Perforation occurred in 5/58 patients treated with colonic stent, including 4 with the WallFlex stent and 1 with the D-type stent, but the difference was not statistically significant[13].

van Halsema *et al*[7], in their meta-analysis, noted that of the 9 most frequently used stent types, the WallFlex, Comvi, and Niti-S D-type had a higher perforation rate (> 10%). A lower perforation rate (< 5%) was found for the Hanarostent and the Niti-S covered stents. Risk factors for perforation include benign etiology of the stricture and chemotherapy with bevacizumab, as confirmed by others studies[7,31-33].

CS vs ES: What are the benefits?

Many studies were proposed to investigate the advantages and disadvantages of CS compared to ES in the management of acute colorectal obstruction.

Data confirmed short-term safety and efficacy of SEMS placement as BTS. The conflicting data reported recently by 3 RCT, stopped prematurely, have opened the debate on the efficacy and safety of the use of SEMS to treat potentially curable patients presenting with MLBO[15,20,22].

Van Hooft *et al*[15,16] did not observe clinical advantages of CS as compared to ES. During their RCT, an interim analysis showed an increase in absolute risk of 30-d morbidity in the CS group as well as a high perforation rate (13%). In this trial, the ES group had an increased stoma rate after initial intervention (75% in ES *vs* 51% in CS), but a reduced frequency of stoma-related problems (1.9% in ES *vs* 10.6% in CS). The differences in the stoma rate disappeared at last follow-up (67% in ES *vs* 57% in CS) due to the high leakage rate of primary anastomosis in the stent group.

Pirlet *et al*[20] failed to demonstrate that CS significantly decreased the need for a stoma, compared to ES. No significant difference was noted regarding the stoma rate, but the high number of stent-related adverse events (6.6% of perforations) and the low technical success rate for stent insertion (47%) led to premature closure of the trial[20].

In contrast, Alcántara *et al*[22] closed their study prematurely because of high morbidity, in particular the high incidence of anastomotic leakage in the ES group (30.7% in ES with intraoperative colonic lavage *vs* 0% in patients having CS)[22].

Since the publication of these data, several meta-analyses were designed to investigate the superiority of the use of CS as BTS compared with ES alone in the treatment of potentially curable patients presenting with MLBO.

Cennamo *et al*[34] confirmed that in patients with ALBO, stent placement improves primary anastomosis without decreasing mortality and morbidity rates.

Zhang *et al*[35] reported that stent placement as BTS did not adversely affect mortality and long-term survival.

Cirocchi *et al*[36] analyzed data from about 197 patients, 97 of them treated with CS, to assess the effectiveness of CS used as BTS in the management of MLBO. The authors showed that when used as BTS, CS improves the primary anastomosis rate (64.9% *vs* 55% respectively for CS and ES groups; $P = 0.003$) and decreases the overall stoma rate (45.3% *vs* 62% respectively for the CS and ES groups; $P = 0.02$)[36].

De Ceglie *et al*[37] showed that CS offers advantages over ES in terms of increase in primary anastomosis, successful primary anastomosis and reduction of stoma creation, infections and other morbidities; no significant statistical difference was found between CS and ES in terms of length of hospitalization, preoperative mortality and long-term survival.

Huang *et al*[25] analyzed data from 7 RCT comparing CS and ES and reported that, compared with the ES group, the CS group achieved significantly more favorable rates of permanent stoma, primary anastomosis, wound infection and overall complications; no significant difference was found between the two groups for anastomotic leakage, mortality or intra-abdominal infection.

Results of our meta-analysis confirmed that in the group of patients treated with CS as BTS, primary anastomosis is significantly more frequent, as stoma creation rate is significantly higher in the ES group. No statistically significant difference was found between the two groups in permanent stoma rate (Figures 4-6).

Is stent placement as BTS oncologically safe?

The negative long-term oncological outcomes of SEMS insertion have to be proven and are still debated after the data reported by Maruthachalam *et al*[9] and Malgras *et al*[10]. Surely, the enforced radial dilatation by SEMS suggests the possibility of increased risk of perforation and tumor manipulation that can induce dissemination of cancer cells into the peritoneal cavity.

Matsuda *et al*[38] conducted a meta-analysis to evaluate long-term outcomes of colonic stent insertion followed by surgery for ALBO. The authors included 11 studies for analysis, with a total of 1136 patients, of whom 432 (38%) underwent CS as BTS and 704 (62%) underwent ES. OS, DFS and recurrence did not differ significantly between the CS as BTS and ES groups.

Kavanagh *et al*[39] conducted an observational comparative study to evaluate medium-term oncological outcomes of CS as BTS and ES with an intention to treat analysis. Data showed no difference in cancer-specific and all-cause mortality between both groups; there were 3 cancer-related deaths in the CS group and 4 in the ES group. Median follow-up (mo) in the CS and ES group was 27.4 (range: 1-81) and 26[39]. Disease recurrence occurred in 4 patients in the CS group and 6 patients in the ES group; sites of recurrence in the CS were local/peritoneal in 2 patients and liver in 2 patients. Both local recurrences occurred in patients who had undergone R1 resections. In the ES group, there was 1 local/liver, 2 peritoneal, and 3 liver recurrences. The local recurrence occurred in a single patient who had a R1 resection. Kavanagh *et al*[39] reported the histological evidence of clinically silent tumor microperforations in 3 patients in the CS group (13%), in comparison with 2 (7%) tumor microperforations in the ES group; this suggested an occasional occurrence in the absence of stent deployment.

Gorissen *et al*[40] reported that SEMS was associated with an increased local recurrence rate in patients aged $\leqslant$ 75 years. In younger patients treated with CS, a significantly higher local recurrence rate was observed at the end of the follow-up (32% *vs* 8%; $P = 0.038$). Of 20 local recurrences, 12 were diffusely peritoneal, 5 were at the large bowel anastomosis/side wall, 2 were ovarian and 1 was on the small bowel.

Sloothaak *et al*[14] reported data about disease recurrence, DFS, disease-specific survival and OS for patients involved in the Dutch Stent-In 2 trial[14-16]. Fifty-eight patients were included in the analysis. Median

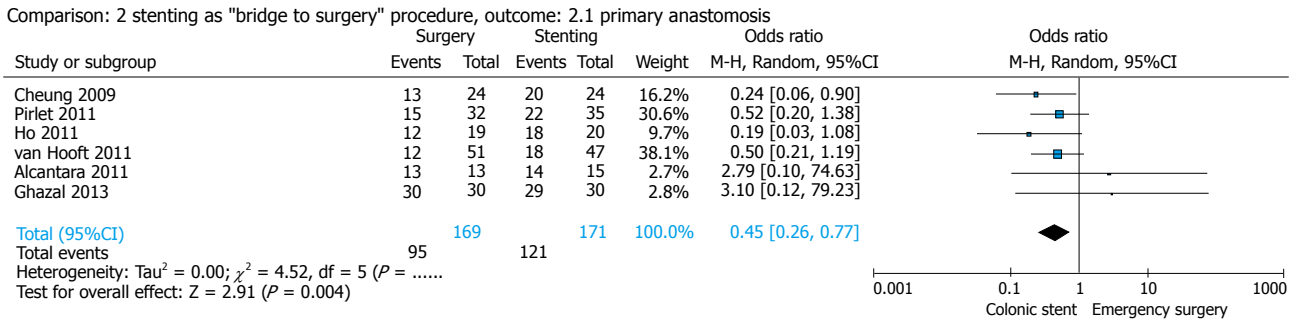


Figure 5 Primary anastomosis rate. Tthis parameter is higher in the colonic stenting group, with a significant difference in comparison with the emergency surgery group.

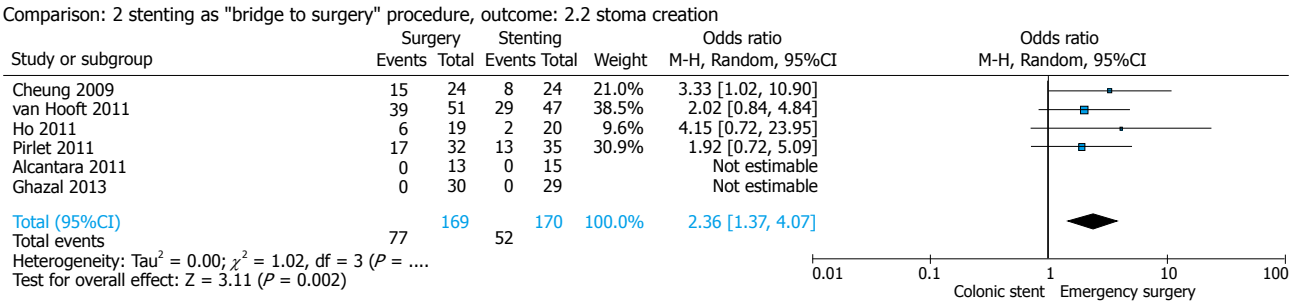


Figure 6 Stoma creation rate. Tthis parameter is higher in the emergency surgery group, with a significant difference between the two groups considered.

follow-up was 4 mo and 41 mo in the ES and CS groups respectively. Loco-regional or distant disease recurrence developed in 9/32 patients in the ES group and 13/26 in the CS group. DFS was worst after a stent-related perforation. The OS rate was 50% for patients with a stent-related perforation and was worse than the rate of 62% in patients without stent-related perforation[14].

Sabbagh *et al*[41] retrospectively analyzed data from 48 patients in the CS group and 39 in the ES group, using a propensity score to correct for selection bias. The authors reported worse OS and DFS for patients with MLBO with SEMS insertion, compared with ES. In the overall population, OS (P = 0.001) and 5-year OS (P = 0.0003) were significantly lower in the CS group than in the ES group, and 5-year cancer-specific mortality was significantly higher in the CS group (P = 0.02). Five-year DFS, recurrence rate, and mean time to recurrence were better in the ES group (no statistically significant difference). For patients with no metastases or perforations at hospital admission, OS (P = 0.003) and 5-year OS (30% *vs* 67%, respectively, P = 0.001) were significantly lower in the CS group than in the ES group[41]. The same authors wanted to explain these data by analyzing pathological specimens from the CS and the ES groups in a case-matched analysis (with the groups matched for the T stage). A total of 84 patients were included in the study (50 in the CS group). Twenty-five patients in the CS group were matched with 25 patients of the surgery-only group. Tumor ulceration (P = 0.0001), peri-tumor ulceration (P = 0.0001), perineural invasion (P = 0.008) and lymph node invasion (P = 0.005) were significantly more frequent in the CS group. In a multivariate analysis of the CS group, T4 status and tumor size were significant risk factors for microscopic perforation, perineural invasion and lymph node invasion[42].

Knight *et al*[43] decided to carry out a retrospective cohort study to determine if preoperative stenting adversely affects long-term survival. The single-center study compared a group of patients having preoperative stenting (group A) with a group of patients having elective surgery for Dukes' B and C cancer, excluding mid and low rectal tumors (group B). The 30-d mortality rates for groups A and B were 6.7% (1 patient) and 5.7% (5 patients) respectively. The 5-year survival rates were 60% and 58% respectively, with a P-value of 0.96. Knight *et al*[43] concluded that patients undergoing CS as BTS have the same long-term survival as those undergoing elective surgery.

Park *et al*[44] retrospectively analyzed data from 67 patients who had undergone SEMS placement as BTS and 35 patients treated by ES, to compare surgical and oncologic outcomes of the groups. The CS group had a higher laparoscopic resection rate (67.2% *vs* 31.4%, P = 0.001) with a lower conversion rate (4.3% *vs* 35.3%, P = 0.003). The rates of local recurrence and distant metastasis, recurrence-free and OS were not significantly different between the two groups[44].

Kim *et al*[45] also carried out a retrospective analysis of data from 43 patients who had undergone radical resection after preoperative CS and 48 who had undergone ES with curative intent to compare short- and long-term outcomes between the two groups. The 5-year DFS and 5-year OS rates were not significantly

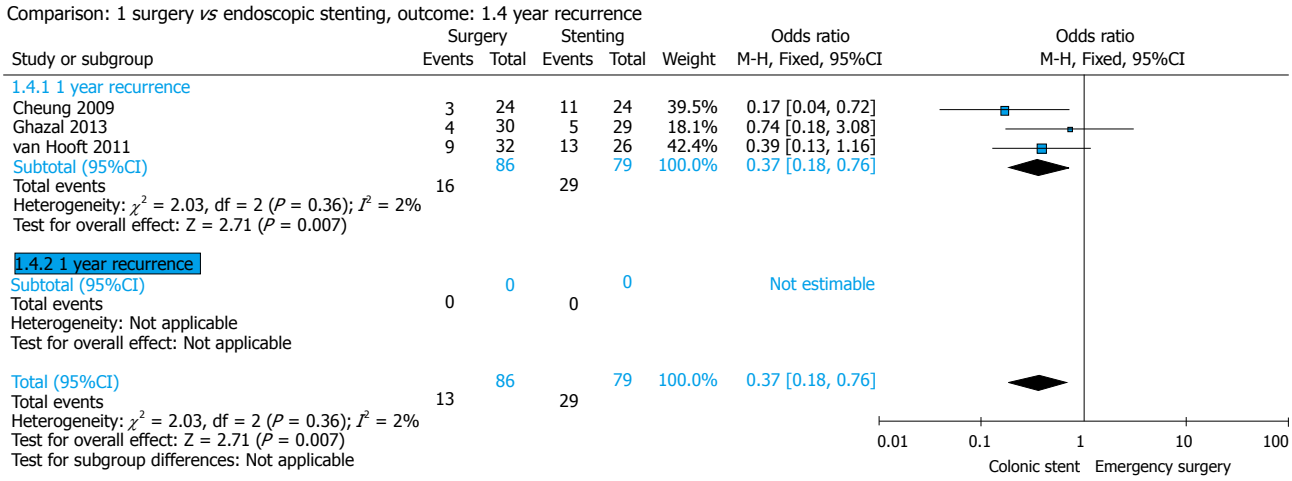


Figure 7 One-year recurrence rate. This parameter is higher in the colonic stenting in comparison with the emergency surgery group, with a significant difference between the two groups.

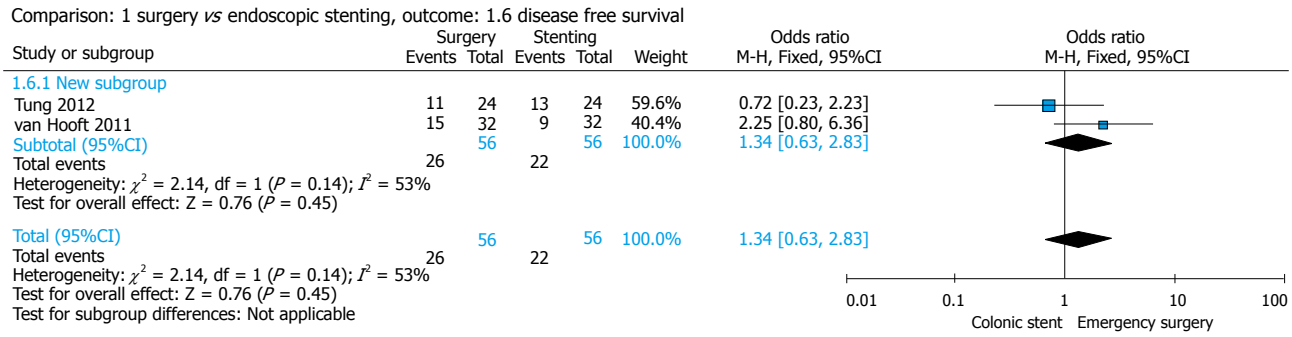


Figure 8 Disease-free survival rate. No significant difference was found between the colonic stenting and emergency surgery groups.

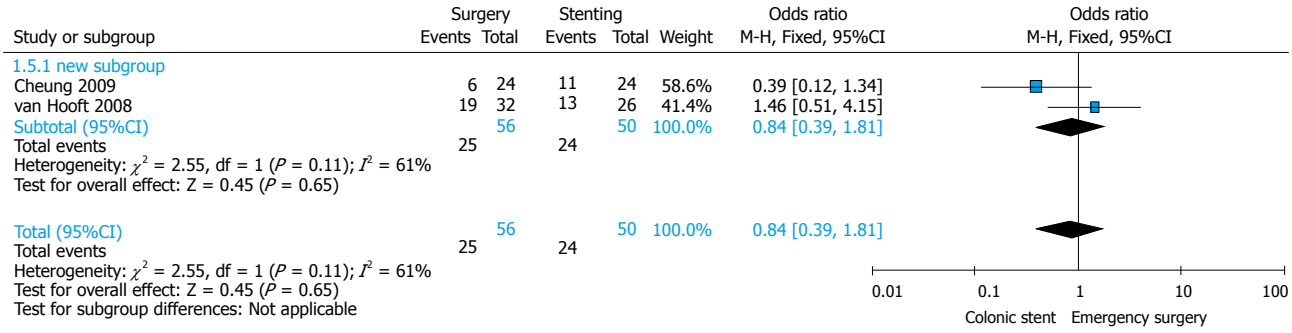


Figure 9 Overall survival rate. No significant difference was found between the colonic stenting and emergency surgery groups.

different between the CS and ES groups[45].

Our meta-analysis showed that 16/86 (18.60%) patients in the ES group and 29/79 (36.70%) patients in the CS group presented with a recurrence at the 1-year follow-up, with a statistically significant difference between the two groups (P = 0.007) (Figure 7). No statistically significant difference was found in terms of DFS and OS between the groups (Figures 8 and 9).

SEMS: International guidelines

Considering the available data, the emergency surgeon is not allowed to treat with SEMS potentially curable patients presenting with obstructing left-sided colon cancer.

The World Society of Emergency Surgeons, after a consensus conference, stated that colonic stents represent a valuable option both for palliation and as a bridge to elective surgery, when skills are available, to treat patients presenting with obstructing left-sided colon cancer and no signs of perforations. High clinical and technical expertise is mandatory to obtain good results; consequently, the group suggests that SEMS

should be used as a bridge to elective surgery in referral center hospitals with specific expertise, in selected patients, and that CS should be preferred to colostomy for palliation in patients not treated with bevacizumab-based therapy, since this technique is associated with similar mortality/morbidity rates and shorter hospital stay, compared to surgery, avoiding the high healthcare costs related to stoma[2,32].

The European Society of Gastrointestinal Endoscopy does not recommend SEMS placement as a standard treatment of symptomatic MLBO. It can, however, be considered for patients with potentially curable ALBO at high risk of postoperative mortality (American Society of Anesthesiologists Physical Status $\geqslant$ III and/or age > 70 years) as an alternative to ES. Moreover, it is recommended as the preferred treatment for palliation, except in patients treated or considered for treatment with anti-angiogenic drugs, such as bevacizumab[46].

The Eastern Association for the Surgery of Trauma conditionally recommended CS (if available) as initial therapy for MLBO, because stent use was associated with decreased mortality and morbidity rates[47].

The Korean Society of Gastrointestinal Endoscopy recommends CS as BTS in order to avoid high morbidity related to ES, above all in patients with unresectable CRC, because SEMS placement can relieve symptoms, improve quality of life and allow chemotherapy and/or radiotherapy for palliation[48].

In conclusion, CS improves primary anastomosis rate, with a low stoma creation in comparison with ES. At 1-year follow-up, the recurrence rate is higher in patients treated with stent, with no statistical difference in terms of DFS and OS. CS is a therapeutic option to take into consideration, when skills are adequate, to treat patients unfit for surgery with palliative intent and considering the high healthcare costs related to stoma.

Considering the available data about oncological outcome of CS, surgery is the only treatment to offer young patients presenting with a potentially curable acute colorectal obstruction.

COMMENTS

Background

Colonic stenting seems to be a good therapeutic option to convert an urgent situation into an elective one. Recently published conflicting results about oncological safety of this technique, used as a bridge to surgery, *vs* emergency surgery, do not allow for surgeons to treat potentially curable patients presenting with large bowel obstruction with stenting.

Research frontiers

Emergency surgery has high morbidity and mortality rates still. The use of colonic stenting in the management of patients presenting with large bowel obstruction can help to decrease morbidity and mortality, delaying surgery. The problem is that colonic stenting can potentially determinate the spreading of tumor cells, but no available data can confirm that it can affect disease-free survival and overall survival rates.

Innovations and breakthrough

In the present study, the authors demonstrated that colonic stenting improves primary anastomosis rate, with a low stoma creation. At 1-year follow-up, the recurrence rate is higher in patients treated with stent, with no statistical difference in terms of disease-free survival and overall survival.

Applications

Colonic stenting is a therapeutic option to take into consideration, when skills are adequate, to treat patients unfit for surgery, with palliative intent, considering the high healthcare costs related to stoma. Considering the available data about oncological outcome of stunting in emergency, surgery is the only treatment to offer young patients presenting with a potentially curable acute colorectal obstruction.

Peer-review

This meta-analysis of randomized controlled trials comparing colonic stenting *vs* emergency surgery in the management of left large bowel obstruction and the systematic review of all the other available studies adds useful information for practice and research.

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Contents

Bimonthly Volume 5 Number 2 April 26, 2017

SYSTEMATIC REVIEWS

14 Environmental tobacco smoke exposure and heart disease: A systematic review

Lee PN, Forey BA, Hamling JS, Thornton AJ

41 Statin use and risk of cancer: An overview of meta-analyses

Undela K, Shah CS, Mothe RK

META-ANALYSIS

54 Is there a difference between 19G core biopsy needle and 22G core biopsy needle in diagnosing the correct etiology? - A meta-analysis and systematic review

Kandula M, Bechtold ML, Verma K, Aulakh BS, Taneja D, Puli SR

63 Mucin expression and the pancreas: A systematic review and meta-analysis

Niv Y

World Journal of Meta-Analysis
Volume 5 Number 2 April 26, 2017

Contents

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SYSTEMATIC REVIEWS

Environmental tobacco smoke exposure and heart disease: A systematic review

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Author contributions: Lee PN and Forey BA planned the study; Thornton AJ and Hamling JS carried out the literature searches, assisted by Lee PN and Forey BA; Forey BA, Hamling JS and Thornton AJ carried out the data entry which was independently checked by one of these or Lee PN; Lee PN and Forey BA discussed any difficulties in interpreting published data or in the appropriate methods for derivation of RRs; Forey BA and Hamling JS conducted the main statistical analyses along lines discussed and agreed with Lee PN; Lee PN drafted the paper which was critically reviewed by the other authors.

Conflict-of-interest statement: Lee PN, Director of P.N. Lee Statistics and Computing Ltd., is an independent consultant in statistics and an advisor in the fields of epidemiology and toxicology to a number of tobacco, pharmaceutical and chemical companies including the sponsors of this study; Forey BA and Hamling JS are employees of, and Thornton AJ, a consultant to, P.N. Lee Statistics and Computing Ltd.

Data sharing statement: Supplementary File 1 provides a description of the reasons for rejection of some papers. Supplementary File 2 gives full details of the meta-analyses conducted. Supplementary File 3 gives full details of the stepwise multiple regression analysis. Supplementary File 4 gives some results for less commonly used indices of ETS exposure. Copies of the database files are available on request from the corresponding author at peterLee@pnlee.co.uk.

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Abstract

AIM

To review evidence relating passive smoking to heart disease risk in never smokers.

METHODS

Epidemiological studies were identified providing estimates of relative risk (RR) of ischaemic heart disease and 95%CI for never smokers for various indices of exposure to environmental tobacco smoke (ETS). "Never smokers" could include those with a minimal smoking experience. The database set up included the RRs and other study details. Unadjusted and confounder-adjusted RRs were entered, derived where necessary using standard methods. The fixed-effect and random-effects meta-analyses conducted for each exposure index included tests for heterogeneity and publication bias. For the main index (ever smoking by the spouse or nearest equivalent, and preferring adjusted to unadjusted data), analyses investigated variation in the RR by sex, continent, period of publication, number of cases, study design, extent of confounder adjustment, availability of dose-response results and biomarker

data, use of proxy respondents, definitions of exposure and of never smoker, and aspects of disease definition. Sensitivity analyses were also run, preferring current to ever smoking, or unadjusted to adjusted estimates, or excluding certain studies.

RESULTS

Fifty-eight studies were identified, 20 in North America, 19 in Europe, 11 in Asia, seven in other countries, and one in 52 countries. Twenty-six were prospective, 22 case-control and 10 cross-sectional. Thirteen included 100 cases or fewer, and 11 more than 1000. For the main index, 75 heterogeneous ($P < 0.001$) RR estimates gave a combined random-effects RR of 1.18 (95%CI: 1.12-1.24), which was little affected by preferring unadjusted to adjusted RRs, or RRs for current ETS exposure to those for ever exposure. Estimates for each level of each factor considered consistently exceeded 1.00. However, univariate analyses revealed significant ($P < 0.001$) variation for some factors. Thus RRs were lower for males, and in North American, larger and prospective studies, and also where the RR was for spousal smoking, fatal cases, or specifically for IHD. For case-control studies RRs were lower if hospital/diseased controls were used. RRs were higher when diagnosis was based on medical data rather than death certificates or self-report, and where the never smoker definition allowed subjects to smoke products other than cigarettes or have a limited smoking history. The association with spousal smoking specifically (1.06, 1.01-1.12, $n = 34$) was less clear in analyses restricted to married subjects (1.03, 0.99-1.07, $n = 23$). In stepwise regression analyses only those associations with source of diagnosis, study size, and whether the spouse was the index, were independently predictive (at $P < 0.05$) of heart disease risk. A significant association was also evident with household exposure (1.19, 1.13-1.25, $n = 37$). For those 23 studies providing dose-response results for spouse or household exposure, 11 showed a significant ($P < 0.05$) positive trend including the unexposed group, and two excluding it. Based on fewer studies, a positive, but non-significant ($P > 0.05$) association was found for workplace exposure (RR = 1.08, 95%CI: 0.99-1.19), childhood exposure (1.12, 0.95-1.31), and biomarker based exposure indices (1.15, 0.94-1.40). However, there was a significant association with total exposure (1.23, 1.12-1.35). Some significant positive dose-response trends were also seen for these exposure indices, particularly total exposure, with no significant negative trends seen. The evidence suffers from various weaknesses and biases. Publication bias may explain the large RR (1.66, 1.30-2.11) for the main exposure index for smaller studies (1-99 cases), while recall bias may explain the higher RRs seen in case-control and cross-sectional than in prospective studies. Some bias may also derive from including occasional smokers among the "never smokers", and from misreporting smoking status. Errors in determining ETS exposure, and failing to update exposure data in long term prospective studies, also contribute to the uncertainty. The tendency for RRs to increase as more factors are adjusted for, argues against the association being due to uncontrolled confounding.

CONCLUSION

The increased risk and dose-response for various exposure indices suggests ETS slightly increases heart disease risk. However heterogeneity, study limitations and possible biases preclude definitive conclusions.

Key words: Passive smoking; Heart disease; Dose-response; Meta-Analysis; Review

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Core tip: We present an up-to-date meta-analysis of the evidence relating environmental tobacco smoke (ETS) exposure to heart disease risk in never smokers. An association is evident for smoking by the spouse (or nearest equivalent) with the relative risk estimated as 1.18 (95%CI: 1.12-1.24), and also with some other indices of ETS exposure. Though the findings suggest a causal relationship, data limitations and bias limit interpretation.

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INTRODUCTION

This review concerns studies of environmental tobacco smoke (ETS) and heart disease in lifelong non-smokers ("never smokers"). In the 1990s some reviewers[1-4] concluded that exposure of non-smokers to ETS increases risk of heart disease, based partly on meta-analyses of epidemiological data from between 12 and 19 studies which reported statistically significant overall increases of about 25%, and partly on evidence from experimental and clinical studies. Their conclusions were accepted by some major bodies[5-8], and supported by some other reviewers[9-13]. However, other reviewers[14-18] disagreed, pointing to omission of relevant studies, inclusion of inappropriate estimates, heterogeneity of findings, study weaknesses and various sources of bias, as well as limitations in the experimental and clinical evidence.

Since then, the number of relevant epidemiological studies has increased, with over 50 now published. However, no recent comprehensive meta-analysis has been conducted, one published in 2015[13] including fewer studies than in some earlier reviews.

Our main objective is to present an updated meta-analysis of the epidemiological data, although we also briefly discuss the experimental evidence, and studies

of smoking bans.

MATERIALS AND METHODS

Study inclusion and exclusion criteria

Attention is restricted to epidemiological prospective, case-control or cross-sectional studies providing relative risk (RR) estimates for never smokers for one or more of these ETS exposure indices: Spouse (including cohabiting partner), other at home exposure, at work, in adulthood, in childhood, in total, and biomarker based. We use the term "relative risk" to include estimates of it, such as the odds ratio or hazard ratio. Results must be available for a disease definition sufficiently close to ischaemic heart disease (IHD) as currently defined. Studies using a near equivalent definition of "never smokers" are accepted when results for stricter definitions are unavailable. Thus, never smokers may include occasional smokers, those with a minimal lifetime duration of smoking or number smoked, or those who quit at least 5 years ago.

Literature searches

At intervals until July 2016 potentially relevant papers were regularly sought from Medline searches, from extensive in-house files accumulated over many years and from references cited in papers obtained. At the end of the process no paper examined cited a possibly relevant paper not previously examined. The latest search used the terms ["tobacco smoke pollution" (MeSH terms)] AND {["heart diseases"(MeSH Terms)] OR ["cardiovascular diseases" (MeSH Terms)] OR ["myocardial infarction" (MeSH Terms)]} AND ("2012/0101"[Date-MeSH]:"3000" [Date-MeSH]), restricted to humans, and published in the last 5 years.

Study identification

Relevant publications were separated into studies, noting multiple papers per study or multiple studies per paper, and any study overlaps.

Data recorded

Details were extracted on study author, publication year, study location and design, sexes included, number of cases, potential confounding variables considered, and definitions of disease and of never smoker. RR estimates, together with associated 95%CIs were obtained, where available, for ETS exposure at home, at work, in childhood, and in total, and using biomarker based estimates (cotinine or COHb). Separate estimates were extracted or calculated for fatal, non-fatal and overall outcomes and for both unadjusted (or for prospective studies, age-adjusted) and covariate-adjusted RRs. If a study provided more than one adjusted estimate, we used that adjusted for most covariates.

RR derivation

Where studies report RRs/CIs only by level of exposure, those for the overall unexposed/exposed comparisons were estimated[19,20]. These methods were also used to estimate significance of dose-related trends, if not given in the source. Similar methods were used to estimate RRs and CIs excluding stroke from a broader circulatory disease definition.

Meta-analyses

Pre-planned fixed-effect and random-effects meta-analyses were conducted using standard methods[21]. Heterogeneity between RR estimates was assessed by the heterogeneity χ^2, the ratio of which to its degrees of freedom, H, relates to the I^2 statistic[22] by I^2 = 100 (H-1)/H. Publication bias tests were also carried out[23].

For our main analyses, we aimed to produce an exposure index most closely equivalent to "spouse ever smoked", since spousal smoking is the traditional index for studying ETS effects, women married to a smoker having a markedly higher ETS exposure, as measured by cotinine, than women married to a non-smoker[24]. Thus, results (sex-specific if available, otherwise combined sex) were selected in the following order of preference for: Exposure (spouse, household, total), time of exposure (ever, during marriage, current, in the past, in the last 10 years, in adulthood), disease type (fatal or non-fatal, fatal only, non-fatal only), disease definition (circulatory disease minus stroke, overall circulatory disease), and definition of no ETS exposure (unexposed to the specific ETS exposure, unexposed to any ETS, low exposure to the specific ETS exposure, never exposed to the specific ETS exposure, unexposed to ETS at home and at work). In addition, results selected were those adjusted for the most confounders for which results were given. This approach of selecting the most relevant result allowed the meta-analyses to include results from each study. Apart from conducting meta-analyses based on all selected estimates, additional meta-analyses using the same set of estimates, investigated variation in RR by the factors sex, continent, publication period, number of cases, study type, number of confounders considered in the study, availability of dose-response results, whether the spouse was the index, and whether (where the spouse was the index), analyses excluded unmarried subjects. Variation was also studied by fatality of cases, definition of disease, whether biomarker data was used to exclude smokers, use of proxy respondents, type of control used, source of diagnosis, and never smoker definition.

Sensitivity analyses repeated the complete set of meta-analyses described above for the main index of exposure with the order of preference for time of exposure revised to favour current rather than ever exposure (current, during marriage, ever, in the past, in the last 10 years, in adulthood), and also preferring unadjusted (or least adjusted) estimates. Further sensitivity analyses were carried out omitting results from: (1) studies by Layard[25] and LeVois *et al*[26]; (2) a study by Enstrom *et al*[27]; or (3) all three studies. These studies have been criticised (see discussion).

For the main exposure index stepwise regression analysis using forward selection[28] was also used to

determine factors independently predicting risk of heart disease.

Similar meta-analyses were also conducted for other indices with sufficient data (household, workplace, childhood, total, biomarker based), though the meta-analyses by subset were more limited.

Results of meta-analyses are displayed in forest plots. Within each plot, study estimates are listed in increasing order of RR. For the main index, the estimates are grouped by location. The estimates are shown both as numbers and in graphical form logarithmically. In the latter representation an RR is shown as a square with area proportional to its inverse-variance weight. Arrows warn if a CI extends outside the range of the plot. Random-effects estimates are also presented, overall and by location, shown by a diamond whose width indicates the 95%CI.

RESULTS

Studies identified

Fifty-eight studies met the inclusion criteria. These come from 57 publications[25-27,29-82], one publication[66] describing results from two studies. Table 1 gives study details including author, reference(s), publication year, location, design, sexes included, disease definition and fatality, and numbers of cases in never smokers. The studies are listed in chronological order of publication and given consecutive study numbers. Minor overlap between cases in studies 16 and 30, was ignored. Table 2 gives variables adjusted for and never smoker definitions. Supplementary File 1 describes why other publications which might be thought possibly relevant are not included.

Of the 58 studies, 10 were published in the 1980s, 15 in the 1990s, 21 between 2000 and 2009 and 12 more recently. Twenty studies were in North America (19 United States, one Canada), 19 in Europe (10 United Kingdom, two Sweden, two Greece, one each in Albania, Germany, Italy and Norway and one in multiple countries), 11 in Asia (two Hong Kong, five in the rest of China, and one each in Iran, Japan, Pakistan and Singapore) and eight in other countries (three in each of Australia and New Zealand, one in Argentina, and one in 52 countries worldwide).

Twenty six studies were prospective, with lengths of follow-up from three to 39 years, while 22 were case-control, and 10 cross-sectional. Thirteen studies were of females, and four of males. The rest included both sexes, though some did not report sex-specific results. Twenty studies considered only fatal cases and 26 only non-fatal cases, the other 12 including both. As shown in Table 1, although IHD specifically was the disease definition used in almost half the studies, various other definitions were used. The studies varied considerably in size, with 13 of < 100 cases and 11 of > 1000 cases, the largest being of 14891, 6280 and 5932 cases.

As Table 2 shows, two studies only provided un-adjusted results. While in a number of the mainly earlier studies there was quite limited adjustment, many studies adjusted for numerous variables. Apart from sex and age, variables adjusted for in > 10 studies included marital status, blood pressure (or hypertension), cholesterol, social class (or similar variables based on education or income), obesity (or weight), alcohol consumption, diabetes, family history of heart disease (or hypertension), race and exercise.

Thirty-five studies were of never smokers, though only nine of these clarified that subjects never smoked cigarettes, pipes or cigars. Nine studies were of never cigarette smokers, 11 allowed a minimal smoking history, such as smoking less than one cigarette a day or fewer than 100 cigarettes in life, while three studies allowed those who quit smoking some time ago. Four studies excluded subjects with cotinine levels indicative of current smoking.

Main exposure index

Our main analyses use an index as close as possible to ever smoking by the spouse. Four studies were not included in the main index analyses, one (study 40) only reporting risk per 10 years living or working with a smoker, and three (studies 33, 36 and 48) providing results only for a biochemical index. Table 3, supported by Figure 1, presents RRs for the main index, and also gives details of ETS exposure, the definitions of the unexposed group being given in Supplementary File 2. RRs for the sensitivity analysis preferring current exposure are also in Table 3, nine studies providing RRs and 95%CIs for both ever and current exposure. RRs for the sensitivity analysis preferring unadjusted to adjusted results are given in Supplementary file 2. Studies 7, 17 and 25 only provided incomplete estimates that could not be included in meta-analyses. Similarly, the result for current exposure from study 4 could not be included in the sensitivity analysis. Otherwise, for each study/sex combination, the RR estimate listed first in Table 3 is that used in the main analysis. Exposure was based on spousal smoking for 24 studies, on at home exposure for 17, and on exposure from multiple sources, including outside the home, for 10. Table 4 presents results of meta-analyses, fuller details being given in Supplementary File 2. Table 5 presents dose-response data, separately for spousal and household exposure.

Table 3 demonstrates clear evidence of a positive association, about three-quarters of the main analysis RR estimates exceeding 1. Seventeen are significantly ($P < 0.05$) increased, and none significantly decreased. Study 16 contributed 31% of the total weight, with studies 20, 27, 30 and 38 each contributing about 10%.

The main meta-analysis (Table 4) shows a clear positive association, with the random-effects RR estimate 1.18 (95%CI: 1.12-1.24) based on 75 individual estimates. The RR is little changed in sensitivity analyses preferring unadjusted to adjusted estimates (1.16, 1.09-1.24), or preferring current to ever exposure estimates (1.19, 1.13-1.26). It is somewhat increased if studies 15, 16 and 30 are excluded (1.23, 1.17-1.29).

Table 1 Studies providing evidence on heart disease and environmental tobacco smoke exposure in never smokers

Study No.	Ref.[1]	Year[2]	Location	Type[3]	Sexes included[4]	Disease fatality[5]	Disease definition[6]	No. of cases[7]
1	Hirayama[29]	1984	Japan	P16	F	F	IHD	494
2	Garland *et al*[30]	1985	United States/California	P10	F	F	IHD	19
3	Lee *et al*[31]	1986	England	CC	M, F	NF	IHD	118
4	Martin *et al*[32]	1986	United States/Utah	CS	F	NF	PHA	23
5	Svendsen *et al*[33]	1987	United States	P9	M	F + NF	IHD	69
6	Butler[34]	1988	United States/California	P6	F	F	IHD	80[8]
7	Palmer *et al*[35]	1988	United States/Not known	CC	F	NF	MI	336
8	Hole *et al*[36]	1989	Scotland	P12	M, F	F, NF	IHD, A/E	120
9	Jackson[37]	1989	New Zealand	CC	M, F	F + NF	IHD + MI	303
10	Sandler *et al*[38]	1989	United States/Maryland	P12	M, F	F	AHD	1358
11	Humble *et al*[39]	1990	United States/Georgia	P20	F	F	CVD	76
12	Dobson *et al*[40]	1991	Australia	CC	M, F	F + NF	IHD + MI	343
13	Gardiner *et al*[41]	1992	Scotland	CC	M+F	F + NF	IHD	12
14	La Vecchia *et al*[42]	1993	Italy	CC	M, F	NF	FMI	113
15	Layard[25]	1995	United States	CC	M, F	F	IHD	1389
16[9]	Le Vois *et al*[26] (CPS I)	1995	United States	P13	M, F	F	AHD	14891
17	Mannino *et al*[43]	1995	United States	CS	M + F	NF	CVD	?
18	Muscat *et al*[44]	1995	United States/4 cities	CC	M, F	NF	NMI	114
19	Tunstall-Pedoe *et al*[45]	1995	Scotland	CS	M + F	NF	IHD	428
20	Steenland *et al*[46]	1996	United States	P7	M, F	F	IHD	3819
21	Janghorbani *et al*[47]	1997	Iran	CC	F	NF	IHD	200
22	Kawachi *et al*[48]	1997	United States	P10	F	F + NF	IHD + MI	152
23	Ciruzzi *et al*[49]	1998	Argentina	CC	M, F	NF	FMI	336
24	McElduff *et al*[50]	1998	Australia	CC	M, F	F + NF	MI	283
25	Spencer *et al*[51]	1999	Australia	CC	M	NF	FMIS	91
26	He *et al*[52]	2000	China/Xi'an	CC	F	NF	MI/CS	115
27	Iribarren *et al*[53]	2001	United States	CS	M, F	NF	HD	4801
28	Rosenlund *et al*[54]	2001	Sweden	CC	M, F	NF	FMI	334
29	Pitsavos *et al*[55]	2002	Greece	CC	M + F	NF	FMI/UA	279
30[9]	Enstrom *et al*[27]	2003	United States/California	P39	M, F	F	IHD	5932
31	Chen *et al*[56]	2004	Scotland	CS	M + F	NF	IHD	385
32	Nishtar *et al*[57][10]	2004	Pakistan	CC	M + F	NF	CAD	?
33[11]	Whincup *et al*[58]	2004	Great Britain	P21	M	F + NF	IHD	111
34	McGhee *et al*[59]	2005	Hong Kong	CC	M, F	F	IHD	584
35	Qureshi *et al*[60]	2005	United States	P11	F	F + NF	CVD	328
							CVD-Stroke	219
36	Hedblad *et al*[61]	2006	Sweden	P19	M	F + NF	IHD + MI, FMI	91
37	Stranges *et al*[62]	2006	United States	CC	M, F	NF	FMI	284
38	Teo *et al*[63]	2006	52 countries	CC	M + F	NF	FMI	6280
39	Wen *et al*[64]	2006	China/Not known	P6	F	F	CVD	272
							CVD-Stroke	115
40	Eisner *et al*[65]	2007	United States	P8	M, F	F	CVD	1057
41	Hill *et al*[66]	2007	New Zealand	P3	M, F	F	IHD	2571
42	Hill *et al*[66]	2007	New Zealand	P3	M, F	F	IHD	1680
43	He *et al*[67]	2008	China/Beijing	CS	F	NF	IHD	431
44	Sulo *et al*[68]	2008	Albania	CC	M + F	NF	ACS	169
45	Vozoris *et al*[69]	2008	Canada	CS	M + F	NF	HD	1773
46	Ding *et al*[70]	2009	Hong Kong	CC	F	NF	IHD	314
47	Gallo *et al*[71]	2010	Europe	P?	M, F	F	CVD[12]	399
					M + F		IHD	81
48	Hamer *et al*[72]	2010	England, Scotland	P7	M + F	F	CVD	96
49[11]	Jefferis *et al*[73]	2010	Great Britain	P11	M + F	F + NF	FMI	74
50	Peineman *et al*[74]	2011	Germany	CS	M + F	NF	IHD	128
51	Chen[75]	2012	China/4 provinces	CS	M + F	NF	IHD	405
							MI	171
52	He *et al*[76]	2012	China/Xi'an	P26	M, F	F	IHD	41
53	Clark *et al*[77]	2013	Singapore	P16	M, F	F	IHD	311
54	Iversen *et al*[78]	2013	Norway	P11	M, F	F + NF	FMI	326
55	Kastorini *et al*[79]	2013	Greece	CC	M + F	NF	ACS	52
56	Rostron[80]	2013	United States	P11	M + F	F	IHD	?
57	Batty *et al*[81][13]	2014	United Kingdom	P17	M, F	F	CVD	98

58	Shiue[82]	2014	Scotland	CS	M + F	NF	MI	255

[1]First author of paper, followed by a number to distinguish multiple studies with the same author; [2]Year of publication; [3]Study types are CC: Case-control, CS: Cross-sectional, P: Prospective. Number after P is estimated mean years of follow-up; ?: Indicates length of follow-up not stated; [4]M + F indicates only results for combined sexes available; M, F indicates separate sex results available; [5]F: Fatal; NF: Non-fatal; F + NF indicates only combined results available; F, NF indicates separate results available; [6]A/E: Angina or ECG abnormality; ACS: Acute coronary syndrome; AHD: Arteriosclerotic heart disease; CAD: Coronary artery disease; CVD: Cardiovascular disease; FMI: First myocardial infarction; FMI/UA: First myocardial infarction or unstable angina; FMIS: First myocardial infarction surviving 28 d, HD: Heart disease; IHD: Ischaemic (coronary) heart disease; MI: Myocardial infarction; MI/CS: Myocardial infarction or coronary stenosis; NMI: Newly diagnosed myocardial infarction; PHA: Previous heart attack. "+" indicates inclusion of cases with either disease, indicates different outcome definitions for fatal and non-fatal analyses respectively; [7]Number of heart disease cases in never smokers are totals in the study. For analyses relating to some exposure indices, numbers may be lower than this. ? indicates numbers not available; [8]For study 6 numbers relate only to the spouse-pairs cohort, the AHSMOG cohort including ex-smokers; [9]Studies 16 and 30 were both part of CPS I. Study 30 covered a smaller geographic area but a longer follow-up period; [10]For study 32, although the source paper does not state that the analyses were restricted to never smokers, this has been confirmed to us by the authors; [11]Study 49 included the same male participants as study 33, but started at the end of the follow-up period of that study, so there was no overlap of cases between the two studies; [12]For study 47, CVD was defined as any circulatory disease excluding cerebrovascular causes; [13]For study 57, results in never smokers were taken from Supplementary tables supplied by the authors.

There is clear (P < 0.001) heterogeneity between estimates for all these analyses. Analyses by subset (based on the main analysis) show highly significant (P < 0.001) variation by various factors:

Sex: Estimates are lower for males than for females or sexes combined.

Continent: Estimates are lower for North America than for Europe, Asia or elsewhere.

Publication period: Estimates are higher for the oldest (1984-1991) and newest (2010-2016) studies than for studies in intermediate periods.

Number of cases: Studies with fewer cases give higher estimates, consistent with the significant (P < 0.001) publication bias for the overall analysis.

Study type: Estimates are lower for prospective than for case-control or cross-sectional studies.

Spouse the index: Estimates are lower where the spouse is the index, and where the analysis is limited to married subjects.

Fatality: Estimates are lower when based on fatal cases.

Heart disease definition: Estimates are lower for IHD specifically than for other definitions.

Type of control: In case-control studies, estimates are lower where hospital/diseased controls rather than healthy controls, are used.

Source of diagnosis: Estimates are lower when diagnosis derives from death certificates or self-report than from medical data.

Definition of never smoker: Estimates are higher where the definition allowed "never smoking" subjects to smoke products other than cigarettes, or to have a limited smoking history.

Despite the heterogeneity, each RR estimate in Table 4 for each data subset exceeds 1.00, generally significantly so. Our analyses demonstrated 11 factors with highly significant (P < 0.001) heterogeneity by level, when considered one at a time. However, many were inter-correlated. To isolate the important factors, stepwise regression analysis was conducted (see Supplementary File 3). Only three of the 11 factors independently predicted heart disease risk at P < 0.05, with source of diagnosis introduced first into the model, then spouse the index, and then number of cases. While, for the factors remaining in the model, the direction of effect remained, the magnitude of variation between levels was slightly reduced from that shown in Table 4.

Further results for exposure at home

Table 3 also shows RRs for household exposure for five studies where separate results are available for both spousal and household exposure. Overall, there are 37 household exposure estimates from 22 studies, 10 showing a significant increase in risk, and none a significant decrease. The combined random-effects estimate is 1.19 (95%CI: 1.13-1.25). There is no marked heterogeneity between the estimates overall, and little indication of variation between males and females, continents, periods of publication or numbers of cases. Estimates do vary by study design (P < 0.01), being higher for case-control studies than other designs.

As shown in Table 5, 13 studies reported dose-response results for smoking by the spouse, 11 for smoking by household members, and one (study 47) for both. While only two studies providing dose-response data for spousal smoking reported a significant (P < 0.05) positive trend, nine did so for exposure to household members. These trend tests included the unexposed group. Had they excluded the unexposed group, they would have been significant for only one (study 26). There were no significant negative trends.

Other exposure indices

Table 6 presents results for ETS exposure at work, in childhood, a combined index of total exposure, and a biochemical index of exposure. For these four indices,

Table 2 Potential confounding variables adjusted for and definition of never smoker

Study No.	Ref.[1]	Variables adjusted for[2]	Definition of never smokers[3]
1	Hirayama[29]	Sex, age, marital status	Never cigarettes
2	Garland *et al*[30]	Sex, age, marital status, blood pressure, cholesterol, obesity	Never cigarettes
3	Lee *et al*[31]	Sex, age, marital status	Never NOS
4	Martin *et al*[32]	Sex, marital status, blood pressure, obesity, alcohol, diabetes, family history of heart disease, exercise	Never NOS
5	Svendsen *et al*[33]	Sex, age, marital status, blood pressure, cholesterol, social class, obesity, alcohol	Never any product
6	Butler[34]	Sex, age, marital status	Never cigarettes
7	Palmer *et al*[35]	Sex, marital status	Never NOS
8	Hole *et al*[36]	Sex, age, blood pressure, cholesterol, social class, obesity	Never NOS
9	Jackson[37]	Sex, age, social class, obesity, family history of heart disease	Never NOS
10	Sandler *et al*[38]	Sex, age, social class, personal history of heart disease	Never any product
11	Humble *et al*[39]	Sex, age, marital status, blood pressure, cholesterol, obesity	Never NOS
12	Dobson *et al*[40]	Sex, age, social class, obesity, personal history of heart disease	Never cigarettes
13	Gardiner *et al*[41]	Sex, age, hospital admission date	Never any product
14	La Vecchia *et al*[42]	Sex, age, marital status, blood pressure, cholesterol, social class, obesity, diabetes, family history of heart disease, coffee	Never NOS
15	Layard[25]	Sex, age, marital status, race	Never 100 cigarettes in lifetime
16	Le Vois *et al*[26] (CPS I)	Sex, age, marital status, race	Never NOS
17	Mannino *et al*[43]	Sex, age, social class, race, housing	Never NOS
18	Muscat *et al*[44]	Sex, age, blood pressure, social class, race	Never one cigarette, pipe or cigar per day for more than a year
19	Tunstall-Pedoe *et al*[45]	Age, blood pressure, cholesterol, housing	Never any product and cotinine < 17.5 mg/mL
20	Steenland *et al*[46]	Sex, age, marital status, blood pressure, social class, obesity, alcohol, diabetes, exercise, personal history of heart disease, occupation, oestrogen use, aspirin use, diuretic use and personal history of arthritis	Never any product daily for as long as a year (men), never cigarettes (women)
21	Janghorbani *et al*[47]	Sex, age, marital status	Never any product
22	Kawachi *et al*[48]	Sex, age, blood pressure, cholesterol, obesity, alcohol, diabetes, family history of heart disease, exercise, occupation, oestrogen use, oral contraceptive use, saturated fat intake, vitamin E intake, menopausal status and use of postmenopausal hormones	Never NOS
23	Ciruzzi *et al*[49]	Sex, age, blood pressure, cholesterol, social class, obesity, diabetes, family history of heart disease, exercise	Never NOS
24	McElduff *et al*[50]	Sex, age, social class, obesity, family history of heart disease	Never cigarettes or quit at least 10 yr ago, and not current other products
25	Spencer *et al*[51]	Sex, age	Never NOS
26	He *et al*[52]	Sex, age, blood pressure, cholesterol, family history of heart disease, personality type	Never NOS
27	Iribarren *et al*[53]	Sex, age, marital status, cholesterol, social class, obesity, alcohol, diabetes, race, exercise, personality type	Never any product
28	Rosenlund *et al*[54]	Sex, age, blood pressure, cholesterol, social class, obesity, diabetes, occupation	Never any product regularly for at least a year
29	Pitsavos *et al*[55]	Sex, age, blood pressure, cholesterol, obesity, alcohol, diabetes, exercise and family history of heart disease	Never cigarettes
30	Enstrom *et al*[27]	Sex, age, marital status, social class, obesity, race, exercise, housing, fruit or fruit juice intake and health status	Never any product[4]
31	Chen *et al*[56]	Sex, age, blood pressure, cholesterol, social class, obesity, alcohol, family history of heart disease, employment status, dietary vitamin C and fibre	Never NOS and cotinine < 17.5 mg/mL
32	Nishtar *et al*[57]	Sex, age, matched pair (conditional logistic regression was used)	Never NOS
33	Whincup *et al*[58]	Sex, age, blood pressure, cholesterol, social class, obesity, alcohol, diabetes, exercise, personal history of heart disease, town of residence, FEV_1, height, triglycerides and white cell count	Never any product and cotinine < 14.1 mg/mL
34	McGhee *et al*[59]	Sex, age, marital status, social class	Never NOS
35	Qureshi *et al*[60]	Sex, age, marital status, blood pressure, cholesterol, obesity, alcohol, diabetes, race	Never NOS
36	Hedblad *et al*[61]	Sex, blood pressure, cholesterol, obesity, alcohol, diabetes, exercise, personal history of heart disease, triglycerides and FEV_1	Never one cigarette per day
37	Stranges *et al*[62]	Sex, blood pressure, cholesterol, social class, obesity, alcohol, diabetes, race, exercise	Never 100 cigarettes in lifetime
38	Teo *et al*[63]	Sex, age, alcohol, exercise, region, consumption of fruits and vegetables	Never any product regularly
39	Wen *et al*[64]	Sex, age, social class, obesity, exercise, occupation, intake of meats, vegetables and fruit	Never NOS
40	Eisner *et al*[65]	Sex, age, marital status, social class	Never cigarettes or quit at least 20 yr ago, and < 10 pack-years
41, 42	Hill *et al*[66]	Sex, age, marital status, social class, race, occupation	Never NOS

43	He *et al*[67]	Sex, age, marital status, blood pressure, cholesterol, social class, obesity, alcohol, diabetes, family history of heart disease, exercise, triglycerides, family history of stroke	Never 100 cigarettes in lifetime
44	Sulo *et al*[68]	Sex, age, blood pressure, social class, obesity, diabetes, family history of heart disease, race, exercise, occupation, financial loss in pyramid schemes, emigration of spouse and/or offspring, religious observance	Never cigarettes
45	Vozoris *et al*[69]	Sex, age, social class, province, immigration status, presence of children younger than 12 yr in household	Never cigarettes
46	Ding *et al*[70]	Sex, age, blood pressure, cholesterol, social class, alcohol, diabetes, family history of heart disease, exercise, oestrogen use, history of stroke, history of gout	Never NOS
47	Gallo *et al*[71]	Sex, age, social class, obesity, exercise, study centre	Never NOS
48	Hamer *et al*[72]	Sex, age, blood pressure, cholesterol, social class, exercise, personality type, survey location, log C-reactive protein, fibrinogen	Never NOS
49	Jefferis *et al*[73]	Sex, age, blood pressure, cholesterol, social class, obesity, alcohol, diabetes, exercise, region, triglycerides, FEV_1, C-reactive protein, interleukin 6, white cell count	Never any product or quit at least 5 yr ago, and cotinine < 15 mg/mL
50	Peinemann *et al*[74]	None	Never NOS
51	Chen[75]	None	Never cigarettes
52	He *et al*[76]	Sex, age, marital status, blood pressure, cholesterol, social class, obesity, alcohol, occupation, triglycerides	Never 100 cigarettes in lifetime
53	Clark *et al*[77]	Sex, age, social class, obesity, dialect, dietary fibre intake	Never NOS
54	Iversen *et al*[78]	Sex, age, blood pressure, cholesterol, obesity, exercise, living with a smoker (for analysis of hours spent in smoke-filled rooms), hours spent in smoke-filled rooms (for analysis of living with a smoker)	Never cigarettes
55	Kastorini *et al*[79]	Sex, age, blood pressure, cholesterol, obesity, diabetes, family history of heart disease, exercise, personality type, Mediterranean Diet Score	Never one cigarette a day
56	Rostron[80]	Sex, age, race, social class, alcohol, blood pressure, obesity, personal history of heart disease	Never 100 cigarettes in lifetime
57	Batty *et al*[81]	Sex, age, social class, alcohol, diabetes, exercise, personal history of heart disease, personal history of cancer	Never NOS
58	Shiue[82]	Sex, age, race, social class, alcohol, survey weighting, exercise, blood pressure, obesity	Never any product

[1]First author of paper; [2]In some cases similar adjustment variables have been considered under one name. Thus blood pressure includes hypertension; social class includes education and income; obesity includes weight; family history of heart disease includes family history of hypertension; and housing includes urban-rural; [3]Never any product: Never smoked cigarettes, pipes or cigars; Never NOS: Never smoked, product unspecified; [4]Questions on pipe and cigar smoking were asked at baseline, but not at the follow-up interviews.

results are available from, respectively, 14, 4, 24 and 8 studies. For some studies the estimates for total exposure are the same as those for the main exposure index. The RRs are supported by Figures 2-5, while Table 7 presents results of meta-analyses, and Table 8 the dose-response data. Again, fuller details of meta-analyses are given in Supplementary File 2. Supplementary File 2 also includes results for spousal smoking specifically.

For workplace exposure, there were 22 estimates, with only one showing a significant increase, the combined estimate of 1.08 (95%CI: 0.99-1.19) being almost significantly raised. There was no evidence of heterogeneity, and little evidence of variation by any factor considered.

For childhood exposure, one of the seven estimates showed a significant increase in risk. However, the combined estimate of 1.12 (95%CI: 0.95-1.31) was not significant.

For total exposure, the 33 estimates showed clear heterogeneity ($P < 0.001$), 11 estimates showing a significant ($P < 0.05$) positive association, and one a significant negative association. However, there was a clear preponderance of positive associations, with the random-effects estimate 1.23 (95%CI: 1.12-1.35). Subgroup analyses showed higher estimates for Asia; for case-control studies, and for females and sexes-combined.

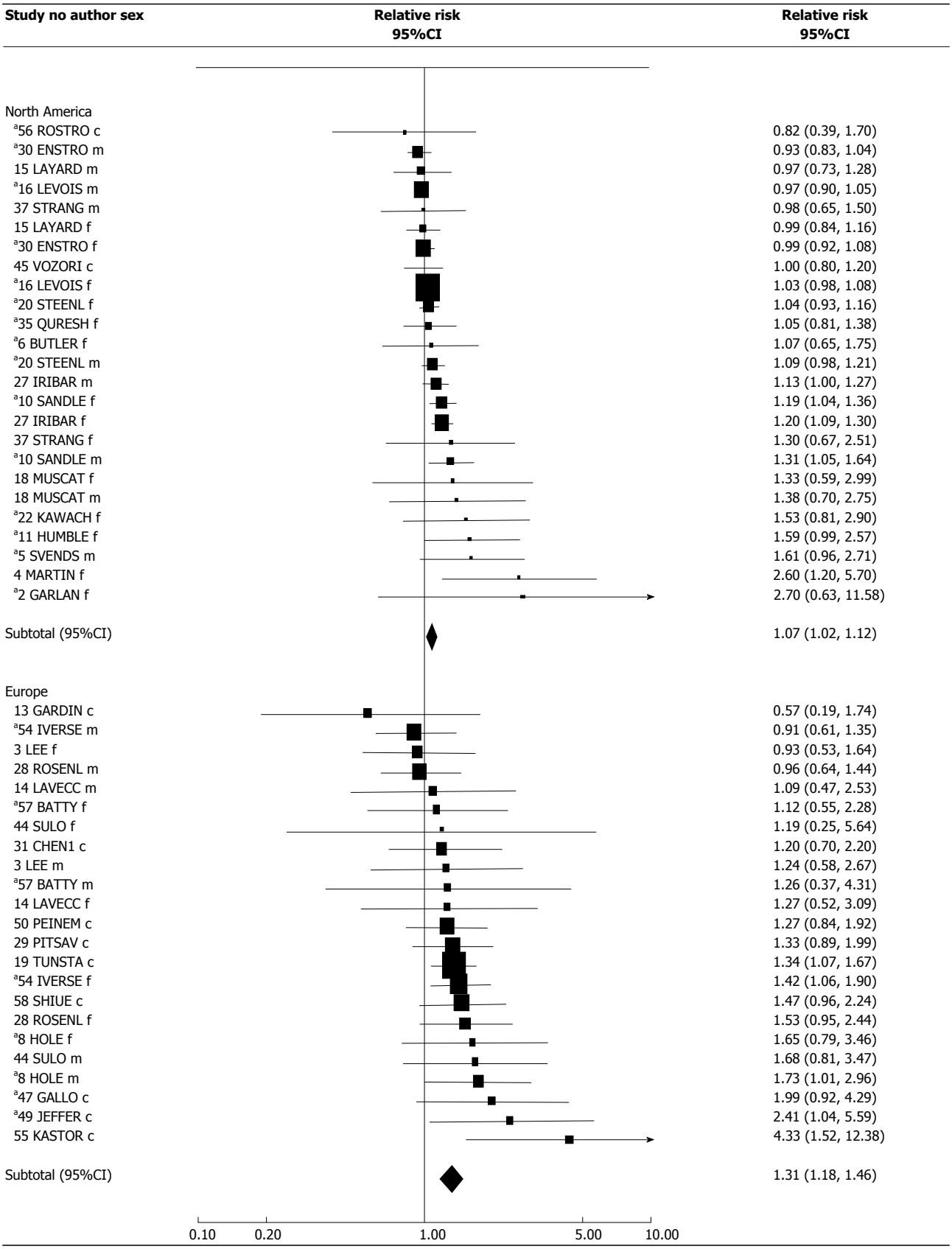
Of nine estimates for biomarker based exposure indices, all were cotinine-based apart from one based on COHb. There was some indication of heterogeneity ($P < 0.1$), the random-effects estimate of 1.15 (95%CI: 0.94-1.40) showing no clear association.

Table 8 presents dose-response data for these exposure indices. For studies reporting dose-response results, significant positive trends were seen (for at least one index) in 12 of 17 studies for total exposure, 3 of 8 studies for biomarker-based exposure, 1 of 5 studies for workplace exposure, and 1 of 2 studies for childhood exposure. No significant negative trends were seen.

Twelve studies presented RR estimates and/or dose-response results for one or more other exposure indices (Supplementary File 4). These results relate to many different indices, and are somewhat variable, with clear evidence of an increase being seen for studies 29 and 32, but a number of other studies showing no relationship with the indices studied.

DISCUSSION

Based on 58 studies, we present meta-analyses relating


Study no author sex
Relative risk 95%CI
Relative risk 95%CI
North America
[a]56 ROSTRO c 0.82 (0.39, 1.70)
[a]30 ENSTRO m 0.93 (0.83, 1.04)
15 LAYARD m 0.97 (0.73, 1.28)
[a]16 LEVOIS m 0.97 (0.90, 1.05)
37 STRANG m 0.98 (0.65, 1.50)
15 LAYARD f 0.99 (0.84, 1.16)
[a]30 ENSTRO f 0.99 (0.92, 1.08)
45 VOZORI c 1.00 (0.80, 1.20)
[a]16 LEVOIS f 1.03 (0.98, 1.08)
[a]20 STEENL f 1.04 (0.93, 1.16)
[a]35 QURESH f 1.05 (0.81, 1.38)
[a]6 BUTLER f 1.07 (0.65, 1.75)
[a]20 STEENL m 1.09 (0.98, 1.21)
27 IRIBAR m 1.13 (1.00, 1.27)
[a]10 SANDLE f 1.19 (1.04, 1.36)
27 IRIBAR f 1.20 (1.09, 1.30)
37 STRANG f 1.30 (0.67, 2.51)
[a]10 SANDLE m 1.31 (1.05, 1.64)
18 MUSCAT f 1.33 (0.59, 2.99)
18 MUSCAT m 1.38 (0.70, 2.75)
[a]22 KAWACH f 1.53 (0.81, 2.90)
[a]11 HUMBLE f 1.59 (0.99, 2.57)
[a]5 SVENDS m 1.61 (0.96, 2.71)
4 MARTIN f 2.60 (1.20, 5.70)
[a]2 GARLAN f 2.70 (0.63, 11.58)
Subtotal (95%CI) 1.07 (1.02, 1.12)
Europe
13 GARDIN c 0.57 (0.19, 1.74)
[a]54 IVERSE m 0.91 (0.61, 1.35)
3 LEE f 0.93 (0.53, 1.64)
28 ROSENL m 0.96 (0.64, 1.44)
14 LAVECC m 1.09 (0.47, 2.53)
[a]57 BATTY f 1.12 (0.55, 2.28)
44 SULO f 1.19 (0.25, 5.64)
31 CHEN1 c 1.20 (0.70, 2.20)
3 LEE m 1.24 (0.58, 2.67)
[a]57 BATTY m 1.26 (0.37, 4.31)
14 LAVECC f 1.27 (0.52, 3.09)
50 PEINEM c 1.27 (0.84, 1.92)
29 PITSAV c 1.33 (0.89, 1.99)
19 TUNSTA c 1.34 (1.07, 1.67)
[a]54 IVERSE f 1.42 (1.06, 1.90)
58 SHIUE c 1.47 (0.96, 2.24)
28 ROSENL f 1.53 (0.95, 2.44)
[a]8 HOLE f 1.65 (0.79, 3.46)
44 SULO m 1.68 (0.81, 3.47)
[a]8 HOLE m 1.73 (1.01, 2.96)
[a]47 GALLO c 1.99 (0.92, 4.29)
[a]49 JEFFER c 2.41 (1.04, 5.59)
55 KASTOR c 4.33 (1.52, 12.38)
Subtotal (95%CI) 1.31 (1.18, 1.46)
0.10
0.20
1.00
5.00
10.00

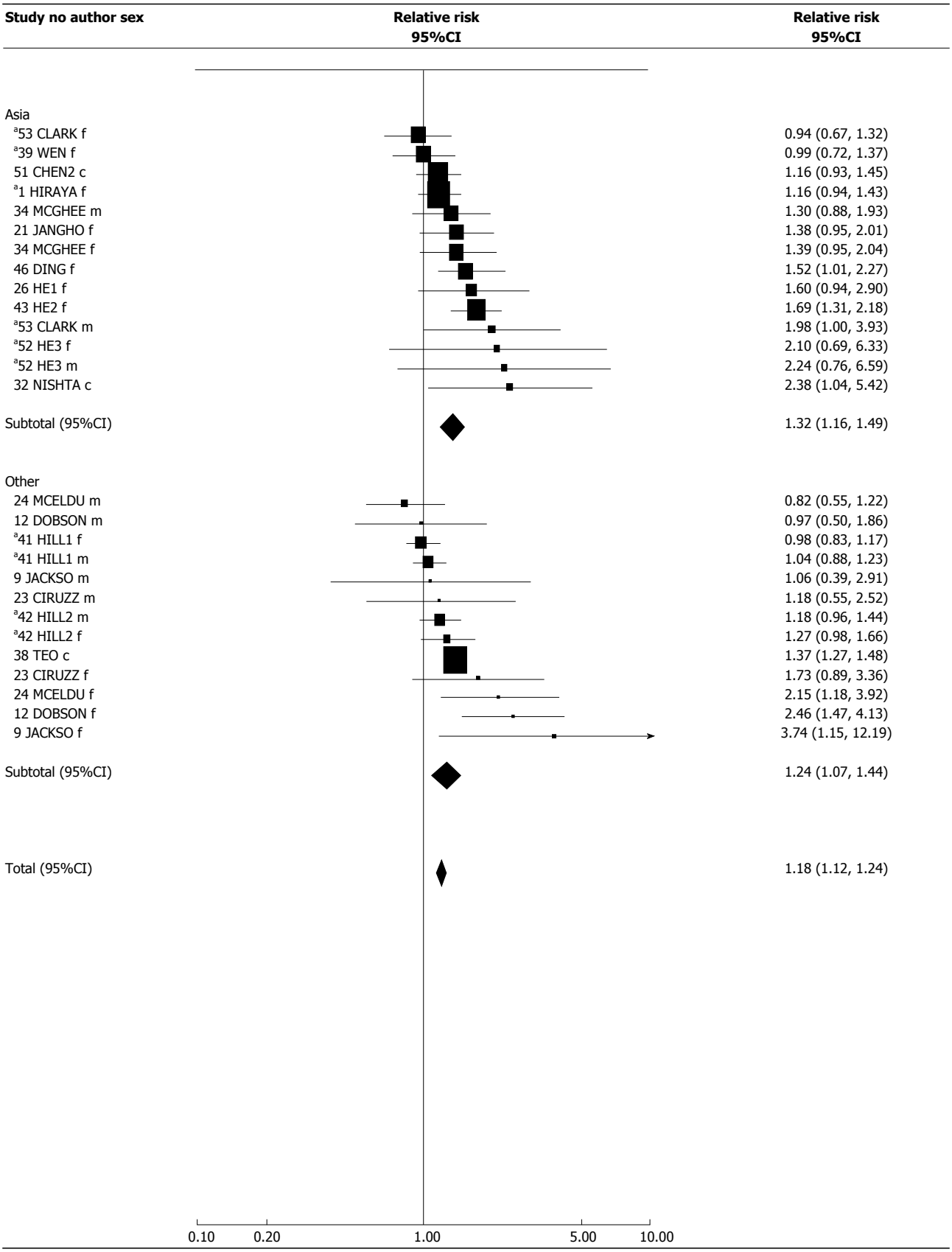


Figure 1 Forest plot for the main index, by continent. Estimates of the RR and its 95%CI are shown separately by continent, sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Estimates are identified by the study number shown in Table 1, an abbreviation of the author name and the sex to which the estimate relates (m = male, f = female, c = combined sex estimate). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight (the inverse of the variance of log RR). Arrows warn if the CI goes outside the range of the plot. Random-effects estimates (RRs and their 95%CIs) are shown for each continent and overall, represented graphically by a diamond whose width indicates the confidence interval. [a]Prospective study.

Table 3 Heart disease relative risk estimates used in the main analysis for spouse ever smoked (or nearest equivalent) and in sensitivity analyses for spouse a current smoker, as well as additional results for household exposure

Study No.[1]	Author[2]	Sex	Exposure index		Fatality[5]	Relative risk (95%CI)[6]
			Source[3]	Timing[4]		
Results used in the main analysis[7]						
1	Hirayama[29]	F	S	E	F	1.16 (0.94-1.43)[8]
2	Garland *et al*[30]	F	S	E	F	2.70 (0.63-11.58)
3	Lee *et al*[31]	M	S	M	NF	1.24 (0.58-2.67)
		F	S	M	NF	0.93 (0.53-1.64)
4	Martin *et al*[32]	F	S	E	NF	2.60 (1.20-5.70)[9]
5	Svendsen *et al*[33]	M	S	C	F + NF	1.61 (0.96-2.71)
6	Butler[34]	F	S	E	F	1.07 (0.65-1.75)
7	Palmer *et al*[35]	F	S	E	NF	1.20
8	Hole *et al*[36]	M	H[10]	E	F	1.73 (1.01-2.96)[11]
		F	H[10]	E	F	1.65 (0.79-3.46)[11]
9	Jackson[37]	M	H	C	F + NF	1.06 (0.39-2.91)
		F	H	C	F + NF	3.74 (1.15-12.19)
10	Sandler *et al*[38]	M	H	C	F	1.31 (1.05-1.64)
		F	H	C	F	1.19 (1.04-1.36)
11	Humble *et al*[39]	F	S	C(N)	F	1.59 (0.99-2.57)
12	Dobson *et al*[40]	M	H	C	F + NF	0.97 (0.50-1.86)
		F	H	C	F + NF	2.46 (1.47-4.13)
13	Gardiner *et al*[41]	M + F	S	M	F + NF	0.57 (0.19-1.74)
14	La Vecchia *et al*[42]	M	S	E	NF	1.09 (0.47-2.53)
		F	S	E	NF	1.27 (0.52-3.09)
15	Layard[25]	M	S	E	F	0.97 (0.73-1.28)
		F	S	E	F	0.99 (0.84-1.16)
16	Le Vois *et al*[26] (CPS I)	M	S	E	F	0.97 (0.90-1.05)
		F	S	E	F	1.03 (0.98-1.08)
17	Mannino *et al*[43]	M + F	H	C	NF	1.12
18	Muscat *et al*[44]	M	S	E	NF	1.38 (0.70-2.75)
		F	S	E	NF	1.33 (0.59-2.99)
19	Tunstall-Pedoe *et al*[45]	M + F	T	C	NF	1.34 (1.07-1.67)
20	Steenland *et al*[46]	M	S	E	F	1.09 (0.98-1.21)
		F	S	E	F	1.04 (0.93-1.16)
21	Janghorbani *et al*[47]	F	S	E	NF	1.38 (0.95-2.01)
22	Kawachi *et al*[48]	F	H	C	F + NF	1.53 (0.81-2.90)[9]
23	Ciruzzi *et al*[49]	M	S	C	NF	1.18 (0.55-2.52)
		F	S	C	NF	1.73 (0.89-3.36)
24	McElduff *et al*[50]	M	T	C	F + NF	0.82 (0.55-1.22)
		F	T	C	F + NF	2.15 (1.18-3.92)
25	Spencer *et al*[51]	M	H	E	NF	No significant association
26	He *et al*[52]	F	S	E	NF	1.60 (0.94-2.90)
27	Iribarren *et al*[53]	M	H	C	NF	1.13 (1.00-1.27)
		F	H	C	NF	1.20 (1.09-1.30)
28	Rosenlund *et al*[54]	M	S	E	NF	0.96 (0.64-1.44)
		F	S	E	NF	1.53 (0.95-2.44)
29	Pitsavos *et al*[55]	M + F	H	C	NF	1.33 (0.89-1.99)
30	Enstrom *et al*[27]	M	S	E	F	0.93 (0.83-1.04)
		F	S	E	F	0.99 (0.92-1.08)
31	Chen *et al*[56]	M + F	H	C	NF	1.20 (0.70-2.20)
32	Nishtar *et al*[57]	M + F	S	E	NF	2.38 (1.04-5.42)
34	McGhee *et al*[59]	M	H	P	F	1.30 (0.88-1.93)
		F	H	P	F	1.39 (0.95-2.04)
35	Qureshi *et al*[60]	F	S	E	F + NF	1.05 (0.81-1.38)[12]
37	Stranges *et al*[62]	M	H	E	NF	0.98 (0.65-1.50)
		F	H	E	NF	1.30 (0.67-2.51)
38	Teo *et al*[63]	M + F	T	C	NF	1.37 (1.27-1.48)
39	Wen *et al*[64]	F	S	M	F	0.99 (0.72-1.37)[13]
41	Hill *et al*[66]	M	H	C	F	1.04 (0.88-1.23)
		F	H	C	F	0.98 (0.83-1.17)
42	Hill *et al*[66]	M	H	C	F	1.18 (0.96-1.44)
		F	H	C	F	1.27 (0.98-1.66)
43	He *et al*[67]	F	T	T	NF	1.69 (1.31-2.18)
44	Sulo *et al*[68]	M	S	C	NF	1.68 (0.81-3.47)
		F	S	C	NF	1.19 (0.25-5.64)
45	Vozoris *et al*[69]	M + F	T	C	NF	1.00 (0.80-1.20)
46	Ding *et al*[70]	F	H	E	NF	1.52 (1.01-2.27)
47	Gallo *et al*[71]	M + F	S	C	F	1.99 (0.92-4.29)[14]
49	Jefferis *et al*[73]	M + F	S	C	F + NF	2.41 (1.04-5.59)

50	Peinemann *et al*[74]	M + F	T	C	NF	1.27 (0.84-1.92)
51	Chen[75]	M + F	T	E	NF	1.16 (0.93-1.45)[15]
52	He *et al*[76]	M	T	E	F	2.24 (0.76-6.59)
		F	T	E	F	2.10 (0.69-6.33)
53	Clark *et al*[77]	M	H	C	F	1.98 (1.00-3.93)
		F	H	C	F	0.94 (0.67-1.32)
54	Iversen *et al*[78]	M	H	A	F + NF	0.91 (0.61-1.35)
		F	H	A	F + NF	1.42 (1.06-1.90)
55	Kastorini *et al*[79]	M + F	T	E	NF	4.33 (1.52-12.38)
56	Rostron[80]	M + F	H	C	F	0.82 (0.39-1.70)
57	Batty *et al*[81]	M	H	C	F	1.26 (0.37-4.31)
		F	H	C	F	1.12 (0.55-2.28)
58	Shiue[82]	M + F	T	C	NF	1.47 (0.96-2.24)
Alternative result used in the analysis of spouse a current smoker						
2	Garland *et al*[30]	F	S	C(N)	F	2.25 (0.32-15.74)
4	Martin *et al*[32]	F	S	C	NF	3.40
6	Butler[34]	F	S	C(N)	F	1.40 (0.51-3.84)
14	La Vecchia *et al*[42]	M	S	C(N)	NF	1.09 (0.39-3.01)
		F	S	C(N)	NF	1.36 (0.46-4.05)
16	Le Vois *et al*[26] (CPS I)	M	S	C(N)	F	0.98 (0.91-1.06)
		F	S	C(N)	F	1.04 (0.99-1.09)
20	Steenland *et al*[46]	M	S	C(N)	F	1.22 (1.07-1.40)
		F	S	C(N)	F	1.10 (0.96-1.27)
28	Rosenlund *et al*[54]	M	S	C(N)	NF	0.98 (0.57-1.69)
		F	S	C(N)	NF	2.59 (1.27-5.29)
30	Enstrom *et al*[27]	M	S	C(N)	F	0.92 (0.80-1.05)
		F	S	C(N)	F	0.97 (0.89-1.06)
37	Stranges *et al*[62]	M	H	C	NF	0.71 (0.40-1.23)
		F	H	C	NF	0.94 (0.48-1.82)
39	Wen *et al*[64]	F	S	C	F	1.19 (0.84-1.67)[16]
Additional household exposure results						
18	Muscat *et al*[44]	M	H	E	NF	1.40 (0.70-2.81)
		F	H	E	NF	1.55 (0.55-4.37)
20	Steenland *et al*[46]	M	H	C(N)	F	1.15 (1.01-1.32)
		F	H	C(N)	F	1.07 (0.98-1.17)
21	Janghorbani *et al*[47]	F	H	E	NF	1.34 (0.94-1.91)
23	Ciruzzi *et al*[49]	M	H[17]	C	NF	1.89 (1.13-3.18)
		F	H[17]	C	NF	1.54 (0.95-2.51)
47	Gallo *et al*[71]	M + F	H	C	F	1.31 (0.83-2.08)[18]

[1]Study 40 omitted as results only available per 10 years of living with a smoker. Studies 33, 36 and 48 omitted as they only provide results for a biochemical index of ETS exposure; [2]First author of paper; [3]S: Spouse (or partner), H: Household member (or exposure at home), T: Total; [4]E: Ever exposed (compared to never exposed) or unspecified; M: During marriage; C(N): Current exposure (compared to never exposed); C: Current exposure (compared to non-current exposure), P: In the past, T: In the last 10 years, A: In adulthood; [5]F: Fatal; NF: Non-fatal; F + NF indicates combined results were analysed; [6]Relative risks are adjusted for covariates if adjusted data are available. Those without 95%CI are not used in the meta-analyses; [7]Except where lacking a 95%CI, as in studies 7, 17 and 25; [8]Adjusted for the age of the husband. Alternative estimates[115] were very similar; [9]Estimates given by Wells[1]; [10]Cohabitant(s) age 45-64 also attending screening; [11]Estimates given by Wells[116]; [12]Result for CVD - Stroke. Result also available for CVD: 1.00 (0.81-1.24); [13]Result for CVD - Stroke. Result also available for CVD: 1.18 (0.92-1.51); [14]Result for CVD. Result for IHD shown in the "household" section of this table; [15]Result for IHD. Result also available for myocardial infarction: 0.93 (0.66-1.31); [16]Result for CVD - Stroke. Results also available for CVD: 1.37 (1.06-1.78); [17]Smoking by close relatives (although not necessarily living in same home); [18]Result for IHD. Result also available for CVD: 1.82 (1.06-3.12). ETS: Environmental tobacco smoke; CVD: Cardiovascular disease; IHD: Ischaemic heart disease; CPS: Cancer Prevention Studies.

ETS exposure to heart disease risk in never smokers. Using an exposure index as equivalent as possible to having a spouse who ever smoked, a random-effects meta-analysis gave a significantly increased RR of 1.18 (95%CI: 1.12-1.24) based on 75 RR estimates. Positive associations, not all significant at $P < 0.05$, were also noted with spousal exposure specifically (1.10, 1.04-1.17, $n = 34$), household exposure (1.19, 1.13-1.25, $n = 37$), workplace exposure (1.08, 0.99-1.19, $n = 22$), childhood exposure (1.12, 0.95-1.31, $n = 22$), and total exposure (1.23, 1.12-1.35, $n = 33$). The overall estimate was also elevated for a biomarker-based index (1.15, 0.94-1.40, $n = 9$). There was also evidence of dose-response.

While the relationship of smoking with heart disease[83] suggests some effect may be evident for ETS, exposure to smoke constituents from ETS is much less than from active smoking. For example, studies of cotinine indicate relative exposure of ETS compared to smoking of 0.6% to 0.4%[84-86], while studies of particulate matter suggest a lower factor, < 0.02%[87-95]. In interpreting our meta-analyses, one must note the clear heterogeneity between the RR estimates. Thus, for the main exposure index, estimates were higher for females, United States studies, and small studies, and smaller for prospective studies and for fatal cases, and varied by definition of exposure and source of diagnosis. Although these factors are not independent, and the variations may reflect characteristics of studies

Table 4 Meta-analyses of heart disease[1] risk among never smokers in relation to ever smoking by the spouse (or nearest equivalent)

Subgroup	*n*[3]	Fixed-effect Relative risk (95%CI)	Random-effects Relative risk (95%CI)	Publication bias *P*[4] value	Heterogeneity[2] χ^2	DF[5]	*P*[6] value
Main analyses[7]							
All	75	1.10 (1.08-1.13)	1.18 (1.12-1.24)	< 0.001	176.45	74	< 0.001
By sex							
Combined	14	1.32 (1.24-1.40)	1.30 (1.14-1.47)	NS	23.54	13	< 0.05
Males	25	1.04 (1.00-1.09)	1.07 (1.01-1.15)	< 0.05	32.90	24	NS
Females	36	1.09 (1.06-1.12)	1.20 (1.12-1.29)	< 0.001	81.04	35	< 0.001
			Between sexes		38.98	2	< 0.001
By continent							
North America	25	1.05 (1.02-1.08)	1.07 (1.02-1.12)	< 0.05	45.67	24	< 0.01
Europe	23	1.31 (1.18-1.46)	1.31 (1.18-1.46)	NS	20.63	22	NS
Asia	14	1.29 (1.17-1.42)	1.32 (1.16-1.49)	< 0.05	18.94	13	NS
Other	13	1.26 (1.19-1.33)	1.24 (1.07-1.44)	NS	37.12	12	< 0.001
			Between continents		54.09	3	< 0.001
By publication period							
1984-1991	16	1.28 (1.17-1.39)	1.35 (1.18-1.54)	< 0.05	21.29	15	NS
1992-1998	18	1.04 (1.00-1.07)	1.06 (1.00-1.12)	< 0.1	24.86	17	< 0.1
1999-2005	13	1.08 (1.03-1.13)	1.13 (1.02-1.24)	< 0.1	28.86	12	< 0.01
2006-2009	13	1.24 (1.17-1.31)	1.19 (1.06-1.34)	NS	32.96	12	< 0.001
2010-2016	15	1.26 (1.11-1.41)	1.31 (1.11-1.55)	< 0.05	21.07	14	< 0.1
			Between periods		47.42	4	< 0.001
By number of heart disease cases[8]							
1-99	13	1.62 (1.32-1.99)	1.66 (1.30-2.11)	NS	14.83	12	NS
100-199	14	1.33 (1.11-1.58)	1.33 (1.11-1.58)	NS	5.78	13	NS
200-999	30	1.26 (1.17-1.35)	1.27 (1.16-1.39)	NS	44.09	29	< 0.05
1000+	18	1.08 (1.05-1.10)	1.08 (1.02-1.15)	NS	76.70	17	< 0.001
			Between numbers		35.06	3	< 0.001
By study design							
Case-control	32	1.29 (1.21-1.36)	1.28 (1.15-1.42)	NS	52.18	31	< 0.05
Prospective	33	1.04 (1.01-1.07)	1.09 (1.03-1.14)	< 0.001	55.43	32	< 0.01
Cross-sectional	10	1.20 (1.14-1.28)	1.24 (1.12-1.37)	NS	16.78	9	< 0.1
			Between types		52.06	2	< 0.001
By number of confounders considered in the study							
0-2	15	1.03 (0.99-1.07)	1.05 (0.92-1.12)	< 0.1	17.51	14	NS
3-4	10	1.27 (1.16-1.39)	1.32 (1.13-1.55)	NS	16.65	9	< 0.1
5-9	38	1.13 (1.09-1.18)	1.19 (1.09-1.30)	< 0.05	94.55	37	< 0.001
10+	12	1.16 (1.10-1.22)	1.21 (1.10-1.32)	< 0.05	21.01	11	< 0.05
			Between groups		26.72	3	< 0.01
By results available in the study on dose-response							
No	24	1.15 (1.08-1.22)	1.19 (1.08-1.32)	< 0.05	44.81	23	< 0.01
Yes	51	1.10 (1.07-1.12)	1.18 (1.11-1.25)	< 0.01	129.74	50	< 0.001
			Between groups		1.90	1	NS
By spouse the index							
Yes	34	1.03 (1.00-1.06)	1.06 (1.01-1.12)	< 0.001	47.62	33	< 0.05
No	41	1.23 (1.19-1.28)	1.24 (1.16-1.32)	NS	72.59	40	< 0.01
			Between groups		56.24	1	< 0.001
Spouse the index, by whether unmarried subjects were excluded							
Yes	23	1.02 (0.99-1.05)	1.03 (0.99-1.07)	< 0.05	27.88	22	NS
No	11	1.30 (1.10-1.54)	1.35 (1.11-1.63)	< 0.01	12.00	10	NS
			Between groups		7.74	1	< 0.01
By heart disease fatality considered							
Fatal	31	1.04 (1.01-1.07)	1.07 (1.02-1.12)	< 0.001	46.74	30	< 0.05
Non-fatal	31	1.27 (1.22-1.33)	1.27 (1.19-1.36)	NS	39.58	30	NS
Both	13	1.25 (1.10-1.43)	1.34 (1.06-1.68)	NS	28.43	12	< 0.01
			Between groups		61.70	2	< 0.001
By heart disease definition							
IHD	32	1.06 (1.03-1.11)	1.12 (1.05-1.19)	< 0.001	56.92	31	< 0.01
MI	18	1.34 (1.25-1.43)	1.29 (1.14-1.46)	NS	23.10	17	NS
Other/Mixed	25	1.08 (1.05-1.12)	1.20 (1.10-1.30)	< 0.001	58.29	24	< 0.001
			Between definitions		38.14	2	< 0.001
By use of biomarker data to exclude smokers							
Yes	6	1.30 (1.08-1.57)	1.30 (1.08-1.57)	NS	3.89	5	NS
No	69	1.10 (1.08-1.13)	1.18 (1.12-1.24)	< 0.001	169.45	68	< 0.001
			Between groups		3.12	1	< 0.1
By any use of proxy respondents							
Yes	11	1.10 (0.99-1.23)	1.23 (0.98-1.53)	NS	26.38	10	< 0.01
No	64	1.10 (1.08-1.13)	1.18 (1.12-1.24)	< 0.001	150.07	63	< 0.001
			Between groups		0.00	1	NS

By type of control							
Healthy	15	1.30 (1.13-1.50)	1.38 (1.12-1.70)	< 0.1	27.67	14	< 0.05
Diseased/hospital	15	1.12 (1.01-1.24)	1.14 (1.01-1.28)	< 0.1	14.72	14	NS
Both	2	1.37 (1.27-1.48)	1.37 (1.27-1.48)	NC	0.29	1	NS
Prospective/cross-sectional	43	1.07 (1.05-1.10)	1.13 (1.08-1.19)	< 0.001	91.01	42	< 0.001
			Between types		42.78	3	< 0.001
			Between types, excluding prospective/cross-sectional		9.51	2	< 0.01
By source of diagnosis							
Death certificate only	27	1.04 (1.01-1.07)	1.06 (1.02-1.11)	< 0.01	41.57	26	< 0.05
Medical data used	41	1.35 (1.28-1.43)	1.34 (1.23-1.46)	NS	51.49	40	NS
Self-report only	7	1.17 (1.10-1.24)	1.17 (1.07-1.27)	NS	8.11	6	NS
			Between sources		75.29	2	< 0.001
By definition of never smoker							
Never any product	11	1.10 (1.05-1.15)	1.15 (1.05-1.27)	NS	32.42	10	< 0.001
Never, product unstated	33	1.05 (1.02-1.09)	1.15 (1.07-1.24)	< 0.001	49.99	32	< 0.05
Never cigarettes	12	1.17 (1.06-1.30)	1.21 (1.05-1.38)	NS	16.54	11	NS
Other	19	1.20 (1.14-1.25)	1.21 (1.07-1.37)	NS	57.89	18	< 0.001
			Between definitions		19.62	3	< 0.001
Sensitivity analyses							
Preferring unadjusted to adjusted estimates	75	1.06 (1.04-1.08)	1.16 (1.09-1.24)	< 0.01	321.31	74	< 0.001
Preferring current to ever exposure	75	1.12 (1.09-1.14)	1.19 (1.13-1.26)	< 0.001	176.96	74	< 0.001
Excluding studies 15 and 16	71	1.16 (1.12-1.19)	1.21 (1.15-1.28)	< 0.01	144.97	70	< 0.001
Excluding study 30	73	1.12 (1.10-1.15)	1.20 (1.14-1.26)	< 0.001	158.21	72	< 0.001
Excluding studies 15, 16 and 30	69	1.20 (1.17-1.24)	1.23 (1.17-1.29)	< 0.05	109.86	68	< 0.001

[1]Nearest equivalent to IHD as shown in Tables 1 and 3; [2]Heterogeneity relates to variation between studies within subgroup, except for results given in italics which relate to heterogeneity between subgroups; [3]N: Number of estimates in meta-analysis; [4]Egger test *P* expressed as < 0.001, < 0.01, < 0.05, < 0.1 or NS ($P \geqslant 0.1$). NC indicates not calculable as too few data points; [5]DF: Degrees of freedom; [6]Expressed as < 0.001, < 0.01, < 0.05, < 0.1 or NS ($P \geqslant 0.1$); [7]Relative risks are adjusted for covariates if adjusted data are available, with estimates for ever exposure preferred to those for current exposure where there is choice; [8]Number of cases was estimated for Nishtar[57] (as category 1-99) and for Rostron[80] (as category 100-199). MI: Myocardial infarction.

with a large weight, they do add to the difficulties in interpreting the overall estimate.

Below, we comment on various aspects of the findings and discuss potential sources of bias.

Study size and publication bias

For the main exposure index, there was clear publication bias ($P < 0.001$), RRs from smaller studies (more likely not to be published if finding no association) being much greater than from larger studies. Thus, for studies of > 1000 cases of heart disease, the RR was 1.08 (95%CI: 1.02-1.15, $n = 18$) while for studies of < 100 cases it was 1.66 (1.30-2.11, $n = 13$). This variation by study size explains why the random-effects estimate (1.18, 1.12-1.24) was higher than the fixed-effect estimate (1.10, 1.08-1.13), as small studies contribute relatively more to random-effects analyses. The random-effects estimate may be an overestimate, due to publication bias.

Definition of never smoker

Some studies clarified that never smoking related to never smoking any product, and others that never smoking related only to cigarettes. However, many studies merely stated the subjects were never smokers. The distinction is more important in countries where smoking of other products is more common. Some studies also made it clear that the definition allowed inclusion of those with a limited history of smoking, and a few rejected individuals with cotinine levels typical of current smokers. However, the estimated RR for the main index varied little depending on the definition.

Misclassification of never smoking status

No study attempted to determine whether self-reported never smokers had in fact smoked previously. However, as noted above and in Table 2, a few studies excluded those with cotinine levels indicative of current smoking In our recent review of ETS and lung cancer[96], we presented analyses demonstrating that correction for misclassification bias substantially reduced the estimated RR for husband's smoking. We did not attempted such correction here, partly because the extent of bias depends on the magnitude of the active smoking RR, which is much lower for heart disease than for lung cancer. However, we are aware of a study[97] which reported particularly high heart disease mortality among smokers who deny smoking, which, if confirmed, suggests misclassification bias might be of some relevance.

Errors in determining ETS exposure

While random errors in determining ETS exposure will tend to underestimate any association with heart disease, errors may not be random. Thus, studies of case-control or cross-sectional design, are subject to recall bias if subjects with heart disease tend to overestimate their exposure relative to those without heart disease. Only two studies[45,56] used biomarker data to try to avoid recall bias. Some support for the existence of recall bias arises from the RRs for the main index being higher for case-control and cross-sectional studies than for prospective studies.

Table 5 Dose-response evidence for heart disease among never smokers in relation to smoking by the spouse or household members in adulthood

Study No.	Ref.[1]	Sex	Exposure grouping	Relative risks by grouping[2]	Significance (trend)[3]
Smoking by the spouse					
1	Hirayama[29]	F	0, 1-19, 20+ (cigs/d)	1.00, 1.10, 1.31[4]	+
5	Svendsen *et al*[33]	M	0, 1-19, 20+ (cigs/d)	1.00, 1.20, 1.75	
14	La Vecchia *et al*[42]	M + F	0, 1-14, 15+ (cigs/d)	1.00, 1.13, 1.30	
15	Layard[25]	M	0, 1-14, 15-34, 35+ (cigs/d)	1.00, 0.76, 1.07, 0.92	
		F	0, 1-14, 15-34, 35+ (cigs/d)	1.00, 0.85, 1.15, 1.06	
16	Le Vois *et al*[26] (CPS I)	M	0, 1-19, 20-39, 40+ (cigs/d)	1.00, 0.99, 0.98, 0.72	
		F	0, 1-19, 20-39, 40+ (cigs/d)	1.00, 1.04, 1.06, 0.95	
20	Steenland *et al*[46]	M	0, 1-19, 20, 21+ (cigs/d)	1.00, 1.33, 1.17, 1.09	
		F	0, 1-19, 20, 21-39, 40+ (cigs/d)	1.00, 1.15, 1.07, 0.99, 1.04	
		M	0, 1-12, 13-21, 22-29, 30+ (year)	1.00, 1.14, 1.13, 1.14, 1.25	
		F	0, 1-14, 15-25, 26-33, 34+ (year)	1.00, 0.84, 0.99, 1.20, 1.20	
		M	0, 1-5, 6-14, 15-27, 28+ (pack year)	1.00, 1.25, 1.33, 1.13, 1.00	
		F	0, 1-12, 13-25, 26-33, 34+ (pack year)	1.00, 0.83, 1.12, 1.09, 1.26	
21	Janghorbani *et al*[47]	F	0, 1-30, 31+ (year)	1.00, 1.74, 0.85	
		F	0, 1-19, 20+ (cigs/d)	1.00, 1.76, 1.11	
		F	0, 1-10, 11+ (pack year)	1.00, 1.95, 1.17	
23	Ciruzzi *et al*[49]	F	0, 1-20, 21+ (cigs/d)	1.00, 0.82, 3.00	
26	He *et al*[52]	F	0, 1-10, 11-20, 21+ (cigs/d)	1.00, 0.93, 1.40, 3.20	+
			0-5, 6-15, 16-30, 31+ (year)	1.00, 0.80, 2.10, 2.30	+
			0, 1-399, 400-799, 800+ (cigs/day × year)	1.00, 1.20, 1.90, 3.60	+
28	Rosenlund *et al*[54]	M + F	0, 1-19, 20+ (cigs/d)	1.00, 1.02, 1.58	
		M + F	0, 1-32, 33+ (year)	1.00, 1.11, 1.25	
		M + F	0, 1-20, 21+ (pack-year)	1.00, 1.09, 1.33	
30	Enstrom *et al*[27]	M	0, 1-9, 10-19, 20, 21-39, 40+ (cigs/d)	1.00, 0.98, 0.82, 0.89, 1.13, 1.24	
		F	0, 1-9, 10-19, 20, 21-39, 40+ (cigs/d)	1.00, 1.03, 0.99, 1.02, 0.88, 0.80	
39	Wen *et al*[64]	F	0, < 8.8, 8.8-17.9, 18.0+ (pack-year)	1.00, 1.10, 1.12, 1.22[5]	
47	Gallo *et al*[71]	M + F	0, 0.5, 1.0, 1.5+ (packs/d)	1.00, 1.87, 1.89, 2.46[6]	
Smoking by household members					
8	Hole *et al*[36]	F	0, 1-14, 15+ (cigs/d)	1.00, 2.09, 4.12	+
9	Jackson[37]	M	None, low, high (exposure)	1.00, 1.30, 0.90	
		F	None, low, high (exposure)	1.00, 2.10, 7.50	+
18	Muscat *et al*[44]	M	None, 1-20, 21-30, 31+ (year)	1.0, 1.7, 1.5, 1.1	
		F	None, 1-20, 21-30, 31+ (year)	1.0, 2.0, 0.9, 1.7	
22	Kawachi *et al*[48]	F	None, occasional, regular	1.00, 1.19, 2.11	+
		F	< 1, 1-9, 10-19, 20-29, 30+ (year)	1.00, 1.19, 1.54, 1.11, 1.50	
27	Iribarren *et al*[53]	M	0, 1-9, 10-39, 40+ (h/wk)	1.00, 1.12, 1.26, 1.20	+
		F	0, 1-9, 10-39, 40+ (h/wk)	1.00, 1.21, 1.31, 1.36	+
29	Pitsavos *et al*[55]	M + F	0, 1-4, 5-9, 10-19, 20-29, 30-39, 40+ (years living with a regular smoker)	1.00, 1.07, 1.16, 1.39, 1.75, 2.20, 3.09	+
34	McGhee *et al*[59]	M + F	0, 1, 2+ (smokers in the home)	1.00, 1.26, 1.68	+
40	Eisner *et al*[65]	M + F	Per 10 years exposure	1.10	
46	Ding *et al*[70]	F	0, < 1, 1+ (packs/d)	1.00, 1.14, 1.69	+
			0, < 5, 5+, (year)	1.00, 1.26, 1.52	+
			0, < 4, 4+, (h/d)	1.00, 1.28, 1.82	+
			0, < 5, 5+, (pack-year)	1.00, 1.44, 1.53	+
			0, < 20, 20+ (h-year)	1.00, 1.22, 1.61	+
47	Gallo *et al*[71]	M + F	0, < 1, 1-2, 3+ (h/d)	1.00, 1.39, 2.08, 1.94[6]	+
54	Iversen *et al*[78]	M	0, < 10, 10-19, 20-29, 30+ (year)	1.00, 0.70, 1.20, 0.70, 1.10	
		F	0, < 10, 10-19, 20-29, 30+ (year)	1.00, 1.00, 1.40, 1.30, 1.60	+

[1]First author of paper; [2]Relative risks are adjusted for covariates if adjusted data are available; [3]Significant ($P < 0.05$) positive (negative) trends are indicated by + (or -). Blank entries indicate non-significance. The trend test includes the unexposed group. Significant trends excluding the unexposed group are only evident for study 26 (all exposed indices); [4]The 1-19 cigs/d group includes ex-smokers. Estimates are adjusted for the age of the husband. Alternative estimates, adjusted for the age of the subject are also given by Hirayama[115]; [5]Results for CVD. Not available for CVD - Stroke; [6]Results for CVD. Not available for IHD. M: Male; F: Female; CVD: Cardiovascular disease; IHD: Ischaemic (coronary) heart disease.

Weaknesses in prospective studies

While prospective studies avoid recall bias, they may underestimate any true association if ETS exposure is determined only at baseline, and not updated. This was the case for the great majority of such studies. Thus, RRs for the index "spouse current smoker" may be underestimated by inclusion of some spouses who give up after baseline. However, the similarity of the RR estimates preferring current to ever spousal exposure and preferring ever to current spousal exposure sug-

Table 6 Relative risk of heart disease among never smokers in relation to four other indices of environmental tobacco smoke exposure

Study No.	Ref.[1]	Sex	Exposure index[2]	Relative risk (95%CI)[3]	Exposure description
3	Lee *et al*[31]	M	Workplace	0.66 (0.26-1.66)	
		F	Workplace	0.69 (0.26-1.87)	
		M	Total	0.39 (0.17-0.90)	Home, work, travel, leisure
		F	Total	0.52 (0.24-1.09)	Home, work, travel, leisure
5	Svendsen *et al*[33]	M	Workplace	1.40 (0.80-2.50)	
		M	Total	1.17 (0.62-1.19)	Spouse, work
9	Jackson *et al*[37]	M	Workplace	1.80 (0.94-3.46)	
		F	Workplace	1.55 (0.48-5.03)	
		M	Total	1.14 (0.76-1.70)	Home, work
		F	Total	1.56 (0.76-3.20)	Home, work
12	Dobson *et al*[40]	M	Workplace	0.95 (0.51-1.78)	
		F	Workplace	0.66 (0.17-2.62)	
		M	Total	1.09 (0.72-1.63)	Home, work
		F	Total	2.24 (1.28-3.91)	Home, work
18	Muscat *et al*[44]	M	Workplace	1.20 (0.60-2.20)	
		F	Workplace	1.00 (0.40-2.50)	
		M	Childhood	0.79 (0.39-1.63)	Mother, father, other relatives
		F	Childhood	0.72 (0.30-1.72)	Mother, father, other relatives
19	Tunstall-Pedoe *et al*[45]	M + F	Total	1.34 (1.07-1.67)	Exposure to tobacco smoke from someone else in the previous three days
		M + F	Biomarker	1.13 (0.93-1.38)	Serum cotinine
20	Steenland *et al*[46]	M	Workplace	1.03 (0.89-1.19)	
		F	Workplace	1.06 (0.84-1.34)	
22	Kawachi *et al*[48]	F	Workplace	1.68 (0.81-3.47)	
		F	Total	1.71 (1.03-2.84)	Home, work
24	McElduff *et al*[50]	M	Total	0.82 (0.55-1.22)	Daily at home, work
		F	Total	2.15 (1.18-3.92)	Daily at home, work
26	He *et al*[52]	F	Workplace	1.85 (0.86-4.00)[4]	
		F	Total	2.87 (1.36-6.05)	Spouse, work
27	Iribarren *et al*[53]	M	Total	1.07 (0.96-1.19)	Home, small spaces, large indoor areas
		F	Total	1.10 (1.01-1.20)	Home, small spaces, large indoor areas
28	Rosenlund *et al*[54]	M	Workplace	1.14 (0.78-1.67)	
		F	Workplace	0.94 (0.59-1.50)	
		M + F	Total	1.18 (0.87-1.60)	Spouse, work
29	Pitsavos *et al*[55]	M + F	Workplace	1.97 (1.16-3.34)	
		M	Total	1.33 (0.94-1.88)	Home, work
		F	Total	1.39 (0.87-2.23)	Home, work
31	Chen *et al*[56]	M + F	Workplace	1.70 (0.90-3.20)	
		M + F	Total	1.50 (1.03-2.20)	Other people's tobacco smoke in the previous three days
		M + F	Biomarker	0.86 (0.64-1.16)	Serum cotinine
32	Nishtar *et al*[57]	M + F	Total	2.87 (1.28-6.42)	Unspecified, but includes spouse and others
33	Whincup *et al*[58]	M	Biomarker	1.67 (1.03-2.72)	Serum cotinine
36	Hedblad *et al*[61]	M	Biomarker	2.22 (1.21-4.09)	Blood carboxyhaemoglobin
37	Stranges *et al*[62]	M	Workplace	0.97 (0.64-1.48)	
		F	Workplace	0.96 (0.60-1.55)	
		M	Childhood	1.04 (0.72-1.52)	Unspecified
		F	Childhood	0.93 (0.57-1.51)	Unspecified
		M	Total	1.11 (0.69-1.77)	Lifetime; home, work, public places; RR is compared to lower tertile of exposure
		F	Total	0.58 (0.33-1.03)	Lifetime; home, work, public places; RR is compared to lower tertile of exposure
38	Teo *et al*[63]	M + F	Total	1.37 (1.27-1.48)	Family, friends, co-workers
39	Wen *et al*[64]	F	Workplace	1.21 (0.74-2.01)[5]	
		F	Childhood	1.49 (1.01-2.22)[5]	In early life from family members
		F	Total	1.25 (0.69-2.25)[5]	Spouse, work, early life
43	He *et al*[67]	F	Total	1.69 (1.31-2.18)	Home, work
45	Vozoris *et al*[69]	M + F	Total	1.00 (0.80-1.20)	Exposed on most days in the previous month
47	Gallo *et al*[71] (EPIC)	M	Workplace	0.93 (0.46-1.90)[6]	
		F	Workplace	0.76 (0.47-1.24)[6]	
		M	Childhood	1.11 (0.72-1.69)[6]	Parents
		F	Childhood	1.18 (0.88-1.57)[6]	Parents
48	Hamer *et al*[72]	M	Biomarker	1.50 (0.85-2.64)	Salivary cotinine
49	Jefferis *et al*[73]	M + F	Biomarker	0.94 (0.59-1.51)	Serum cotinine
50	Peinemann *et al*[74]	M + F	Total	1.27 (0.84-1.92)	Home, work, other

51	Chen[75]	M + F	Total	1.16 (0.93-1.45)[7]	Home, work, other
52	He *et al*[76]	M	Total	2.24 (0.76-6.59)	Lifetime; home, work
		F	Total	2.10 (0.69-6.33)	Lifetime; home, work
54	Iversen *et al*[78]	M	Total	0.97 (0.61-1.55)	Time spent in smoke-filled rooms
		F	Total	0.70 (0.44-1.12)	Time spent in smoke-filled rooms
55	Kastorini *et al*[79]	M + F	Total	4.33 (1.52-12.38)	Partner, parents, children, roommates, colleagues; 30+ min/d
56	Rostron[80]	M + F	Biomarker	1.02 (0.70-1.47)	Serum cotinine
57	Batty *et al*[81]	M	Biomarker	0.49 (0.19-1.25)	Salivary cotinine
		F	Biomarker	1.26 (0.70-2.24)	Salivary cotinine
58	Shiue[82]	M + F	Total	1.47 (0.96-2.24)	Home, work, other

[1]First author of paper; [2]Biomarker RRs are all based on cotinine measurement except for study 36 which is based on COHb; [3]Relative risks are adjusted for covariates if adjusted data are available. Some of the RRs are repeats of those given in Table 3; [4]Estimate given by an earlier report of the same study[117]; [5]Results for CVD-Stroke. Results also available for CVD: workplace 0.92 (0.64-1.32), childhood 1.26 (0.94-1.69), total 1.45 (0.95-2.22); [6]Results for CVD-Stroke. Not available for IHD; [7]Result for IHD. Result for MI also available: 0.93 (0.66-1.31). M: Male; F: Female; CVD: Cardiovascular disease; IHD: Ischaemic (coronary) heart disease; MI: Myocardial infarction.

Table 7 Meta-analyses of heart disease[1] risk among never smokers in relation to four other indices of environmental tobacco smoke exposure

Index of exposure	n[2]	Fixed-effect Relative risk (95%CI)	Random-effects Relative risk (95%CI)	Publication bias P[3]	Heterogeneity χ^2	DF[4]	P[5] value
Workplace	22	1.08 (0.99-1.19)	1.08 (0.99-1.19)	NS	20.12	21	NS
Childhood	7	1.12 (0.95-1.31)	1.12 (0.95-1.31)	< 0.1	4.77	6	NS
Total	33	1.21 (1.16-1.26)	1.23 (1.12-1.35)	NS	90.21	*32*	$P < 0.001$
Biomarker	9	1.11 (0.98-1.26)	1.15 (0.94-1.40)	NS	15.40	8	$P < 0.1$

[1]Nearest equivalent to IHD as shown in Tables 1 and 6; [2]n: Number of estimates in meta-analysis; [3]Egger test P expressed as < 0.001, < 0.01, < 0.05, < 0.1 or NS ($P \geqslant 0.1$); [4]DF: Degrees of freedom; [5]Expressed as < 0.001, < 0.01, < 0.05, < 0.1 or NS ($P \geqslant 0.1$).

gests this is not a major issue.

Inappropriate controls in case-control studies

In some case-control studies using population controls, the control group may not have been fully representative of the population from which the cases derived, while some hospital studies merely ensured that the controls were not suffering from heart disease, and may have included patients with other diseases associated with ETS exposure.

Weaknesses of cross-sectional studies

Ten of the 58 studies considered were of cross-sectional design. Apart from the possibility of recall bias, this design does not exclude the theoretical possibility that disease onset might have occurred before ETS exposure.

Diagnosis and classification of heart disease

A major determinant of heterogeneity for the main index related to source of diagnosis, with RRs substantially lower for estimates based only on death certificates (1.06, 95%CI: 1.02-1.11), than when based on medical data (1.34, 1.23-1.46), the few estimates based on self-report giving intermediate results (1.17, 1.07-1.27). Note, however, that this classification correlates considerably with that for study type. Thus, all the estimates based on self-report are from cross-sectional studies, nearly all those based only on death certificates are from prospective studies, with case-control studies contributing largely to estimates based on medical data.

The actual disease for which results are available varies by study, with some studies presenting results for multiple definitions. Higher RRs were seen for the main index where the definition was based on MI (1.29, 95%CI: 1.14-1.46) rather than on IHD (1.12, 1.05-1.19) or other/mixed definitions (1.20, 1.10-1.30). However, again there is a correlation with study type, there being few prospective studies using a definition of MI.

Confounding by other risk factors

There are manifold risk factors for heart disease, a study published in 1986[98] mentioning over 300. As several studies[53,99-103] showed differences in many lifestyle factors between smoking and non-smoking households, a potential for confounding is certainly present. Though difficult to assess precisely, partly because of the numerous risk factors involved, and partly because studies rarely present results showing the effect of adjustment for individual factors, some insight can be gained by comparing RR estimates across studies according to the number of risk factors adjusted for. Though the number of risk factors may be correlated with other aspects of the study, the results did not suggest the association was due to confounding, RRs being somewhat higher where more confounders were accounted for.

Inclusion of studies rejected in other meta-analyses

Three meta-analyses published in the late 1990s[2-4] deliberately excluded results reported by Layard[25], based on the National Mortality Followback Survey (NMFS), and by LeVois and Layard[26], based on the American Cancer Society (ACS) Cancer Prevention Studies Ⅰ (CPS Ⅰ) and

Table 8 Other indices of environmental tobacco smoke exposure - dose response results among never smokers

Study No.	Author[1]	Sex	Exposure grouping	Relative risk by grouping (95%CI)[2]	Significance[3]
Workplace exposure					
22	Kawachi *et al*[48]	F	No, occasional, regular	1.00, 1.49, 1.92	
26	He *et al*[52]	F	0-5, 6-10, 11-20, 21+ cigs/d	1.00, 0.87, 2.95, 3.56	+
		F	0-5, 6-15, 16+ year	1.00, 3.08, 1.56	
		F	0, 1-2, 3, 4+ smokers	1.00, 1.16, 5.06, 4.11	+
		F	0, 1-2, 3-4, 5+ h/d	1.00, 0.62, 4.03, 21.32	+
		F	0, 1-2000, 2001-4000, 4000+, cigs/d × year × smokers × h	1.00, 1.00, 2.05, 9.23	+
28	Rosenlund *et al*[54]	M + F	0, 1-31, 32+ yr	1.00, 1.04, 1.30	
		M + F	0, 1-68, 69+ h-year (= h/d × year)	1.00, 0.99, 1.48	
39	Wen *et al*[64]	F	0, < 10, 10-24, > 24 yr	1.00, 0.86, 0.96, 0.93[4]	
40	Eisner *et al*[65]	M + F	Per 10 yr exposure	1.04	
Childhood exposure					
18	Muscat *et al*[44]		Exposure to mother, father, other relatives		
		M	None, 1-17, > 17 yr	1.0, 0.9, 0.7	
		F	None, 1-17, > 17 yr	1.0, 0.6, 0.8	
39	Wen *et al*[64]	F	In early life from family members[5]		
			0, < 20, 20+, year	1.00, 1.21, 1.36[4]	+
Total exposure					
3	Lee *et al*[31]		Home, work, travel, leisure combined index		
		M	Score: 0-1, 2-4, 5-12	1.00, 0.43, 0.43	
		F	Score: 0-1, 2-4, 5-12	1.00, 0.59, 0.81	
5	Svendsen *et al*[33]		Spousal and/or workplace exposure		
		M	Neither, spouse, work, both	1.0, 1.2, 1.0, 1.7	
9	Jackson[37]		Exposure at home and/or work[6]		
		M	No, yes	1.00, 1.14 (0.76-1.70)	
		F	No, yes	1.00, 1.56 (0.76-3.20)	
12	Dobson *et al*[40]		Exposure at home and/or work		
		M	No, yes	1.00, 1.09 (0.72-1.63)	
		F	No, yes	1.00, 2.24 (1.28-3.91)	+
19	Tunstall-Pedoe *et al*[45]		Exposure to tobacco smoke from someone else in the previous three days		
		M + F	None, little, some, a lot, (self-classified)	1.00, 1.2, 1.5, 1.6	+
22	Kawachi *et al*[48]		Exposure at home and/or work		
		F	None, occasional, regular	1.00, 1.58, 1.91	+
26	He *et al*[117]		ETS exposure from spouse and/or work		
		F	Neither, spouse, work, both	1.00, 2.07, 2.53, 4.18	+
27	Iribarren *et al*[53]		Exposure at home, in small spaces, in large indoor areas		
		M	0, 1-9, 10-39, 40+ total h/wk	1.00, 0.90, 1.08, 1.13	+
		F	0, 1-9, 10-39, 40+ total h/wk	1.00, 0.86, 1.07, 1.17	+
28	Rosenlund *et al*[54]		Exposure from spouse and/or work		
		M + F	0, > 16, 7-16, 1-6, < 1, year ago	1.00, 0.92, 1.11, 1.30, 1.39	
		M + F	0, 1-12, 13-23, 24-34, 35+, year	1.00, 0.72, 0.97, 1.54, 1.48	+
		M + F	0, 1-17, 18-41, 42-89, 90+, h-year, (= year × h/d)	1.00, 0.70, 1.22, 1.27, 1.55	+
29	Pitsavos *et al*[55]		Exposure at home and/or work		
		M	None, occasional, regular	1.00, 1.25, 1.47	+
		F	None, occasional, regular	1.00, 1.29, 1.56	+
31	Chen *et al*[56]		Exposure to tobacco smoke from someone else in the previous three days		
		M + F	None, a little, some, a lot	1.00, 1.30, 1.50, 1.80	+
			Exposure to other people's tobacco smoke		
		M + F	0, > 0-2, 3-5, ⩾ 6 h/d	1.00, 1.20, 1.60, 1.70	
37	Stranges *et al*[62]		Cumulative lifetime ETS exposure at home, work and in public settings		
		M	Tertile: 1, 2, 3	1.00, 0.93, 1.40	
		F	Tertile: 1, 2, 3	1.00, 0.50, 0.67	
38	Teo *et al*[63]		Exposure from family, friends, co-workers		
		M + F	< 1, 1-7, 8-14, 15-21, 22+ h/wk	1.00, 1.32, 1.52, 1.73, 1.49	+
43	He *et al*[67]		Exposed at home and/or work		
		F	0, 1-9, 10-19, 20+, cigs/d	1.00, 1.41, 1.85, 1.77	+
			0, 1-20, 21-40, 41+, min/d	1.00, 1.46, 1.78, 1.86	+
52	He *et al*[76]		Exposed at home and/or work[7]		
		M + F	None Low Moderate High	1.00, 1.74, 2.25, 3.79	+
54	Iversen *et al*[78]		Time spent in a smoke-filled rooms		
		M	0, 1-6, > 6, h/d	1.00, 1.00, 0.80	
		F	0, 1-6, > 6, h/d	1.00, 0.70, 0.70	
58	Shiue[82]		Exposed at home, work, other people's home		
		M + F	0, 1, 2+ of these places	1.00, 1.37, 2.64	+

Biomarker					
19	Tunstall-Pedoe *et al*[45]		Serum cotinine (ng/mL)		
		M + F	0, > 0-1.05, 1.06-3.97, 3.98-17.49	1.00, 1.00, 1.30, 1.20	
31	Chen *et al*[56]		Serum cotinine (ng/mL)		
		M + F	0, > 0-1.05, 1.06-3.97, 3.98-17.49	1.00, 0.70, 1.00, 1.10	
33	Whincup *et al*[58]		Serum cotinine (ng/mL)		
		M	≤ 0.7, 0.8-1.4, 1.5-2.7, 2.8-14.0	1.00, 1.54, 1.89, 1.67	+
36	Hedblad *et al*[61]		Blood carboxyhaemoglobin (%)		
		M	0.13-0.49, 0.50-0.57, 0.58-0.66, 0.67-5.47 (quartiles)	1.00, 1.26, 1.77, 3.71	+
48	Hamer *et al*[72]		Salivary cotinine (ng/mL)		
		M + F	≤ 0.05, 0.06-0.70, 0.71-14.99	1.00, 1.33, 2.00	+
			Per unit increase in log cotinine	1.60 (1.11-2.31)	
49	Jefferis *et al*[73]		Serum cotinine (ng/mL)		
		M + F	≤ 0.05, 0.06-0.19, 0.20-0.70, 0.71-15	1.00, 0.91, 0.99, 0.94	
			Per doubling of cotinine	1.00 (0.86-1.16)	
56	Rostron[80]		Serum cotinine (ng/mL)		
		M + F	< 0.1, 0.1- < 1, 1- < 15	1.00, 0.97, 1.41	
57	Batty *et al*[81]		Salivary cotinine (ng/mL)		
		M	≤ 0.3, 0.4-1.2, 1.3-15.0	1.00, 0.41, 0.62	
		F	≤ 0.3, 0.4-1.2, 1.3-15.0	1.00, 0.99, 1.70	

[1]First author; [2]Relative risks presented are adjusted for covariates if adjusted data are available. When two groups only are being compared (or results for log cotinine are given), the relative risk and 95%CI limits for the exposed group (per unit increase) are shown; when more than two exposure groups are being compared, only the set of relative risks is shown; [3]Significant ($P < 0.05$) positive (or negative) differences or trends are indicated by + (or -). ? indicates not known whether significant or not. Blank entries indicate non-significance. The trend test includes the unexposed group; [4]Results for CVD. Not available for CVD - Stroke; [5]For study 39 the results for any childhood exposure (yes/no) shown in Table 4 relate to CVD minus stroke but the results by years exposed shown here relate to CVD as a whole; [6]The data shown here for study 9 come from the publication describing study 24; [7]The index of exposure was a combination of exposure at home (four categories of pack-years) and exposure at work (four categories of pack-years × h/d). M: Male; F: Female; CVD: Cardiovascular disease.

Ⅱ (CPS Ⅱ). The results from these studies showed no evidence of a relationship of spousal smoking to heart disease mortality. Though we have not used the cited CPS Ⅱ results, more detailed results being reported later by the ACS[46], we included the results from NMFS[25] and CPS Ⅰ[26]. Apart from wishing to consider all the evidence, and particularly not omit data from the very large CPS Ⅰ, we found the reasons for excluding these studies to be unconvincing.

One reason given[2] was that their results were inconsistent with other data, and reported by tobacco industry consultants. As regards inconsistency, it seems better to include all data, and investigate reasons for inconsistency, than to reject results not fitting in with preconceptions. As regards tobacco industry support, the test is whether the analyses presented were sound. We note no attempt was made by any critic to check the results from the publicly available NMFS, or by the ACS to check results from their CPS Ⅰ. The ACS did conduct their own analyses of CPS Ⅱ[46] using somewhat different methodology, their findings failing to indicate errors in the results of LeVois and Layard[26].

Another reason[4] given was that results were only presented for ever spousal exposure, rather than current spousal exposure. Apart from not noting that results for current spousal exposure were readily available from the CPSI data presented[26], the results being included in our analysis, Thun *et al*[4] also did not mention that their own analyses included results from other studies (studies 1, 2 and 8) based on ever spousal exposure! In fact, as we show, the overall RRs as can be seen in our main analysis, are very similar whether preferring ever to current spousal exposure (1.18, 95%CI: 1.12-1.24), or preferring current to ever spousal exposure (1.19, 1.13-1.26).

We have also included results reported by Enstrom and Kabat[27] in our analysis (Study 30), despite publication of the paper in the BMJ being subject to a large number of critical responses. As the authors noted in a final rapid response in the BMJ, none of the responses identified "any impropriety, bias, or omission in the review process" with "only about 3%" referring to "actual data in the paper". "No one has identified a single error in the paper, not even Thun, who is in a position to check our findings". We agree with Enstrom and Kabat that "the unethical tactics used by the ACS and others, including *ad hominem* attacks and condemnation of legitimate research based solely on the source of funding, have no place in scientific discourse". The authors noted that "Our current research funding comes from Philip Morris USA and three other sources not connected with the tobacco industry". As shown in Table 4, exclusion from our meta-analysis of the three studies in question (studies 15, 16 and 30) slightly increased the RR estimate for our main index, from 1.18 (95%CI: 1.12-1.24) to 1.23 (95%CI: 1.17-1.29), but did not affect the conclusion that there was a clear association of ETS exposure with heart disease risk.

Evidence from studies of smoking bans

Since the first study in 2004[104], which reported a 40% reduction in hospital admissions from AMI following introducing a local law banning smoking in public places and workplaces, numerous further studies have investigated ban effects at national, regional and local level. In a recent review[105], based on 45 studies, we used a

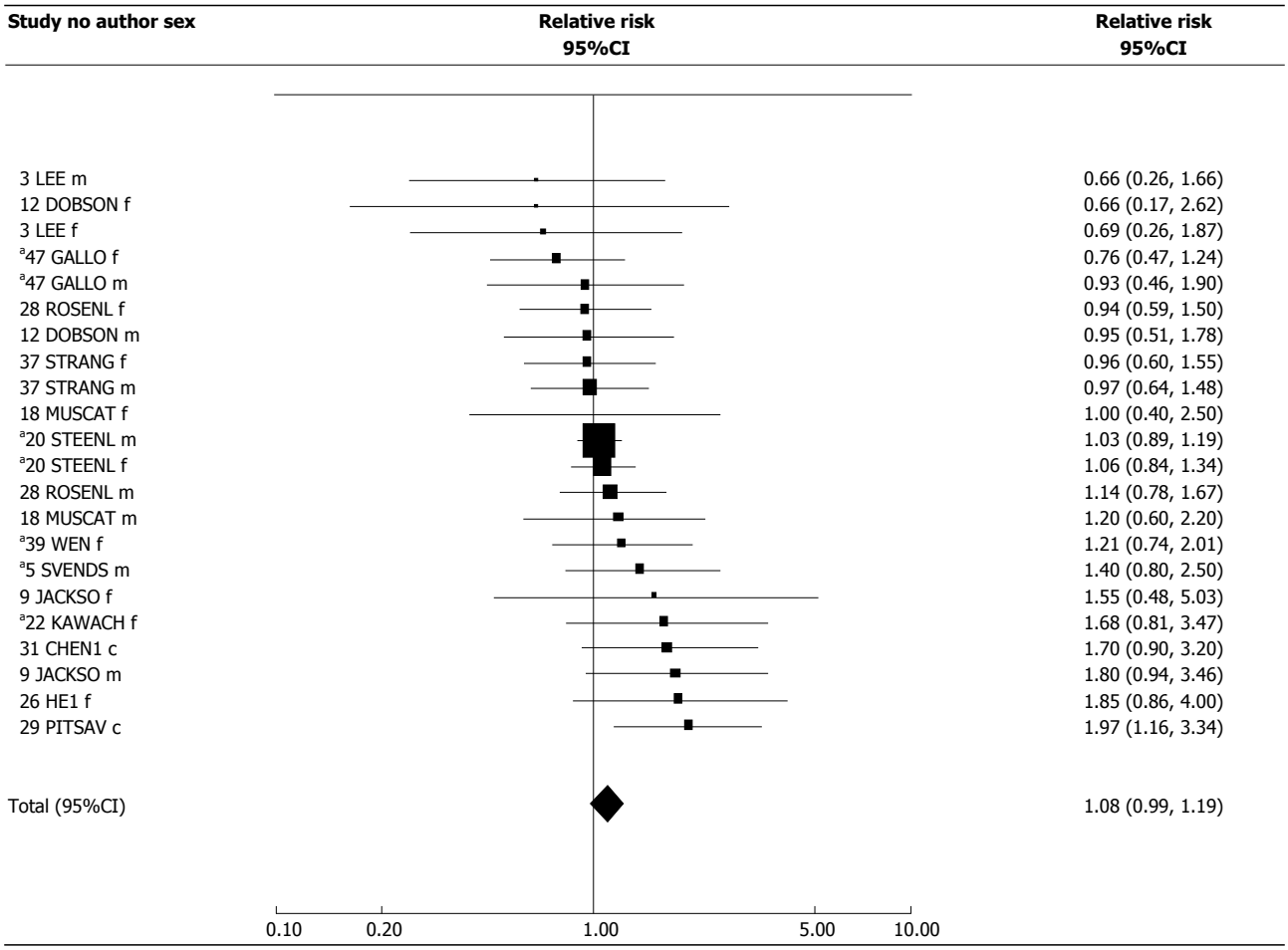


Figure 2 Forest plot for workplace exposure. Estimates of the RR and its 95%CI are shown sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Estimates are identified by the study number shown in Table 1, an abbreviation of the author name and the sex to which the estimate relates (m = male, f = female, c = combined sex estimate). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight (the inverse of the variance of log RR). The overall random-effects estimate (RRs and 95%CI) is shown, represented graphically by a diamond whose width indicates the confidence interval. [a]Prospective study.

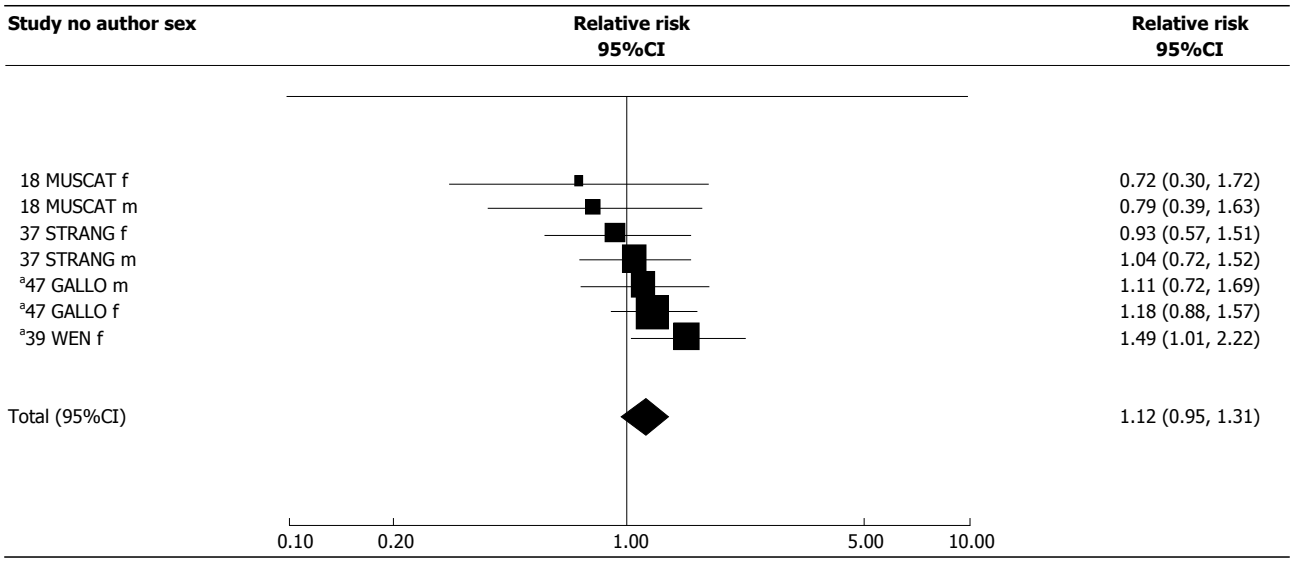


Figure 3 Forest plot for childhood exposure. Estimates of the RR and its 95%CI are shown sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Estimates are identified by the study number shown in Table 1, an abbreviation of the author name and the sex to which the estimate relates (m = male, f = female, c = combined sex estimate). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight (the inverse of the variance of log RR). The overall random-effects estimate (RRs and 95%CI) is shown, represented graphically by a diamond whose width indicates the confidence interval. [a]Prospective study.

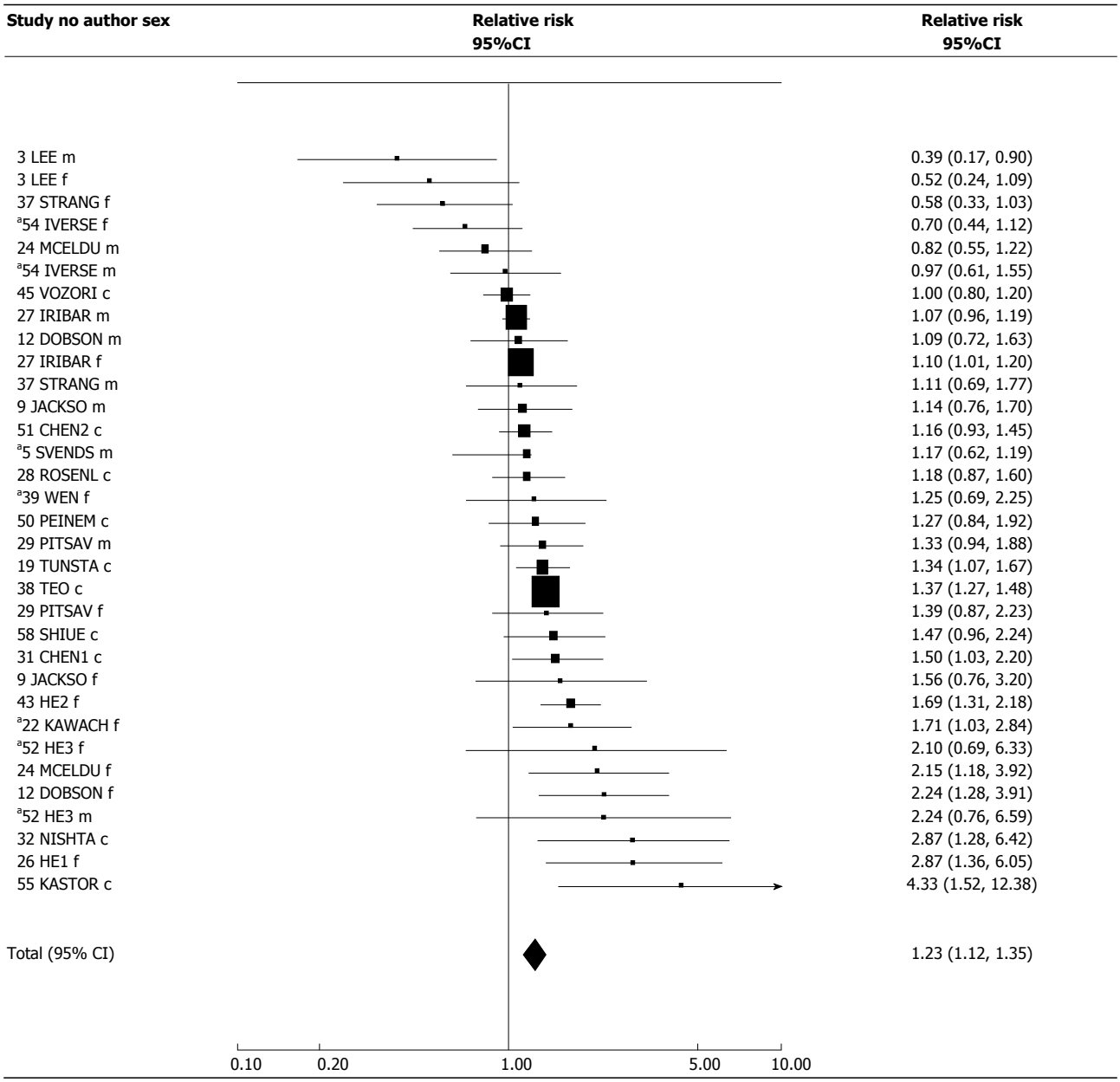


Figure 4 Forest plot for total environmental tobacco smoke exposure. Estimates of the RR and its 95%CI are shown sorted in increasing order of RR. These are shown numerically, and also graphically on a logarithmic scale. Estimates are identified by the study number shown in Table 1, an abbreviation of the author name and the sex to which the estimate relates (m = male, f = female, c = combined sex estimate). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight (the inverse of the variance of log RR). The overall random-effects estimate (RRs and 95%CI) is shown, represented graphically by a diamond whose width indicates the confidence interval. [a]Prospective study.

consistent approach to adjust for time trends and seasonal effects. We estimated the post-ban risk reduction as 4.2% (95%CI: 1.8%-6.5%) initially, which reduced to 2.6% (1.1%-4.0%) after excluding regional studies where national estimates were available, and also studies where adjustment for the underlying trend in the heart disease rate was not possible. Although these estimates are much less than those from some earlier reviews[106-108] which used less precise techniques, they do suggest a small true ban effect. However, the effect cannot be directly attributed to reductions in risk arising from reduced ETS exposure. Some of the estimated effect might be because smokers reduced their daily cigarette consumption due to the more limited number of places where they are allowed to smoke.

Experimental evidence

The Institute of Medicine (IOM) report[7] discussed "pathophysiologic experiments that have investigated the cardiovascular effects of mainstream and sidestream tobacco smoke in cells, in animals and in humans", noting that cigarette smoke could produce CVD by various "interrelated modes of action, including oxidative stress, hemodynamic and autonomic effects, endothelial dysfunction, thrombosis, inflammation, hyperlipidemia or other effects". While beyond the scope of this paper to

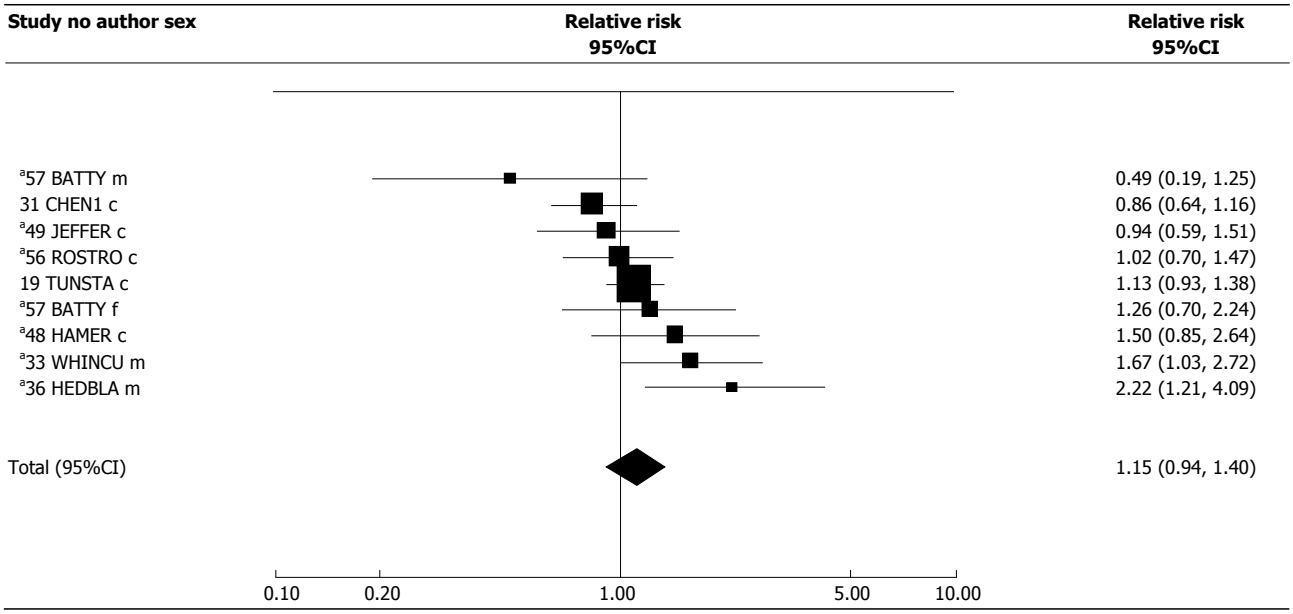


Figure 5 Forest plot for biomarker based indices of environmental tobacco smoke exposure. Estimates of the RR and its 95%CI are shown sorted in increasing order of RR. These are shown numerically and also graphically on a logarithmic scale. Estimates are identified by the study number shown in Table 1, an abbreviation of the author name and the sex to which the estimate relates (m = male, f = female, c = combined sex estimate). In the graphical representation, individual RRs are indicated by a solid square, with the area of the square proportional to the weight (the inverse of the variance of log RR). The overall random-effects estimate (RRs and 95%CI) is shown, represented graphically by a diamond whose width indicates the confidence interval. [a]Prospective study.

consider such evidence, we note that the report states most of the observed changes "have not been formally validated as clinical tests and there is not a consensus within the scientific community that they are predictive of actual clinical disease." While the IOM Committee considered that these effects can "contribute to the biological plausibility that decreasing second-hand smoke could lead to a decrease in acute myocardial infarction", they did not consider that the results, on their own, demonstrated a causal relationship of ETS exposure to heart disease.

Comment on a recent systematic review

In the introduction we referred to various other, conflicting, reviews of ETS and heart disease. Though it is beyond our scope to consider all these in detail, it is worth referring to a recently published systematic review[109] which concluded that ETS exposure "significantly increased the risk for …CVD". This review was limited to prospective and case-control studies, but included studies of stroke, which we have reviewed separately[110]. While the authors' combined RR estimate for cardiovascular disease of 1.23 (95%CI: 1.16-1.31) was similar to our main analysis estimate of 1.18 (1.12-1.24), we note they excluded a number of prospective and case-control studies we included. While some omissions were because they excluded abstracts and theses, and biomarker studies using COHb, we noted eight studies (13, 16, 21, 25, 32, 38, 46 and 55) where there seemed no good reason for the omission. Also, they did not separate results by source of ETS exposure or present any dose-response results.

Association of ETS with other diseases

In recent years, our group has carried out systematic reviews and meta-analyses of the relationship of ETS with various diseases in never smoking adults. These include lung cancer[111], breast cancer[112], other cancers[113], stroke[110] and COPD (submitted for publication). It is of interest to note that spousal smoking is associated with about 20% increased risk in never smokers, not only for heart disease, as we report here, but most studied diseases - stroke, COPD, lung cancer and breast cancer. Estimates are more limited for other cancers, many sites not showing any evidence of an effect, though significant increases were noted for cervix, nasosinus and kidney cancer. Whether evidence of an association for other diseases adds support to the argument that ETS exposure causes heart disease is unclear, as many of the problems of bias noted to affect the association with heart disease may also affect the association with other diseases.

Some, but not all, of the biases may be removed by limiting attention to prospective studies of ETS and total mortality. However, at this point in time, we have not carried out a review of the evidence, though we note that about half the prospective studies cited in Table 1 do give results for total mortality.

Overall assessment

Do the results show that ETS exposure increases risk of heart disease? Here one can usefully cite the classic paper by Hill[114] which specified nine criteria to be considered when attempting to conclude causation. We consider these in turn below.

Strength: The observed association is clearly weak, with our main analyses estimating only an 18% increase in risk associated with ETS exposure.

Consistency: While some studies report no increased risk and a number do not report a statistically significant increased risk, this may reflect the difficulty in demonstrating a weak association, particularly with limited data. Even though there is clear heterogeneity for our main index of exposure, the meta-analysis estimates by level of a range of factors are all increased, and nearly always significantly increased. Thus, for example, significant increases are seen in each sex, in four continents, in prospective, case-control and cross-sectional studies, and in smaller and larger studies. There is certainly an element of consistency.

Specificity: ETS exposure is certainly not a necessary or sufficient cause of heart disease. While it is much easier to demonstrate causation where an agent is such a cause, this criterion is not really relevant here.

Temporality: While theoretically possible in the cross-sectional studies that some cases of heart disease might have preceded exposure to ETS, this could not be so for most cases in the 58 studies we considered.

Biological gradient: Though not all the studies demonstrate a dose-response relationship, many do. However, the significant trends observed are generally calculated including the unexposed group, and evidence of a dose-response within ETS exposed subjects is less clear.

Plausibility: There is clearly plausibility, given smoking causes heart disease and given the experimental evidence referred to above. However, the dose of smoke constituents from ETS is very much less than that from smoking, and it is unclear whether the short-term effects of ETS observed experimentally are actually predictive of heart disease.

Coherence: A cause-and-effect interpretation of the data does not, as far as we are aware, seriously conflict with other generally known facts concerning the history and biology of heart disease.

Experiment: The epidemiological evidence considered lacks any useful material to determine how the risk of heart disease varies following cessation of ETS exposure. However, the evidence from studies of smoking bans suggests that the introduction of smoking bans in public places has caused a modest reduction in risk of heart disease though, as noted, such studies, generally do not separate out effects of reduced ETS exposure in never smokers and of reduced opportunities to smoke in smokers.

Analogy: Whether effects of smoking and of ETS can be regarded as analogous is doubtful, given the substantial differences in extent of exposure and the somewhat different distribution of chemicals for the two types of exposure.

Considering all these points, there seems some inconclusive support for ETS exposure causing heart disease. An important issue not specifically considered in the Bradford Hill criteria, much more relevant for weak than strong associations, is whether the association might be explained by confounding or bias. As regards confounding, the observation that many studies adjusted for numerous risk factors for heart disease, and that RR estimates if anything, increase as more factors are adjusted for, suggests that confounding could not explain the relationship. Nor does it seem likely that the relationship could be fully explained by publication bias or recall bias, though the smaller estimates for large studies and for prospective studies suggest that these biases might have led to some overestimation of the association. Nor is it probable that misclassification of smoking status, or the inclusion of some smokers of products other than cigarettes or occasional or ex-smokers could explain the observed association. While we feel there may well be a true effect of ETS on heart disease risk, it is clear that it is difficult to come to a definitive conclusion, and even more difficult to estimate any true effect precisely.

In conclusion, Taken together with the known relationship of heart disease with smoking, the significantly increased risk for various indices of ETS exposure which can be seen in many study subsets, the evidence of a dose-response relationship, and the lack of any source of bias or confounding that can clearly explain the relationship, the evidence suggests that ETS exposure may cause some increase in the risk of heart disease. That said, the weakness of the overall relationship, the evidence of heterogeneity, the limitations of some of the studies, and the various possibilities of bias, certainly mean that any true effect of ETS exposure is very difficult to quantify precisely.

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COMMENTS

Background

The authors consider evidence that environmental tobacco smoke (ETS)

exposure might cause heart disease by presenting an up-to-date meta-analysis of the available evidence.

Research frontiers

Based on 58 studies providing relevant data, the authors demonstrate an increase in heart disease risk in never smokers associated with ETS exposure by the spouse (or nearest equivalent), with an overall RR estimate of 1.18 (1.12-1.24). While increases were observed in all data subsets considered, there was evidence of heterogeneity, with risk estimates lower for North American studies, larger studies, prospective studies, and when based on fatal cases or death certificate data. Positive associations, not all significant at $P < 0.05$, were also seen with spousal exposure specifically (1.10, 1.04-1.17), workplace exposure (1.08, 0.99-1.19), childhood exposure (1.12, 0.95-1.31), total exposure (1.23, 1.12-1.35) and biomarker-based exposure (1.15, 0.94-1.40) and there was evidence of a dose-response relationship. Although the evidence has various limitations, it is suggestive of a causal relationship. However, the various possibilities of bias mean that any true effect of ETS exposure is very difficult to quantify precisely.

Innovations and breakthroughs

The new feature of the paper is the extent of the evidence considered, and the detail of the analyses conducted.

Applications

The authors analyses emphasise the difficulties in drawing inferences from weak associations seen in non-randomized epidemiological studies, where various biases may exist.

Peer-review

This is a meta-analysis of 58 studies that address the issue of environmental tobacco smoke and the development of heart disease. Overall, the authors found an association between exposure and heart disease risk.

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SYSTEMATIC REVIEWS

Statin use and risk of cancer: An overview of meta-analyses

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Abstract

AIM

To conduct an overview of meta-analyses to critically appraise the evidence and present a comprehensive evaluation of the association between statin use and risk of site specific cancers.

METHODS

MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews and Web of Science databases were searched from inception until 31st May 2016. The electronic database search was supplemented by a hand search in PROSPERO and relevant journals which are not indexed in above databases. Meta-analyses that examined the association between statin use and risk of site specific cancers were included. Two reviewers independently screened the literature, abstracted data, and assessed study quality using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.

RESULTS

Overall, 38 meta-analyses covered 13 site specific cancers were included. More than half (68%) of the meta-analyses were moderate in quality with an AMSTAR score 4-7 out of a possible 11. Based on current evidence from meta-analyses, use of statin decreases the risk of certain cancers, such as colorectal (8%-12%), gastric (27%-44%), hematological (19%), liver (37%-42%), oesophageal (14%-28%), ovarian (21%) and prostate cancer (7%). On the other side, evidence from meta-analyses also suggests that there is no association between statin use and risk of bladder, breast, endometrial, kidney, lung, pancreatic and skin cancers.

CONCLUSION

This overview of meta-analyses with variable quality has been shown that the statins may have a potential role in cancer chemoprevention and reduce the risk of some site specific cancers, but not all.

Key words: Statin; Cancer; Meta-analysis

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Core tip: Statins are one of the most commonly prescribed pharmaceutical agents worldwide and atorvastatin remained the largest source of spending in the class. In recent years, emerging experimental evidence suggests that statins may have a potential role in cancer chemoprevention. However, a large number of randomized controlled trials and observational studies published to examine the association between statin use and risk of site specific cancers were given conflicting results. This overview of meta-analyses with variable quality has been shown that the statins may have a potential role in cancer chemoprevention and reduce the risk of colorectal (8%-12%), gastric (27%-44%), hematological (19%), liver (37%-42%), oesophageal (14%-28%), ovarian (21%) and prostate cancer (7%).

Undela K, Shah CS, Mothe RK. Statin use and risk of cancer: An overview of meta-analyses. *World J Meta-Anal* 2017; 5(2): 41-53 Available from: URL: http://www.wjgnet.com/2308-3840/full/v5/i2/41.htm DOI: http://dx.doi.org/10.13105/wjma.v5.i2.41

INTRODUCTION

Statins (HMG-CoA reductase inhibitors) are a class of drugs that reduce serum cholesterol levels by inhibiting HMG-CoA reductase, a rate-limiting enzyme in the mevalonate synthesis pathway[1]. They are commonly used in the management and prevention of cardiovascular diseases. Statins are one of the most commonly prescribed pharmaceutical agents worldwide and atorvastatin remained the largest source of spending in the class[2]. With the effect of recommendations for primary prevention with statins by the recent American College of Cardiology/American Heart Association guidelines on the assessment of cardiovascular risk and on the treatment of blood cholesterol, more than a Billion people are expected take statins[3]. Cancers are among the foremost causes of morbidity and mortality worldwide. There were approximately 14 million new cancer cases and 8.2 million cancer related deaths in 2012. Over the next 2 decades, the number of new cancer cases are expected to rise by about 70%[4].

Apart from reduction in cholesterol level and cardiovascular mortality due to substantially increased use of statins during past three decades[5], there is a long-lasting debate on the potential association between statin use and the risk of cancer. In recent years, emerging experimental evidence suggests that statins may have a potential role in cancer chemoprevention[6-8]. It has been proven that statins activates several mechanisms to cancer cell death. Statins induce cell apoptosis by influencing the expression/activity of proteins involved in cell cycle such as cyclins, cyclin-dependent kinases (CDK), and/or inhibitors of CDK. Statins may inhibit cell cycle progression by both extrinsic and intrinsic pathways. By inhibiting isoprenoid synthesis, statins may lead to changes in molecular pathways dependent on the epidermal growth factor receptor. Also, statins may weakens the cell membrane by inhibiting cholesterol synthesis[9]. A large number of randomized controlled trials (RCTs) and observational studies published to examine the association between statin use and risk of site specific cancers were given conflicting results[10]. Many researchers conducted meta-analyses to provide more reliable findings on this association.

In spite of the fact that the meta-analysis show up at the highest level of the evidence in the evidence based practice, comparative data across different domains are often lacking. Overviews are a relatively new approach to generate evidence from several systematic reviews/meta-analyses and become popular in generating the evidence in health care[11].

Therefore, the objective of this overview is to summarize and critically appraise the evidence of relevant meta-analyses to evaluate the association between statin use and risk of site specific cancers.

MATERIALS AND METHODS

Protocol

A protocol for our overview of meta-analyses were drafted using the Cochrane Handbook for overviews of reviews[10]. The drafted protocol was circulated to subject experts and methodologists for feedback purpose. Based on the feedback, the protocol was revised and final version published in PROSPERO International prospective register of systematic reviews (Registration Number: CRD42014013160) (Supplementary Table).

Literature search

A comprehensive literature search was performed in MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews and Web of Science from inception to 31st May 2016 to identify the relevant studies. The search strategy included both medical subject headings (MeSH) and free text terms related to statin and cancer. "Hydroxymethylglutaryl-CoA Reductase Inhibitors and Neoplasms" were the MeSH terms used for statin and cancer, respectively. "Statin(s) or HMG-CoA reductase inhibitor(s) or lipid-lowering agent(s) or atorvastatin or pravastatin or fluvastatin or lovastatin or cerivastatin or mevastatin or rivastatin or rosuvastatin or simvastatin and cancer(s) or neoplasm(s) or malignancy(ies)" were the free text terms used for search strategy. Search strategies were limited to systematic reviews and meta-analyses focused on human participants. In addition, specific journals and cross references of relevant studies were searched manually to capture relevant systematic reviews/meta-analyses and also PROSPERO database was searched to identify completed, unpublished systematic reviews/meta-analyses[12].

Screening

Two authors (KU and CSS) were independently involved

in title/abstract based and full text based screening to capture all relevant articles using a predefined inclusion and exclusion criteria. Disagreements were resolved by discussion and a third author (RKM) was approached whenever required.

Eligibility criteria

We included meta-analyses (didn't find any systematic reviews without meta-analysis) that focused on risk of getting site specific cancers among statin users. Meta-analyses conducted by using RCTs and/or observational studies and published at any point in time were included. Meta-analyses focused on total cancer (*i.e.*, the aggregate of all malignancies) were excluded as all original studies included in these meta-analyses were also included in meta-analyses on site specific cancers with some additional studies. Meta-analyses conducted to identify the effect of statin use on management or prognosis of cancer and also at risk of recurrence of cancer were excluded.

Data abstraction

To abstract the relevant data from each included study, specific data abstraction form was drafted, pilot-tested by all authors independently on a random sample of five articles and same were revised after this exercise, as necessary. After finalizing the data abstraction form, two authors (KU and CSS) have analysed all articles independently to capture relevant data. Discrepancies were resolved by discussion and third author (RKM) was approached whenever required. The following information was captured from each study: (1) first author's last name, year of publication, and country where the study conducted; (2) search methods followed, number of studies identified, type of study designs included, and criteria for study selection and data extraction; (3) methods followed to check the quality of individual studies and to identify the heterogeneity and publication bias; (4) number of subjects and cancer cases involved, outcomes of quality, heterogeneity and publication bias tests, and pooled RR estimates with 95%CIs for primary outcome, secondary outcome and subgroup analyses; and (5) conclusions and if any limitations of the study.

Quality appraisal

Risk of bias assessment of included studies was performed by using the Assessment of Multiple Systematic Reviews (AMSTAR) tool[13]. AMSTAR is highly reliable and validated tool assesses the degree to which review methods avoided bias by evaluating the methods against 11 distinct criteria[14]. Quality rating was as follows: A score of 8-11 is high quality; 4-7 is moderate quality and 3 or lower is low quality. Each included meta-analysis was appraised for quality by two authors independently (KU and RKM) and conflicts were resolved by discussion or the involvement of a third author (CSS).

Data synthesis

The present work was performed as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Checklist S1).

RESULTS

Search results

The literature search resulted in 830 titles and abstracts, of which 766 were excluded for not fulfilling the eligibility criteria. Of the 59 full-text articles retrieved and screened in duplicate, 27 were excluded for reasons depicted in Figure 1. Resulted 32 full-text meta-analyses[15-46] in addition to five relevant conference abstracts[47-51] and one relevant full-text published in World Journal of Meta-analysis[52] were included in this overview. We didn't find any completed, unpublished systematic reviews/meta-analyses on this topic in PROSPERO.

Study characteristics

A total of 38 included meta-analyses covered 13 site specific cancers as an outcome for statin use. Majorly seven meta-analyses published on colorectal cancer[18-20,47-50], followed by gastric (4)[21-24], liver (4)[29-31,52], esophageal (4)[35-37,51], skin (4)[43-46], lung (3)[32-34], prostate (3)[40-42], breast (2)[16,17], hematological (2)[26,27], pancreatic cancers (2)[38,39] and each on bladder[15], gynecological[25] and kidney cancers[28]. The characteristics of the included meta-analyses are presented in Table 1.

All included meta-analyses published between 2005 and 2014; majority [25 (66%)] were published in and after 2012. The first authors of the meta-analyses predominantly based in China (15 studies) followed by Greece (7), United States (7), Canada (2), India (2), United Kingdom (2), and each in Australia, Italy and Japan. Except two studies[42,49] where the information on databases searched not available, remaining 36 (95%) studies searched MEDLINE for relevant studies, followed by EMBASE [22 studies (58%)], Web of Science/Web of Knowledge/Science Citation Index [20 studies (53%)] and Cochrane Library [15 studies (39%)]. Out of 38 included studies, 22 (58%) were included both RCTs and observational studies, nine (24%) studies included only RCTs and five (13%) studies included only observational studies, and information not available for remaining two studies[42,51]. For the assessment of heterogeneity, 34 studies used both Cochrane Q test and I^2 test, and information not available for remaining four studies[28,47-49]. Majority [34 (89%)] of the studies assessed publication bias either by using Begg and Mazumdar adjusted rank correlation test and the Egger regression asymmetry test or funnel plot. Two studies[35,36] not assessed publication bias and information not available for remaining two studies[21,29].

Quality appraisal results

More than half [26 (68%)] of the meta-analyses were deemed moderate quality with an AMSTAR score 4-7 out of a possible 11. Only six (16%) studies were found to be high quality with score $\geqslant$ 8, among these one study was a Cochrane systematic review with the highest quality

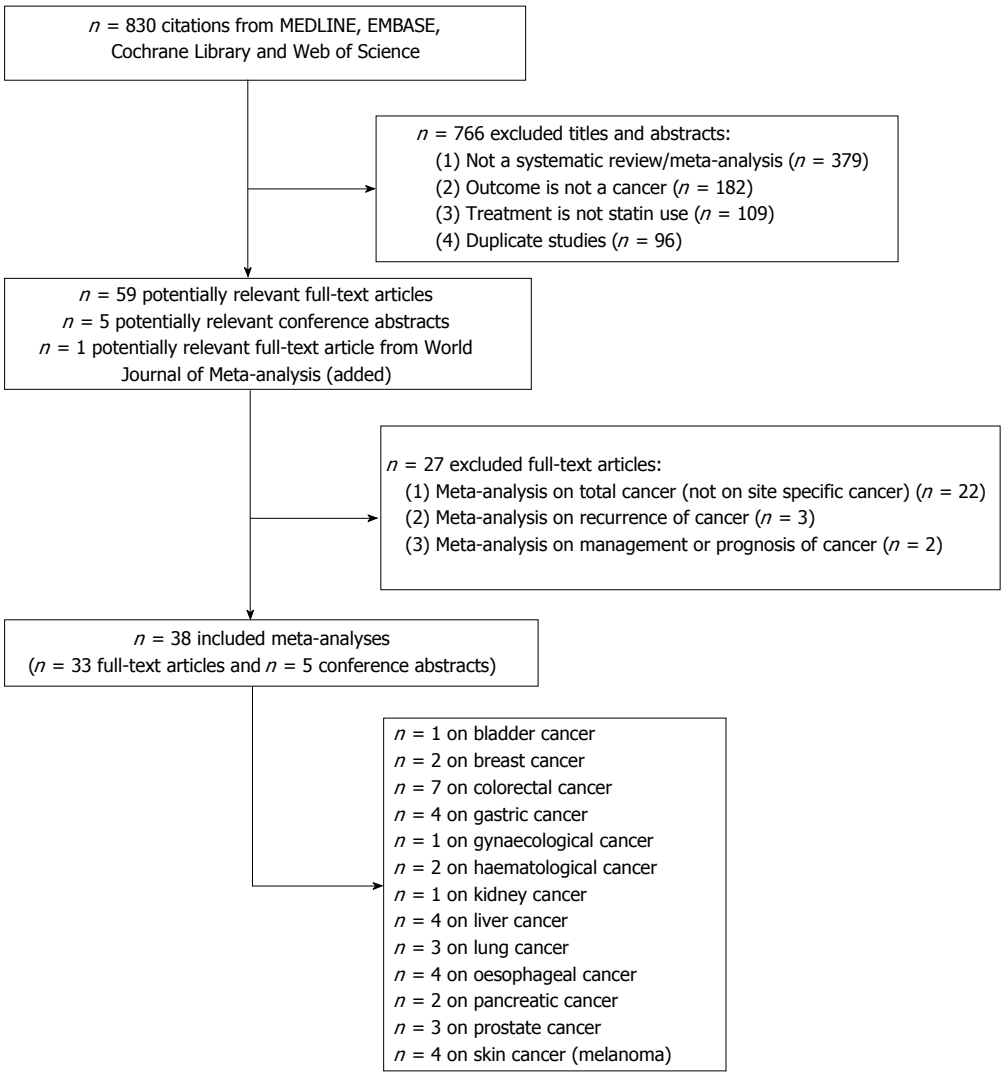


Figure 1 Study flow.

score 10[43]. One study[21] found to be low quality with the score 0 and five studies[47-51] were not having sufficient information to calculate AMSTAR quality score. Majority of meta-analyses were degraded due to lack of "a priori" design, not searched for gray literature, not provided a list of excluded studies from screening of potentially relevant full-text articles and not used any scale to assess the scientific quality of the included studies in formulating conclusions.

Outcome results

The pooled relative risk with 95%CI of the primary outcome of all included studies is shown in forest plot (Figure 2) and it is depicted with sub-group analysis based on cancer type.

Statin use and risk of bladder cancer: Only one meta-analysis[15] was conducted to identify the risk of bladder cancer among statin users. There was no association found between statin use and risk of bladder cancer and the result was same even after subgroup analysis of study design and for long-term statin use.

Statin use and risk of breast cancer: A meta-analysis published by Bonovas *et al*[16] in 2005 to estimate the association between use of statin and risk of breast cancer by including seven RCTs and nine observational studies. There was no association found between statin use and risk of breast cancer with no heterogeneity among studies. The association becomes same even after subgroup analysis of study design. In 2012, Undela *et al*[17] updated this meta-analysis by including 15 more observational studies published after previous meta-analysis. This study also gives an almost similar conclusion, though there was a heterogeneity identified among studies. Additionally, this updated meta-analysis found 47% reduced risk of recurrence of breast cancer among statin users, but no association between long-term statin use and risk of breast cancer.

Statin use and risk of colorectal cancer: Seven meta-analyses (3 full-text[18-20] and 4 conference abstracts[47-50]) published on this association between 2007 and 2014. Almost all the studies included both RCTs and observational studies published between 1995

Table 1 Characteristics of the included meta-analyses

First author, Year[a] (Country)[b]	Databases searched (Period)[c]	Studies included (*n*)	Studies published between (Years)	Total subjects involved	Total cancer cases	Heterogeneity presents?	Pooled RR (95%CI) for primary outcome (*n*)[d]	Pooled RR (95%CI) for secondary outcome (*n*)	Pooled RR (95%CI) for Sub-group analysis[e]	AMSTAR score
Bladder cancer										
Zhang X, 2013 (China)[15]	MEDLINE, EMBASE and Ovid (January 1966 to October 2012)	RCTs (3), Cohort (5) and CC (5)	2001-2012	1266268	2511	Yes (q = 0.001, I^2 = 62.6%)	1.07 (0.95-1.21) (↔)	LSU = 1.21 (0.92-1.51) (8) (↔)	RCTs = 0.83 (0.63-1.10) (↔); Cohort = 1.11 (0.91-1.35) (↔); CC = 1.12 (0.98-1.28) (↔)	7
Breast cancer										
Bonovas S, 2005 (Greece)[16]	MEDLINE (1966 to March2005) and SCI (1970 to March2005)	RCTs (7), Cohort (4) and CC (5)	1993-2005	327238	24599	No (q = 0.12, I^2 = 30%)	1.03 (0.93-1.14) (↔)	None	RCTs = 1.04 (0.81-1.33) (↔) ; Cohort = 1.06 (0.92-1.21) (↔); CC = 0.99 (0.83-1.18) (↔)	7
Undela K, 2012 (India)[17]	PubMed (1966 to January 2012) and ASCO, AACR conference abstracts	Cohort (13) and CC (11)	1993-2011	2440988	76759	Yes (q < 0.001, I^2 = 57%)	0.99 (0.94-1.04) (↔)	LSU = 1.03 (0.96-1.11) (10) (↔); Recurrence 0.53 (0.37-0.76) (2) (↓)	Cohort = 1.01 (0.98-1.04) (↔); CC = 0.95 (0.84-1.08) (↔)	5
Colorectal cancer										
Bonovas S, 2007 (Greece)[18]	MEDLINE (1966 to December 2006) and WS (1970 to December 2006)	RCTs (6), Cohort (3) and CC (9)	2000-2007	1527721	38734	No (q = 0.35, I^2 = 7%)	0.92 (0.90-0.95) (↓)	None	RCTs = 0.95 (0.81-1.11) (↔); Cohort = 0.96 (0.84-1.11) (↔); CC = 0.92 (0.89-0.95) (↓)	7
Bardou M, 2010 (Canada)[f][47]	EMBASE, MEDLINE, CENTRAL, and ISI WK	RCTs (11)	NA	95984	1659	No (NA)	0.94 (0.85-1.04) (↔)	None	NA	--
Bardou M, 2010 (Canada)[f][48]	EMBASE, MEDLINE, CENTRAL, and ISI WK	Cohort (8) and CC (13)	NA	1606234	NA	No (NA)	0.92 (0.87-0.98) (↓)	None	Cohort = 0.89 (0.75-1.05) (↔); CC = 0.92 (0.90-0.94) (↓)	--
Ditah I, 2010 (United States)[f][49]	NA	RCTs (6), Cohort (6) and CC (12)	Up to Jun 2010	> 1.7 million	NA	NA	0.89 (0.85-0.94) (↓)	None	RCTs = 0.95 (0.80-1.13) (↔); Cohort = 0.89 (0.85-0.94) (↓); CC = 0.86 (0.79-0.94) (↓)	--
Samadder NJ, 2010 (United States)[f][50]	MEDLINE, EMBASE, WS and abstracts of national GI conferences (up to October 2009)	Cohort (5) and CC (17)	NA	2.5 million	NA	Yes (q < 0.01, I^2 = 47%)	0.88 (0.84-0.93) (↓)	Rectal = 0.81 (0.62-1.05) (8) (↓)	Cohort = 0.88 (0.84-0.93) (↓); CC = 0.90 (0.86-0.94) (↓)	--
Liu Y, 2014 (China)[19]	PubMed, EMBASE, WS, Cochrane Library (up to 30th July 2013)	RCTs (11), Cohort (13) and CC (18)	1995-2013	7908674	519317	Yes (q < 0.001, I^2 = 66.5%)	0.90 (0.86-0.95) (↓)	LSU = 0.96 (0.88-1.04) (20) (↔)	RCTs = 0.96, (0.85-1.08) (↔); Cohort = 0.93 (0.87-0.99) (↓); CC = 0.84 (0.76-0.93) (↓)	7
Lytras T, 2014 (Greece)[20]	MEDLINE (1966 to July 2013)	RCTs (8), Cohort (13) and CC (19)	1996-2013	8224019	130992	Yes (q < 0.001, I^2 = 71%)	0.91 (0.87-0.96) (↓)	None	RCTs = 0.90 (0.78-1.04) (↔); Cohort = 0.91 (0.83-1.00) (↓); CC = 0.92 (0.87-0.98) (↓)	0034
Gastric cancer										
Shimoyama S, 2011 (Japan)[21]	PubMed Central (1993 to 2008)	RCTs (6)	1994-2007	37851	284	No (q = 0.42, I^2 = 0.0%)	1.37 (0.57-3.25) (3) (↔)	UGIC = 1.20 (0.94-1.53) (3) (↔)	None	0
Singh PP, 2013 (United States)[22]	PubMed (1966 to 1st December 2012), EMBASE (1988 to	RCTs (*post-hoc* analyses) (3),	2004-2012	5459975	5581	Yes (q < 0.01, I^2 = 89%)	0.68 (0.51-0.91) (↓)	None	RCTs = 0.83 (0.66-1.05) (↔); OSs = 0.65 (0.45-0.93) (↓)	8

	1st December 2012) and WS (1993 to 1st December 2012)	Cohort (1) and CC (7)							
Wu X, 2013 (China)[23]	PubMed and EMBASE (up to March 2013)	RCTs (3), Cohort (3) and CC (5)	2004-2013	1136918	7611	Yes (q < 0.001, I^2 = 88.9%)	0.73 (0.58-0.93) (↓)	None	RCTs = 0.84 (0.61-1.14) (↔); Cohort = 0.87 (0.77-0.99) (↓); CC = 0.56 (0.31-1.01) (↔)	6
Ma Z, 2014 (China)[24]	Cochrane CRCT (Issue 12, 2012), PubMed, EMBASE, ISI WK, CNKI, CBML, CSJFD and Wanfang Database	CC (6)	2004-2013	60793	5993	Yes (q < 0.001, I^2 = 97%)	0.56 (0.35-0.90) (↓)	None	None	6
Gynaecologic cancer										
Liu Y, 2014 (China)[25]	PubMed, EMBASE and Cochrane Library (up to 10th February 2014)	RCTs (4), Cohort (5) and CC (5)	2000-2013	928721	12904	Yes (q = 0.016, I^2 = 42.3%)	0.89 (0.78-1.01) (↔)	Endometrial = 0.90 (0.75-1.07) (10) (↔); Ovarian = 0.79 (0.64-0.98) (5) (↓)	RCTs = 0.97 (0.62-1.50) (↔); Cohort = 0.97 (0.87-1.09) (↔); CC = 0.61 (0.40-0.91) (↓)	7
Haematological cancer										
Bonovas S, 2007 (Greece)[26]	MEDLINE (1966 to December 2006) and WS (1970 to December 2006)	RCTs (6), Cohort (1) and CC (7)	1996-2006	412053	5619	Yes (q < 0.001, I^2 = 71%)	0.85 (0.64-1.12) (↔)	None	RCTs = 0.92 (0.72-1.16) (↔); OSs = 0.83 (0.53-1.29) (↔)	5
Yi X, 2014 (China)[27]	PubMed, EMBASE and Cochrane CRCT (January 1966 to July 2013)	RCTs (6), Cohort (4), CC (10)	1996-2012	1139584	15297	Yes (q < 0.001, I^2 = 59%)	0.81 (0.70-0.92) (↓)	None	RCTs = 0.92 (0.77-1.09) (↔); OSs = 0.79 (0.67-0.93) (↓)	4
Kidney cancer										
Zhang X, 2014 (China)[28]	MEDLINE, EMBASE and Cochrane Library (January 1966 to October 2012)	RCTs (2), Cohort (5) and CC (5)	2001- 2012	3143236	2829	Yes (q < 0.001, I^2 = 87.8%)	0.92 (0.71- 1.19) (↔)	LSU = 1.01 (0.83-1.22) (6) (↔)	RCTs = 1.01 (0.57-1.79) (↔); Cohort = 1.07 (0.96-1.20) (↔); CC = 0.74 (0.45-1.23) (↔)	5
Liver cancer										
Pradelli D, 2013 (Italy)[29]	MEDLINE (up to March 2012)	Cohort (3) and CC (2)	NA	NA	2574	Yes (q < 0.001, I^2 = 65%)	0.58 (0.46-0.74) (↓)	LSU = 0.66 (0.55-0.80) (↓)	None	6
Singh S, 2013 (United States)[30]	MEDLINE (1966 to 25th May 2012), EMBASE (1988 to 25th May 2012) and WS (1993 to 25th May 2012)	RCTs (3), Cohort (4) and CC (3)	2005-2012	1459417	4298	Yes (q = 0.08, I^2 = 58%)	0.63 (0.52-0.76) (↓)	None	RCTs = 0.95 (0.62-1.45) (↔); OSs = 0.60 (0.49-0.73) (↓)	8
Zhang H, 2013 (China)[52]	MEDLINE, EMBASE and Cochrane Library (January 1966 to March2013)	Cohort (4) and CC (3)	2005-2013	4725593	9785	Yes (q = 0.004, I^2 = 68.6%)	0.61 (0.49-0.76) (↓)	None	Cohort = 0.62 (0.3-0.89) (↓); CC = 0.63 (0.49-0.82) (↓)	5
Shi M, 2014 (China)[31]	PubMed, BIOSIS Previews, WS, EMBASE, EBSCO and Cochrane Library (from inception to 5th March 2014)	RCT (IPD analysis) (1), Cohort (5) and CC (6)	2005-2013	5640313	35756	Yes (q < 0.001, I^2 = 65%)	0.58 (0.51-0.67) (↓)	HCDS = 0.53 (0.36-0.79) (6) (↓)	RCT = 1.06 (0.66-1.71) (↔); Cohort = 0.51 (0.44-0.58) (↓); CC = 0.63 (0.54-0.73) (↓)	6

Lung cancer									
Deng Z, 2013 (China)[g][32]	MEDLINE, EMBASE and WS (from inception to September 2013)	RCTs (8) Cohort (7) and CC (8)	1998-2012	2795302	38024	OSs = Yes (q < 0.001, I^2 = 94.9%) RCTs = No (q = 0.483, I^2 = 0.0%)	1.03 (0.96-1.11) (↔)	None	RCTs = 0.95 (0.85-1.06) (↔); Cohort = 0.94 (0.82-1.07) (↔); CC = 0.85 (0.62-1.16) (↔)	6
Tan M, 2013 (China)[33]	PubMed (up to March 2012)	RCTs (5), Cohort (7) and CC (7)	1998-2011	5009404	38013	Yes (q < 0.001, I^2 = 93.3%)	0.89 (0.77-1.03) (↔)	LSU = 0.81 (0.42-1.56) (↔)	RCTs = 0.91 (0.76-1.09) (↔); Cohort = 0.94 (0.82-1.07) (↔); CC = 0.82 (0.57-1.16) (↔)	6
Wang J, 2013 (China)[34]	MEDLINE, EMBASE and Cochrane Library (January 1966 to November 2012)	RCTs (5), Cohort (8) and CC (7)	1998-2012	4980009	37560	Yes (q < 0.001, I^2 = 93.6%)	0.89 (0.78-1.02) (↔)	LSU = 0.80 (0.39-1.64) (6) (↔)	RCTs = 0.92 (0.79-1.06) (↔); Cohort = 0.93 (0.82-1.06) (↔); CC = 0.81 (0.57-1.16) (↔)	8
Oesophageal cancer									
Alexandre L, 2012 (United Kingdom)[35]	PubMed, EMBASE and Cochrane CRCT (up to December 2011)	Cohort (3)	2004-2011	35214	9310	No (q = 0.88, I^2 = 0.0%)	0.86 (0.78-0.94) (↓)	In patients with BE = 0.53 (0.36-0.78) (↓)	None	7
Andrici J, 2013 (Australia)[f][51]	MEDLINE, PubMed, EMBASE and Current Contents Connect (up to 29th October 2012)	7 studies	NA	NA	NA	No (q = 0.31, I^2 = 15%)	0.75 (0.67-0.84) (↓)	In patients with BE = 0.56 (0.41-0.76) (↓); LSU = 0.45 (0.31-0.67) (↓)	Prospective = 0.75 (0.67-0.86) (↓); Retrospective = 0.68 (0.54-0.86) (↓)	--
Beales ILP, 2013 (United Kingdom)[36]	The PubMed, EMBASE, Cochrane Library, WS, Wiley Interscience and Google Scholar (up to 1st February 2013)	Cohort (5) and CC (6)	2004-2012	6454353	371203	No (q = 0.42, I^2 = 0.0%)	0.81 (0.75-0.88) (6) (↓)	In patients with BE = 0.56 (0.41-0.76) (4) (↓)	None	6
Singh S, 2013 (United States)[37]	MEDLINE (1980 to 31st Aug 2012), EMBASE (1988 to 31st Aug 2012) and WS (1993 to 31st August 2012)	RCT (*Post hoc* analyses) (1), Cohort (5) and CC (7)	2004-2012	1132969	9285	Yes (q < 0.01, I^2 = 74%)	0.72 (0.60-0.86) (↓)	In patients with BE = 0.59 (0.45-0.78) (5) (↓); LSU = 0.44 (0.24-0.78) (2) (↓)	RCT = 0.98 (0.69-1.40) (↔); Cohort = 0.79 (0.62-1.02) (↔); CC = 0.66 (0.51-0.85) (↓)	8
Pancreatic cancer									
Bonovas S, 2008 (Greece)[38]	MEDLINE, Scopus, Google Scholar, and SCI (up to December 2007) and AACO and AACR conference abstracts	RCTs (3), Cohort (4) and CC (5)	1993-2007	914601	3521	Yes (q < 0.001, I^2 = 86%)	0.88 (0.63-1.23) (↔)	None	RCTs = 0.99 (0.44-2.21) (↔); Cohort = 1.11 (0.95-1.29) (↔); CC = 0.70 (0.37-1.33) (↔)	7
Cui X, 2012 (China)[39]	MEDLINE, BIOSIS Previews and Cochrane Library (from inception to 30th August 2011)	RCTs (3), Cohort (5) and CC (8)	2001-2011	1692863	7807	Yes (q < 0.001, I^2 = 81%)	0.89 (0.74-1.07) (↔)	LSU = 0.97 (0.76-1.23) (5) (↔)	RCTs = 0.99 (0.44-2.21) (↔); Cohort = 1.05 (0.93-1.19) (↔); CC = 0.74 (0.51-1.07) (↔)	8
Prostate cancer									
Bonovas S, 2008 (Greece)[40]	MEDLINE (1966 to November 2007) and WK-SCI Expanded	RCTs (6), Cohort (6) and CC (7)	1993-2007	> 884871	62372	Yes (q < 0.001, I^2 = 98%)	0.95 (0.73-1.23) (↔)	LSU = 0.93 (0.77-1.13) (6) (↔); APC = 0.77 (0.64-0.93) (5) (↓)	RCTs = 1.06 (0.93-1.20) (↔); Cohort = 0.98 (0.89-1.09) (↔); CC = 0.74 (0.46-1.20) (↔)	5

	(1970 to November 2007)									
Bansal D, 2012 (India)[41]	PubMed (up to February 2012)	Cohort (15) and Case-control (12)	1993-2011	1893571	56847	Yes (q < 0.001, I^2 = 82%)	0.93 (0.87-0.99) (↓)	LSU = 0.94 (0.84-1.05) (11) (↔); APC = 0.80 (0.70-0.90) (7) (↓)	Cohort = 0.93 (0.87-1.01) (↔); CC = 0.87 (0.72-1.05) (↔)	7
Zhang Y, 2013 (China)[42]	NA	7 studies	2005-2010	NA	NA	NA	1.19 (1.01-1.40) (↑)	NA	NA	6
Skin cancer (Melanoma)										
Dellavalle R, 2005 (United States)[43]	Cochrane Skin Group Specialised Register (up to February 2003) and CENTRAL (Issue 1, 2005), MEDLINE (up to March 2003), EMBASE (up to September 2003), CANCERLIT (up to October 2002), WS (up to May 2003)	RCTs (7)	1993-1998	31198	126	No (q = 0.23, I^2 = 29%)	0.90 (0.56-1.44) (↔)	Lovastatin = 0.52 (0.27-0.99) (1) (↓)	None	10
Freeman SR, 2006 (United States)[44]	MEDLINE (from January 1966 to March 2003), EMBASE (from January 1980 to September 2003), The Cochrane CRCT (up to March2003), CANCERLIT (from January 1975 to October 2002), and WS - SCI (from January 1970 to May 2003)	RCTs (12)	1993-2003	39426	127	No (q = 0.31, I^2 = 16.6%)	0.87 (0.61-1.23) (↔)	Lovastatin = 0.52 (0.27-0.99) (1) (↓)	None	6
Bonovas S, 2010 (Greece)[45]	MEDLINE, Scopus, Google Scholar and SCI Expanded (up to June 2009)	RCTs (16)	1994-2006	62568	165	No (q = 0.25, I^2 = 22%)	0.92 (0.67-1.26) (↔)	None	None	6
Li X, 2014 (China)[46]	PubMed (up to 2013) anwd WS (1985-2013)	RCTs (17), Cohort (4) and CC (7)	1995-2013	517887	11787	Yes (q < 0.07, I^2 = 33.8%)	0.94 (0.85-1.04) (24) (↔); NMSC = 1.03 (0.90-1.19) (14) (↔)	None	None	4

[a]Publication year; [b]Country of study conducted; [c]Period of literature search; [d]*n* mentioned only where the number of studies differ from studies included; [e]Though many subgroup analyses conducted in individual studies, here we focused mainly on subgroup analysis based on study design due to space constraint; [f]Conference abstracts; [g]Conducted among elderly people. APC: Advanced prostate cancer; BE: Barrett's oesophagus; CBML: China BioMedical Literature; CC: Case-control; CNKI: Chinese National Knowledge Infrastructure; CRCT: Central Register of Controlled Trials; CSJFD: Chinese Scientific Journal Full-text Database; GI: Gastro-intestinal; HCDS: Higher cumulative dosage of statin; I^2: I^2 test value; IPD: Individual patient data; ISI WK: Institute for Scientific Information Web of knowledge (Former term for Web of science); LSU: Long-term statin use; *n*: Number of studies; NA: Not available; NMSC: Non-melanoma skin cancer; Oss: Observational studies; q: Cochran Q test P value; RCTs: Randomized controlled trials; RR: Relative risk; SCI: Science citation index; UGIC: Upper gastrointestinal cancer; WS: Web of science; ↔: Non-significant association; ↓: Statistically significantly decreased risk; ↑: Statistically significantly increased risk.

and 2013 and identified heterogeneity among studies. Except the study by Bardou *et al*[48] (which included only RCTs), remaining all the studies found 8%-12% reduced risk of colorectal cancer among statin users. However, a modest reduction in risk or an effect may be associated with higher doses of statins[18]. Based on the subgroup analyses by two meta-analyses[19,20] published in 2014 (which are full-text and included a maximum number of observational studies), risk reduction was 7%-9% among cohort studies and 8%-16% among case-control studies. Studies included RCTs reported no association between use of statin and risk of colorectal cancer alone for RCTs. One study[50] found there was a 19% reduction in the risk of rectal cancer among statin users. Another study[19] found no association between long-term statin use and risk of colorectal cancer.

Statin use and risk of gastric cancer: Four meta-analyses[21-24] published between 2011 and 2014 to identify the risk of gastric cancer among statin users. Except the study conducted by Shimoyama *et al*[21] (published in 2011, searched only PubMed Central and included only RCTs), remaining all studies suggested that the statin use reduces the risk of gastric cancer by 27%-44%, though they identified the heterogeneity among studies. In subgroup analysis, observational studies were found to identify this reduced risk, but not RCTs.

Statin use and risk of gynecological cancer: A meta-analysis[25] published recently to identify the association between statin use and risk of gynecological cancer. The study included both RCTs and observational studies published between 2000 and 2013 on this association. It didn't find any association between statin use and risk of gynecological cancer. On subgroup analysis, the association remains same for RCTs and cohort studies, but case-control studies alone show 39% decreased risk of gynecological cancer among statin users. On secondary analysis using available studies, there was no association found between statin use and risk of endometrial cancer, but decreased (21%) risk of ovarian cancer.

Statin use and risk of hematological cancer: A meta-analysis published by Bonovas *et al*[26] in 2007 to estimate the association between statin use and risk of hematological cancer by including six RCTs and eight observational studies. No association identified between statin use and risk of hematological cancer. The association found to be same even after subgroup analysis of study design. In 2014, Yi *et al*[27] updated this meta-analysis by including six more observational studies published after Bonovas *et al*[26] meta-analysis and gave contrast results by finding 19% decreased risk of hematological cancer among statin users. On subgroup analysis, this association remains same for observational studies, but not for RCTs.

Statin use and risk of kidney cancer: Only one meta-analysis[28] published to estimate the effect of statin use on kidney cancer by including two RCTs and 10 observational studies published between 2001 and 2012. This study found no association between statin use and risk of kidney cancer with heterogeneity among studies. On subgroup and secondary analysis the association remains same among RCTs, cohort and case control studies and also for long-term statin use.

Statin use and risk of liver cancer: Four meta-analyses[29-31,52] published in 2013 and 2014 regarding statin use and risk of liver cancer. All studies included observational studies but different in number and only two studies[30,31] included RCTs. All studies found significant heterogeneity among the studies included and shown 37%-42% decreased risk of liver cancer among statin users. This chemoprotective association is more pronounced in the Asian population, where viral hepatitis is the most important risk factor for liver cancer[30]. On subgroup analysis by study design, the risk remains similar (37%-49% decreased risk) among observational studies but not for RCTs.

Statin use and risk of lung cancer: Three meta-analyses[32-34] published in 2013 including almost similar number of RCTs and observational studies to identify the association between statin use and risk of lung cancer. All the three found significant heterogeneity among studies and no association between statin use and risk of lung cancer. On subgroup and secondary analysis the association remains same among RCTs, cohort and case control studies and also for long-term statin use.

Statin use and risk of oesophageal cancer: Four meta-analyses (3 full-text[35-37] and 1 conference abstract[51]) published in 2012 and 2013 on the association. Only observational studies contributed to the analysis in all studies except the Singh *et al*[37] study also included one RCT (*post hoc* analysis). Results were consistent among all studies with 14%-28% decreased risk of esophageal cancer among statin users. On subgroup analysis, only case-control studies found with 44% decreased risk of esophageal cancer but not cohort studies and RCT. By using available studies, all the meta-analyses conducted secondary analysis on the risk of Barrett's esophagus among statin users and found 41%-47% decreased risk. Two studies[37,51] also identified 55% decreased risk of esophageal cancer among long-term statin users.

Statin use and risk of pancreatic cancer: A meta-analysis published by Bonovas *et al*[38] in 2008 to estimate the co-relation between statin use and risk of pancreatic cancer by including three RCTs and nine observational studies. There was no relationship between statin use and risk of pancreatic cancer with heterogeneity among studies. The association found to be same even after subgroup analysis of study design. In

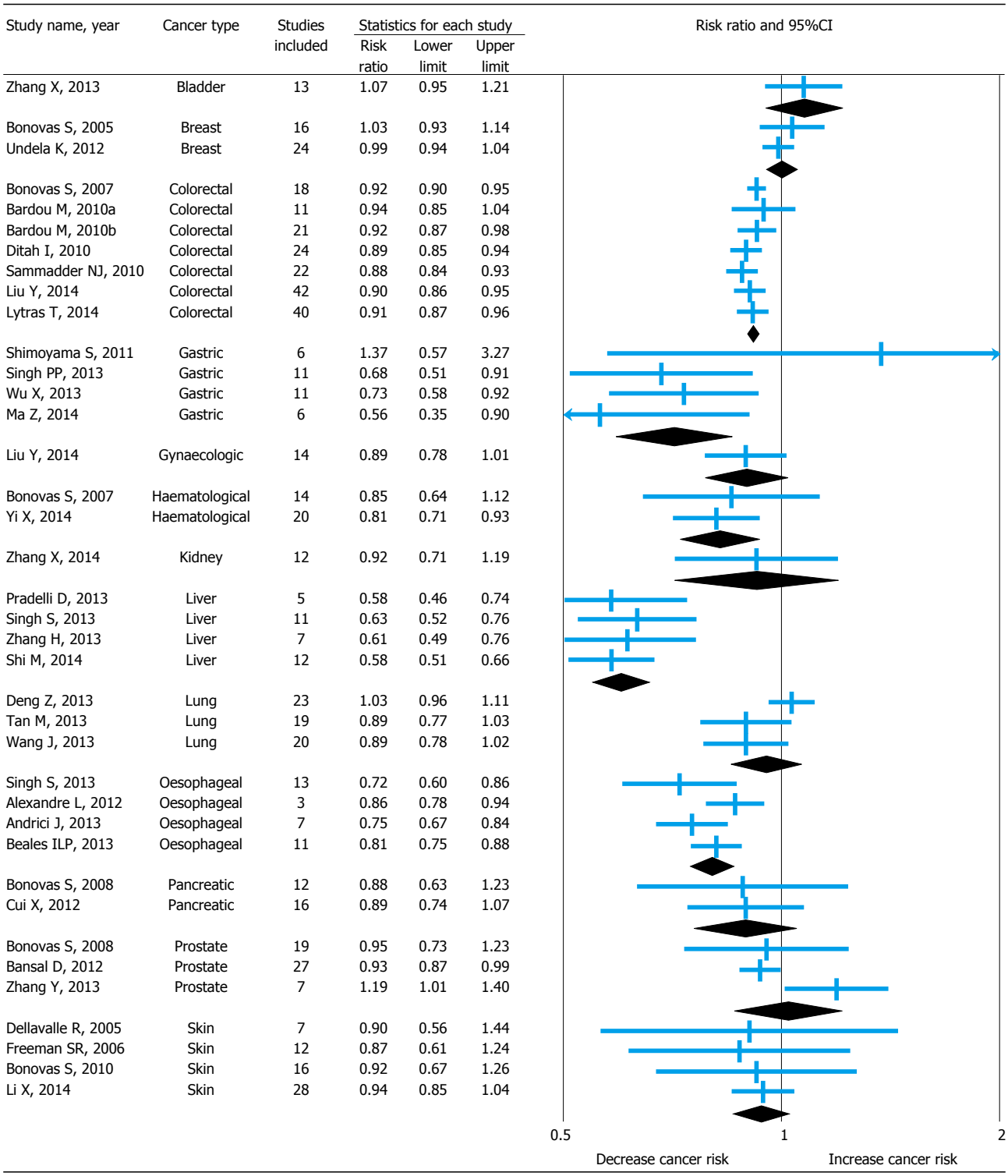


Figure 2 Forest plot of pooled relative risk with 95%CI of primary outcome from all included studies.

2012, Cui *et al*[39] updated this meta-analysis by including four more observational studies published after previous meta-analysis. This study also gives an almost similar conclusion. Additionally, this updated meta-analysis reported no association between long-term statin use and risk of pancreatic cancer.

Statin use and risk of prostate cancer: A meta-analysis published by Bonovas *et al*[40] in 2008 to estimate the association between statin use and risk of prostate cancer by including six RCTs and 13 observational studies. No association identified between statin use and risk of prostate cancer. The association remains same even after subgroup analysis of study design and also for long-term statin use. In 2012, Bansal *et al*[41] updated this meta-analysis by including

14 more observational studies published after Bonovas *et al*[40] meta-analysis and gave contrast results by finding small (7%) but significant decreased risk of prostate cancer among statin users. But in a subgroup analysis of study design, no association observed between cohort and case-control studies alone. Both the studies also tried to identify the risk of advanced prostate cancer among statin users and found 23%-30% decreased risk. On the other hand, a study conducted by Zhang *et al*[42] in 2013 by including only seven studies published after Bonovas *et al*[40] meta-analysis and found a 19% increased risk of prostate cancer among statin users.

Statin use and risk of skin cancer (melanoma): Four meta-analyses[43-46] conducted on this association, including one Cochrane systematic review published in 2005. All studies included only RCTs except the study by Li *et al*[46] also included 11 observational studies. All the studies found no association between statin use and risk of melanoma and also the association found to be same for non-melanoma skin cancer by Li *et al*[46] study. Interestingly, one RCT[43,44] suggested that the lovastatin can decrease the risk of melanoma by 48%.

DISCUSSION

Meta-analytic evidence of association between statin use and risk of site specific cancers was piling since last decade. This overview of 38 meta-analyses covered 13 site specific cancers revealed that the statin use may reduce the risk of certain types of cancers like colorectal (8%-12%), gastric (27%-44%), hematological (19%), liver (37%-42%), esophageal (14%-28%), ovarian (21%) and prostate (7%). On the other hand, some evidence also suggests that there is no association between statin use and risk of bladder, breast, endometrial, kidney, lung, pancreatic and skin cancers. On secondary analysis, few meta-analyses suggested that statin use can also reduce the risk of rectal cancer (19%), advanced prostate cancer (23%-30%), Barret's esophagus (47%) and also reduce the risk of recurrence of breast cancer (47%).

In this review, we tried to identify the change in the risk of cancer among different types, doses and duration of statin use with the available information. Some of the meta-analyses categorized statins according to whether they were lipophilic (simvastatin, lovastatin, fluvastatin, and atorvastin) or hydrophilic (pravastatin and rosuvastatin) and conducted subgroup analysis. The studies didn't find any statistically significant association between lipophilic or hydrophilic statins and risk of colorectal cancer[18,20], haematological cancer[26], lung cancer[33], pancreatic cancer[38,39] and skin cancer[45]. In contrast, one meta-analysis showed an association between lipophilic statin use and colorectal cancer risk (RR = 0.88, 95%CI: 0.85-0.93) and a null association between hydrophilic statin use and colorectal cancer risk (RR = 0.88, 95%CI: 0.76-1.02)[19]; and another meta-analysis found a significant decrease in liver cancer risk for both lipophilic statins (RR = 0.57, 95%CI: 0.50-0.65) and hydrophilic statins (RR = 0.59, 95%CI: 0.41-0.84). The same study also revealed that higher cumulative dose of statin use, defined as statin use over 180 cumulative defined daily doses or 0.5 years (cumulative duration), showed a trend towards more risk reduction of liver cancer (RR = 0.53, 95%CI: 0.36-0.79)[31]. Some of the studies also conducted secondary analysis to identify the association between long-term statin use (usually $\geqslant$ 5 years) and risk of cancer, and identified reduced risk of oesophageal cancer (55%)[37,51], ovarian cancer (52%)[25], but not for bladder[15], breast[17], colorectal[19], endometrial[25], kidney[28], Lung[33], pancreatic[39] and prostate cancers[40,41].

Recently published overview to identify the role of statin use in cancer prevention and modifying cancer-related outcomes also come out with similar conclusions[53]. However, this study suffers with some limitations in methodology and not covered few cancer types. Moreover, a recent meta-analysis of long-term efficacy and safety of statin treatment confirmed that statin treatment did not increase the incidence of cancer and deaths from cancers[54]. Despite the examinations on statins consequences for tumor cells have proceeded from the mid 1990s, the exact mechanism that could clarify the anticancer effect of statins still unclear. Different types, dose and route of administration of statins being used, type/stage of tumors and time of exposure to statins may impact the mechanisms that lead to cell-cycle arrest and induction of apoptosis. One review observed that statins may decrease the cholesterol levels, leads to further changes in cell flagging[9].

According to recent laboratory studies, statins seems to have chemo-preventive affect against cancer at various sites. Evidence suggests that statins are selectively localized to the liver, and only < 5% dose reaches the systemic circulation. This low systemic availability uncertians chemo-protective nature of statin[15,16].

We have made efforts to minimize the risk of bias in every step of this overview. However, this overview has few limitations. First, glitches in the nature of the primary data included in 38 meta-analyses; RCTs have not been adequately powered to detect potentially small differences in cancer risk due to the small number of cancer cases as it was not the primary outcome of these trials and the observational data may have suffered some common limitations of pharmacoepidemiological studies. Secondly, as most of the findings come from observational studies, there may be a chance of presenting "healthy-user bias" for part of the beneficial effects of statins.

Statins are a promising group of drugs in cancer treatment because of their ability to reduce both cholesterol and isoprenoid levels. Meta-analyses of variable quality showed that the statins may have a potential role in cancer chemoprevention and reduce the risk of certain site specific cancers, but not all. Until a definitive benefit is demonstrated by randomized controlled trials, statins cannot be recommended either for cancer prevention or

for modifying cancer-related outcomes.

COMMENTS

Background

In recent years, emerging experimental evidence suggests that statins may have a potential role in cancer chemoprevention. However, a large number of randomized controlled trials and observational studies published to examine the association between statin use and risk of site specific cancers were given conflicting results.

Research frontiers

The objective of this overview is to summarize and critically appraise the evidence of relevant meta-analyses and present a comprehensive evaluation of the association between statin use and risk of site specific cancers.

Innovations and breakthroughs

This overview of 38 meta-analyses covered 13 site specific cancers revealed that the statin use may reduce the risk of certain types of cancers like colorectal (8%-12%), gastric (27%-44%), hematological (19%), liver (37%-42%), esophageal (14%-28%), ovarian (21%) and prostate cancer (7%). On the other hand, some evidence also suggests that there is no association between statin use and risk of bladder, breast, endometrial, kidney, lung, pancreatic and skin cancers. On secondary analysis, few meta-analyses suggested that statin use can also reduce the risk of rectal cancer (19%), advanced prostate cancer (23%-30%), Barret's esophagus (47%) and also reduce the risk of recurrence of breast cancer (47%).

Applications

Statins are a promising group of drugs in cancer treatment because of their ability to reduce both cholesterol and isoprenoid levels. Meta-analyses of variable quality showed that the statins may have a potential role in cancer chemoprevention and reduce the risk of certain site specific cancers, but not all. Until a definitive benefit is demonstrated by randomized controlled trials, statins cannot be recommended either for cancer prevention or for modifying cancer-related outcomes.

Peer-review

These authors made a comprehensive review of meta-analyses on statin use and risk of cancer. They also made tables and figures, which make readers easy to catch the study methods, strength and results from each meta-analysis. It will be informative for readers interested in this topic.

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META-ANALYSIS

Is there a difference between 19G core biopsy needle and 22G core biopsy needle in diagnosing the correct etiology? - A meta-analysis and systematic review

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Abstract

AIM

To compare the accuracy of endoscopic ultrasonography (EUS) 19G core biopsies and 22G core biopsies in diagnosing the correct etiology for a solid mass.

METHODS

Articles were searched in Medline, PubMed, and Ovid journals. Pooling was conducted by both fixed and random effects models.

RESULTS

Initial search identified 4460 reference articles for 19G and 22G, of these 670 relevant articles were selected and reviewed. Data was extracted from 6 studies for 19G (n = 289) and 16 studies for 22G (n = 592) which met the inclusion criteria. EUS 19G core biopsies had a pooled sensitivity of 91.6% (95%CI: 87.1-95.0) and pooled specificity of 95.9% (95%CI: 88.6-99.2), whereas EUS 22G had a pooled sensitivity of 83.3% (95%CI: 79.7-86.6) and pooled specificity of 64.3% (95%CI: 54.7-73.1). The positive likelihood ratio of EUS 19G core biopsies was 9.08 (95%CI: 1.12-73.66) and EUS 22G core biopsies was 1.99 (95%CI: 1.09-3.66).

The negative likelihood ratio of EUS 19G core biopsies was 0.12 (95%CI: 0.07-0.24) and EUS 22G core biopsies was 0.25 (95%CI: 0.14-0.41). The diagnostic odds ratio was 84.74 (95%CI: 18.31-392.26) for 19G core biopsies and 10.55 (95% CI: 3.29-33.87) for 22G needles.

CONCLUSION

EUS 19G core biopsies have an excellent diagnostic value and seem to be better than EUS 22G biopsies in detecting the correct etiology for a solid mass.

Key words: Endoscopic ultrasound guided fine needle aspiration; Solid mass lesions; Endoscopic ultrasound; Pancreatic mass; Pancreatic cytology; Core biopsies; 19G procore needle; Meta-analysis; Systematic review; 22G procore needle

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Core tip: Management of pancreatic solid mass lesions relies greatly on accuracy of diagnosis of these lesions. Procore fine needle biopsy needles have been found to have a diagnostic accuracy comparable to, if not better than the standard needles in diagnosing the intestinal and extra-intestinal mass lesions. Amongst the Procore needles, the 19G and 22G Procore needles have both been shown to obtain good quality core tissue samples but both have unique characteristics of their own. This meta-analysis compares the feasibility and accuracy of 19G and 22G Procore needles in determining the diagnosis of solid mass lesions.

Kandula M, Bechtold ML, Verma K, Aulakh BS, Taneja D, Puli SR. Is there a difference between 19G core biopsy needle and 22G core biopsy needle in diagnosing the correct etiology? - A meta-analysis and systematic review. *World J Meta-Anal* 2017; 5(2): 54-62 Available from: URL: http://www.wjgnet.com/2308-3840/full/v5/i2/54.htm DOI: http://dx.doi.org/10.13105/wjma.v5.i2.54

INTRODUCTION

Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) is the recommended procedure for the sampling of solid mass lesions within the gastrointestinal tract and extra-intestinal organs, especially pancreatic mass lesions[1-4]. It has been reported from previous studies that EUS-FNA has high diagnostic accuracy (78%-95%)[5,6], sensitivity (64%-95%) and specificity (75%-100%)[6,7] for cytological diagnosis. To make an accurate diagnosis though, histological studies are essential in addition to cytological studies. Although cytological study can detect cellular findings like anisonucleosis and nuclear enlargement that suggest malignancy, inflammation in the tissue causes regenerative and reactive changes that make it hard to distinguish it from well differentiated neoplasia based on cytological study alone. Moreover, there are certain neoplasms like lymphomas and stromal tumors that would require tissue architecture and cell morphology for accurate pathological assessment and this is not possible without obtaining histological samples[8-10]. Other factors that influence the diagnostic accuracy of EUS-FNA include the availability of an onsite cytopathologist to render a diagnosis, experience of the endosonographer, location of the lesion, the method of preparation and the type and size of the needle used to obtain the sample[11-14].

Currently, there are three needle sizes (19G, 22G and 25G) that are commercially available, of which 22G is probably the most widely used. Theoretically, it is difficult to obtain histological samples with smaller needles. Hence, the trucut biopsy needle (Cook Medical, Bloomington, IN, United States) was developed with 19G needles[15]. EUS-trucut needle biopsy (EUS-TNB) technique was more accurate than FNA for neoplasms requiring histological analysis, but the 19G caliber posed certain difficulties. It was difficult to maneuver the needle owing to its rigidity, and the mechanical friction of the firing mechanism limited its use in evaluating pancreatic head masses and duodenal lesions where a transduodenal approach was required[8].

The Procore EUS-fine needle biopsy (EUS-FNB) needle, a newer generation, with reverse beveled technology was developed to improve quality of core tissue samples for histologic analysis. These needles (Procore, Cook Medical, Winston-Salem, NC, United States) available in different sizes were shown to have promising results. The histologic samples obtained by the 19G procore needle had a diagnostic accuracy of more than 90% as shown in a large prospective study done in Europe[16]. There were still some technical problems encountered with the 19G Procore when performing transduodenal passes. Hence the same FNB device was developed in the 22G caliber. In several other studies, the 22G Procore needle was found to require lower number of passes to achieve the same contributive sample rate as the FNA needles[17-19].

There have been a lot of studies comparing the Procore FNB needles with standard FNA and TNB needles. These studies have established that the feasibility, yield and accuracy of the Procore needles in diagnosing intestinal, extra-intestinal mass lesions as well as peri-intestinal lymphadenopathy is comparable, if not better than the standard needles. We conducted a meta-analysis from the relevant studies done so far, and reviewed the literature to determine if there was a difference in the diagnostic accuracy of 19G Procore *vs* 22G Procore biopsy needles in the evaluation of solid mass lesions.

MATERIALS AND METHODS

Study selection criteria

Only EUS 19G and 22G core biopsy studies on solid mass lesions confirmed by surgery or appropriate follow-up were selected. Only studies from which a 2 × 2 table

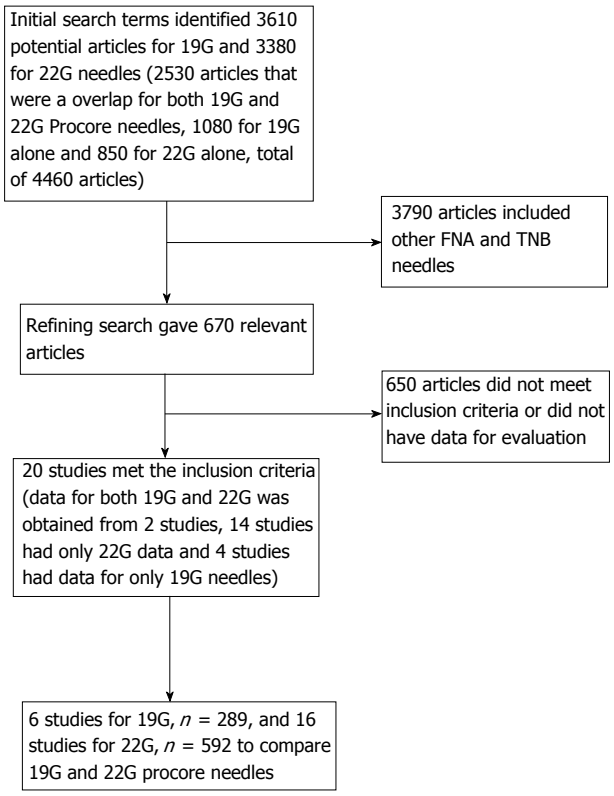


Figure 1 Flow chart showing search results and study selection. FNA: Fine needle aspiration; TNB: Trucut needle biopsy.

could be constructed for true positive, false negative, false positive and true negative values were included.

Data collection and extraction

Articles were searched in MEDLINE, PubMed, Ovid journals, Cumulative Index for Nursing and Allied Health Literature, ACP journal club, DARE, International Pharmaceutical Abstracts, old MEDLINE, MEDLINE nonindexed citations, OVID Healthstar, and Cochrane Controlled Trials Registry. Search included articles of all languages from the year 1946 to present. The search terms used were EUS-FNA, ultrasound, endosonography, solid mass lesions, pancreatic mass, pancreatic cytology, core biopsies, 19G procore needle, 22G needle, surgery, histopathology, sensitivity, specificity, positive predictive value, and negative predictive value. Data included in the meta-analysis was obtained by intention to treat analysis of the original data. Two plus two tables were constructed with the data extracted from each study. Two authors independently searched and extracted the data into an abstraction form. No additional data was obtained from the authors. Any differences were resolved by mutual agreement.

Quality of studies

Clinical trial with a control arm can be assessed for the quality of the study. A number of criteria have been used to assess this quality of a study (*e.g.,* randomization, selection bias of the arms in the study, concealment of allocation, and blinding of outcome)[20,21]. There is no consensus on how to assess studies without a control arm. Hence, these criteria do not apply to studies without a control arm[21]. Therefore, for this meta-analysis and systematic review, studies were selected based on completeness of data and inclusion criteria.

Statistical analysis

Meta-analysis for the accuracy of EUS guided 19G core biopsies and 22G core biopsies in diagnosing solid mass lesions was performed by calculating pooled estimates of sensitivity, specificity, likelihood ratios, and diagnostic odds ratios. Pooling was conducted using both Mantel-Haenszel Method (fixed effects model) and DerSimonian Laird Method (random effects model). The confidence intervals were calculated using the F Distribution Method[22]. Forrest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forrest plots indicates the assigned weight to that study. For 0 value cells, a 0.5 was added as described by Cox[23]. The heterogeneity of the sensitivities and specificities were tested by applying the likelihood ratio test[24]. The heterogeneity of likelihood ratios and diagnostic odds ratios were tested using Cochran's *Q* test based upon inverse variance weights[25]. Heterogeneity among studies was also tested by using summary receiver operating characteristic (SROC) curves. SROC curves were used to calculate the area under the curve (AUC). The effect of publication and selection bias on the summary estimates was tested by Egger bias indicator[26] and Begg-Mazumdar bias indicator[27]. Also, funnel plots were constructed to evaluate potential publication bias using the standard error and diagnostic odds ratio[28,29].

RESULTS

Initial search identified 3610 reference articles for 19G core biopsies and 3380 reference articles for 22G core biopsies (4460 total as there was an overlap of the articles), of these, 670 relevant articles were selected and reviewed. Six studies (n = 289) for 19G core biopsies and 16 studies (n = 592) for 22G core biopsies which met the inclusion criteria were included in this analysis. Figure 1 shows the search results and Table 1 shows the characteristics for EUS studies included in this meta-analysis. Of the 20 studies included in this analysis, 12 were published as full-text articles and 8 were abstracts in peer reviewed journals. The pooled estimates given are estimates calculated by the fixed and random effects model.

Accuracy of EUS guided 19G core biopsies to diagnose solid mass lesions

Pooled sensitivity of EUS 19G core biopsies in diagnosing solid mass lesions was 91.6% (95%CI: 87.1%-95.0%). 19G Procore needle had a pooled specificity of 95.9% (95%CI: 88.6%-99.2%). Forrest plot in Figure 2 shows

Table 1 Basic characteristics of the studies

Ref.	Type of article/study	Needle type	Number of biopsies	Type of lesion	Accurate diagnoses (TP and TN)
Irions *et al*[40], 2011	Abstract	22G	6	Pancreatic adenocarcinoma, esophageal SCC	4
Barresi *et al*[44], 2014	Full article	22G	60	Pancreatic lesions	36
Alatawi *et al*[17], 2015	Full article	22G	50	Pancreatic lesions	48
Vanbiervliet *et al*[33], 2014	Full article	22G	80	Adenocarcinoma, metastatic lung cancer	67
Ganc *et al*[19], 2014	Full article	22G	15	Pancreatic mass lesions	8
Ramay *et al*[48], 2013	Abstract	22G	24	Perigastric, peripancreatic subcarinal, mediastinal lymph nodes	24
Larghi *et al*[43], 2011	Full article	22G	61	Adenocarcinoma, neuroendocrine tumors, lymphoma	54
Strand *et al*[34], 2014	Full article	22G	28	Solid pancreatic neoplasms	7
Bang *et al*[32], 2012	Full article	22G	28	Pancreatic masses	25
Ganc *et al*[19], 2014	Abstract	22G	30	Pancreatic masses	28
Krishnamurthy *et al*[45], 2013	Abstract	22G	37	Adenocarcinoma, neuroendocrine tumors	24
Komanduri *et al*	Abstract	22G	10	Pancreatic lesions	10
Kim *et al*	Full article	22G	12	GI stromal tumors, pancreatic masses, lymphoma	9
Ramay *et al*[48], 2013	Abstract	22G	40	Pancreatic lesions	40
Park *et al*[47], 2012	Abstract	22G	43	Solid pancreatic lesions	32
Fabbri *et al*[46], 2015	Full article	22G	68	Solid pancreatic lesions, pancreatic cystic lesions	56
Petrone *et al*[39], 2012	Abstract	19G	49	Pancreatic mass, submucosal lesions, mediastinal mass	46
Iglesias-García *et al*[41], 2014	Full article	19G	114	Pancreatic tumors, mediastinal lymphadenopathy, intraabdominal masses	106
Komanduri *et al*	Abstract	19G	10	Pancreatic lesions	10
Lovacheva *et al*[35], 2013	Abstract	19G	23	Mediastinal lymph nodes	19
Iglesias-García *et al*[41], 2014	Full article	19G	87	Pancreatic tumors, mediastinal lymphadenopathy, intraabdominal masses	83
Irions *et al*[40], 2011	Abstract	19G	6	Pancreatic adenocarcinoma, GIST, benign lymph nodes	4

TP: True positives; TN: True negatives; SCC: Squamous cell carcinoma; GI: Gastrointestinal; GIST: Gastrointestinal stromal tumors.

the sensitivity and specificity of 19G core biopsies to diagnose solid mass lesions. The positive likelihood ratio was 9.07 (95%CI: 1.12-73.65) and negative likelihood ratio was 0.12 (95%CI: 0.06-0.24). The diagnostic odds ratio, the odds of having the correct histologic etiology of a mass in positive as compared to negative EUS-FNB studies was 84.7 (95%CI: 18.3-392.2). All the pooled estimates calculated by fixed and random effect models were similar. SROC curves showed an area under the curve of 0.95. Figure 3 shows the SROC curves for EUS 19G core biopsies to diagnose solid mass lesions. The p for chi-squared heterogeneity for all the pooled accuracy estimates was > 0.10.

Accuracy of EUS 22G core biopsies to diagnose solid mass lesions

Pooled sensitivity of EUS 22G core biopsies in diagnosing solid mass lesions was 83.3% (95%CI: 79.7%-86.6%). 22G Procore needle had a pooled specificity of 64.3% (95%CI: 54.7%-73.1%). The positive likelihood ratio was 1.99 (95%CI: 1.09%-3.66%) and negative likelihood ratio was 0.25 (95%CI: 0.14%-0.41%). The diagnostic odds ratio, the odds of having the correct histologic etiology of a mass in positive as compared to negative EUS-FNB studies was 10.55 (95%CI: 3.28%-33.87%). All the pooled estimates calculated by fixed and random effect models were similar. SROC curves showed an area under the curve of 0.95. The *P* for χ^2 heterogeneity for all the pooled accuracy estimates was > 0.10.

Bias estimates

The publication bias calculated by Begg-Mazumdar bias indicator gave a Kendall's tau *b* value of -0.2, *P* = 0.21 and Egger bias indicator gave a value of -0.56 (95%CI: -2.28 to 1.16, *P* = 0.50). Funnel plots in Figure 4 show no effect of publication bias on the pooled estimates calculated for 19G or 22G core biopsies.

DISCUSSION

The Procore needles with reverse bevel technology for EUS-FNB are a recent development in the EUS-platform for maximizing acquisition of core tissue specimens for histopathological analysis. The 19G Procore needle was initially developed to overcome the limitations encountered with EUS-TNB, like rigidity of the 19G caliber needle as well as the mechanical friction of the firing mechanism produced by the torqued endoscope[8]. The same device was developed in the 22G platform because of the difficulties encountered during transduodenal passes with the 19G needle (the needle had to be advanced out of the scope in the stomach before reaching the duodenum)[30]. Obtaining core biopsy specimens would allow for detailed analysis of preserved tissue architecture and also provide the opportunity to immunostain the tissue, thus increasing diagnostic accuracy. It has also been shown to be not inferior to rapid onsite cytological examination, which is known to be a significant factor in decreasing the number of inadequate diagnoses, thus also playing a role in economical cost saving[31,32]. The 19G and 22G Procore needles have been studied significantly as to their feasibility and yield in the sampling of solid pancreatic lesions and all these studies have shown that they are comparable to the standard

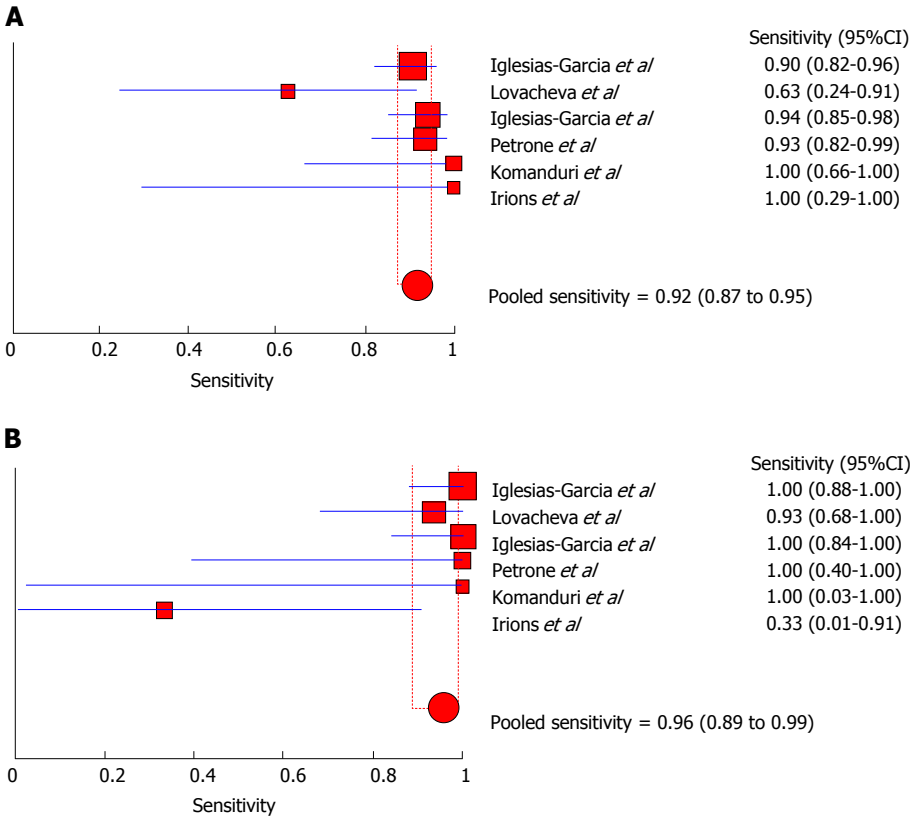


Figure 2 Forest plot showing sensitivity (A) and specificity (B) of 19G Procore needle.

FNA needles[31-34]. Our meta-analysis showed that of these two Procore needles, the 19G needle is superior to the 22G needle in core histology yield and diagnostic accuracy.

In the study by Iglesias-Garcia *et al*[16], EUS-FNB by 19G Procore needle of 114 lesions were evaluated for sample quality for histological evaluation, and over-all diagnostic accuracy compared with a standard diagnosis. It was found that the 19G Procore needle offered the possibility of obtaining a core sample for histological evaluation with a diagnostic accuracy of over 85%. It reached an accuracy of 92.9% for the detection of malignancy[16]. Lovacheva *et al*[35] confirmed that 19G Procore needle had a high diagnostic yield when it came to malignancies and histological diagnosis, although there was no significant difference to FNA for cytology in benign diseases. This is much better than the EUS-biopsy with the quick-core needle where the overall accuracy ranged between 61% and 84%[36-38]. Although transduodenal passes were difficult with the 19G Procore needle, it was still better than the Quick-Core needle where the sample quality was significantly affected for lesions that needed to be punctured from the duodenum. Petrone *et al*[39] had even better results where the needle provided adequate histological sample in 98% of the cases with an overall accuracy reaching 94% with regard to the final gold standard diagnosis. Irions *et al*[40] studied both the 19G and 22G Procore needles and determined that samples could be obtained safely and with high yield using either of them. Core samples in this study were obtained with more than one pass in 80% of the lesions. In another recent study by Iglesias-García *et al*[41] with the 19G Procore needle, there were no complications related to the procedure in their 87 patients and it was determined to be as safe as the standard FNA needle. Moreover, this study showed that a single pass of the needle obtained the same results as multiple passes in previous studies by Yasuda *et al*[42] and Larghi *et al*[43] done with the standard needle, as well as other recent studies with the Quick-Core needle. This may be because of the reverse bevel technology in the Procore needle that cuts the tissue in to and fro movements during a single needle pass and thus obtains an adequate core tissue specimen.

Bang *et al*[32] did a study in 2012 to compare 22G FNA and FNB needles and found no significant difference in the yield or quality of the histologic specimens in these groups. They did not find any difference in the median number of passes required to establish an on-site diagnosis. The rate of optimal specimens in this study was 80% as compared to 92.9% reported with the 19G needle in the Iglesias-Garcia study. Over-all, the quality of specimens obtained by the small caliber 22G needle was unsatisfactory for histologic analysis, though this could also be because there were passes that were performed for onsite analysis before specimens were collected for cell block. On the safety front, the 22G FNB needle was similar to the FNA needle and comparable to the 19G needle, with only a couple of minor complications[32]. Barresi *et al*[44] followed this up and studied the feasibility

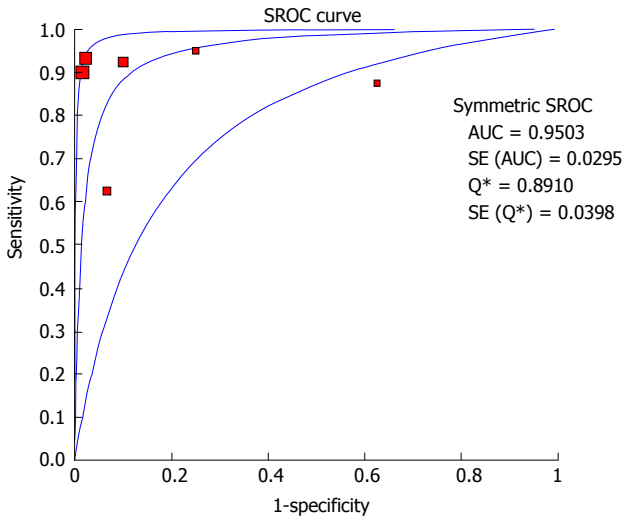


Figure 3 Summary receiver operating characteristic curves for endoscopic ultrasonography 19G core biopsies to diagnose solid lesions. SROC: Summary receiver operating characteristic; AUC: Area under the curve.

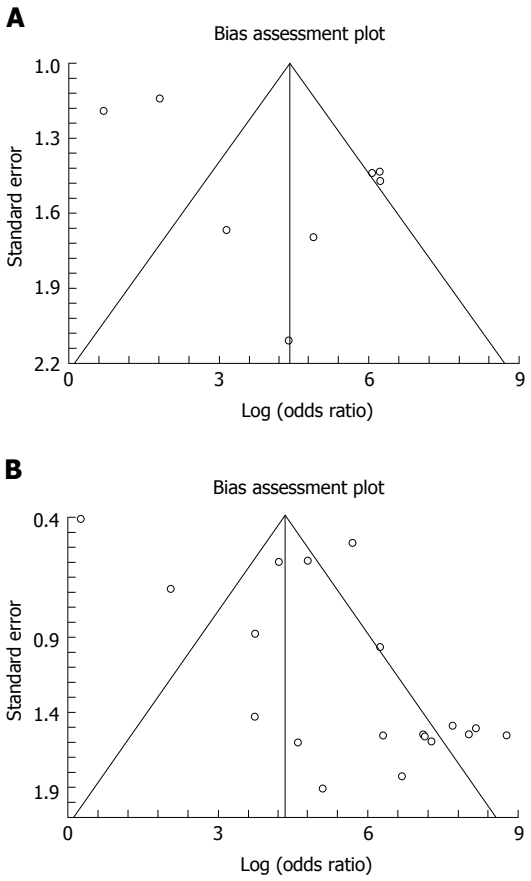


Figure 4 Bias assessment plot for 19G (A) and 22G (B) Procore needle.

and diagnostic yield of 22G Procore needle for EUS-FNA and biopsy of pancreatic cystic lesions. In a subgroup analysis of malignant lesions and lesions with a solid component, the adequacy for cyto-histological diagnosis of the samples obtained by 22G FNB needle was found to be 100% and 94.4% respectively, which is superior to conventional standard FNA needles[44]. Some studies looked at different aspects of FNB needle sampling, like stromal fragments in the sample allowing for a more precise histologic diagnosis, or FNB needles making the procedure quicker, and lower number of needle passes required with Procore needles when compared to standard needles[19,45-48]. There were several other studies done previously that showed that there was no improvement in diagnostic yield with FNB as compared to FNA needles. Strand et al did a study that did not show a significant advantage of using FNB over FNA in terms of being a core biopsy needle although it was comparable in terms of providing material for cytology[34]. However, this was a small study and there were also concerns about technical quality of the procedures. Vanbiervliet *et al*[33] compared the standard and core 22G needle and showed that the diagnostic accuracy was comparable for solid pancreatic lesions although each patient had two passes with the standard needle and one pass with the core needle, thus biasing the study. Alatawi *et al*[17] compared 22G FNA and FNB needles in 100 patients and concluded that despite similar diagnostic accuracy, FNB needles required lower number of needle passes and yielded samples of higher histological quality, thus mitigating previous studies on the limited contribution of FNB needles in pancreatic cancer work up.

From the above discussion, it is clear that Procore needles, both 19 gauge and 22 gauge, with reverse bevel technology has been very promising in obtaining samples for the diagnosis of solid mass lesions. In this pooled analysis, it has been shown that the 19G procore needle is better at obtaining samples for diagnosing solid mass lesions than 22G Procore needle. The sensitivity of the 19G needle is 91.6% as compared to 83.3% for the 22G. The difference in specificity is even higher with the 19G having 95.9% specificity while the 22G has a specificity of only 64.3% when it came to the adequacy of specimens and diagnostic accuracy with that histologic sample for solid mass lesions. Further studies are required to determine the factors that may have influenced the relatively low specificity of 22G Procore needle seen in this pooled analysis, which may include the differences in sample yield and method of obtaining the sample. Diagnostic odds ratio is defined as the odds of having the correct histologic etiology of the mass in positive as compared to negative EUS-FNB studies. To diagnose the histologic etiology of a solid mass lesion in the intestinal and extra-intestinal organs, the EUS-FNB using the 19G Procore needle had a very high diagnostic odds ratio (approximately 84 times) as compared to the 22G Procore needle (approximately 10 times). For example, if a core biopsy of solid pancreatic mass is done using a 19G Procore needle, the odds of having the correct histologic diagnosis is around 84 times as compared to only 10 times with the 22G needle. The positive likelihood ratio of a test is a gauge of how well the test identifies a disease state. Higher the positive likelihood ratio, the better the test performs in identifying the true disease status. On the other hand, a negative

likelihood ratio of a test is a gauge of how well the test performs in excluding a disease state. The lower the negative likelihood ratio, the better the test performs in excluding a disease. For diagnosing a solid mass lesion, EUS-FNB using a 19G Procore needle had a higher positive likelihood ratio than the 22G needle but the negative likelihood ratio was low for both of them. This indicates that the 19G Procore needle performs better in ruling in a diagnosis than the 22G needle though both of them fared fairly low in excluding a diagnosis.

In our study, the 19G Procore was found to be superior in almost every aspect. One limitation that this needle had was that the authors in these studies notably reported failures when it came to transduodenal passes with the 19G Procore needle. The FNB needle had to be advanced out of the echoendoscope while in the stomach before the scope could be passed into the duodenum[16,41]. This difficulty was not present with the 22G Procore needle where the FNB needle exited the sheath with relative ease in all the patients in the study by Bang *et al*[32]. Another limitation is that there are several factors influencing the diagnostic accuracy that include experience and expertise of the endosonographers and pathologists, as well as size and location of the lesion. Some of the studies had on-site pathologists and others did not and this may affect the difference in the diagnostic accuracy between the 19G and 22G core biopsies depending on whether they used them or not. When comparing diagnostic yield based on number of needle passes, comparing FNA and FNB needles in the same patient, although makes a study more statistically significant, would be difficult as subsequent needle passes would follow the same pathway as the first one and some studies[17,18] compared them in different patients to overcome this bias. The number of studies from which data was extracted was not equal for 19G (6 studies) and 22G (16 studies) as there were not as many studies done on the 19G yet, with only two studies that directly compared them, and this may have affected the results.

Heterogeneity among different studies was determined by drawing SROC curves and finding the AUC, since different studies might use slightly different criteria for staging. An AUC of 1 for any test indicates that the test is excellent. SROC curves for 19G Procore needle showed that the value for AUC was very close to 1, indicating that this needle has an excellent diagnostic value in detecting the correct histologic etiology of a solid mass lesion.

Studies with statistically significant results tend to be published and cited. Smaller studies may show larger treatment effects due to fewer case-mix differences (*e.g.,* patients with only early or late disease) than larger trials. This bias can be estimated by bias indicators and construction of funnel plots. This publication and selection bias may affect the summary estimates. Also, bias among studies can affect the shape of the funnel plot. In this meta-analysis and systematic review, bias calculations using Egger bias indicator[26] and Begg-Mazumdar bias indicator[27] showed no statistically significant bias. Furthermore, analysis using funnel plots showed no significant publication among the studies included in this analysis.

In conclusion, EUS 19G core biopsies have an excellent diagnostic value and seem to be superior to the EUS 22G biopsies in detecting the correct etiology for a solid mass lesion. The specificity and sensitivity are both higher for the 19G Procore needle when compared to the 22G Procore needle. Though the 22G may be easier to maneuver for lesions requiring transduodenal passes, the overall diagnostic accuracy is greater for 19G. In conclusion, 19G needles may be strongly considered over 22G needles when evaluating solid mass lesions. Further randomized controlled trials comparing the two needles directly are required for more definitive conclusions.

COMMENTS

Background

Procore fine needle biopsy needles have been found to have a diagnostic accuracy comparable to, if not better than the standard needles in diagnosing intestinal and extra-intestinal mass lesions. This is a meta-analysis and systematic review comparing the 19G and 22G core biopsy needles in making the correct etiologic diagnosis.

Research frontiers

Management of pancreatic solid mass lesions relies greatly on accuracy of diagnosis of these lesions. Research has been directed towards the various fine biopsy needles used in the diagnosis which will in turn affect the management and prognosis in a patient.

Innovations and breakthroughs

In the present study, the authors investigated the outcomes of two commonly used Procore needles in the diagnosis of solid mass lesions. This is the first meta-analysis that compares 19G procore and 22G procore needles with regards to their overall accuracy and efficacy.

Applications

This study gives information about both procore needles and their outcomes with solid mass lesions, thus helping the endoscopist in choosing the appropriate needle for their specific procedure.

Peer-review

This is an interesting paper and is worth to be published.

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META-ANALYSIS

Mucin expression and the pancreas: A systematic review and meta-analysis

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Abstract

AIM

To assess mucin expression in pancreatic premalignant and malignant states, and to establish its role as a prognostic marker.

METHODS

English Medical literature searches were conducted for "mucin" and "pancreas". Observational studies were included. Meta-analysis was performed by using Comprehensive meta-analysis software. Pooled odds ratios and 95%CIs were calculated.

RESULTS

Out of 949 eligible papers we found 20 according to the inclusion criteria, including 4262 patients, published till May 31, 2016. Mucin expression increased in pancreatic lesions with OR 10.206 (95%CI: 4.781-21.781, $P < 0.0001$). Measure of heterogeneity was high: Q = 296.973, df (Q) = 55.00, I^2 = 81.48%. We found a significant increase in the expression of MUC2, MUC4 and MUC5AC, 13.39, 118.43 and 13.91 times respectively, in pancreatic lesion in comparison with normal pancreatic tissue, and decreased expression of MUC5B.

CONCLUSION

Mucin expression may serve as prognostic marker for transformation of intraductal papillary mucinous neoplasms to ductal adenocarcinoma, for aggressiveness of the pancreatic tumor, and as targets for potential therapy.

Key words: Mucin; Pancreas; Pancreatic cancer; Gene expression

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Core tip: There is a higher mucin expression in intraductal papillary mucinous neoplasms (IPMN) and ductal pancreatic cancer. Mucin expression may be a bad prognostic factor. MUC2, MUC4, MUC5AC and probably MUC1, are expressed in IPMN advanced to ductal adenocarcinoma. These mucins are also bad prognostic factors for ductal adenocarcinoma.

and meta-analysis. *World J Meta-Anal* 2017; 5(2): 63-70 Available from: URL: http://www.wjgnet.com/2308-3840/full/v5/i2/63.htm DOI: http://dx.doi.org/10.13105/wjma.v5.i2.63

INTRODUCTION

Mucins are high-molecular-weight glycoproteins, heavily glycosylated, synthesized and secreted by all mucosal surfaces of the human body and have an important role in healthy state and malignant diseases[1-3]. Change in mucins synthesis and secretion may be primary event or secondary to carcinogenesis or inflammation.

There are 21 known mucin genes in the human genome, encode for 2 types of mucins: Secreted and membrane-bound[4]. Membrane-bound mucins are involved in cell signaling and have a role in cellular processes such as growth, immune modulation, motility and adhesion.

Pancreatic carcinogenesis is associated with genetic and epigenetic changes, than may affect MUCs (mucin genes). MUCs may be expressed *de novo* during carcinogenesis. Mucins have potential value for diagnosis and follow-up of pancreatic neoplasms and for therapeutic interventions[5]. Mucin expression patterns may serve as a criterion for classification of intraductal papillary mucinous neoplasms (IPMN).

Several studies looked at mucins expression, comparing pancreatic lesions with normal pancreatic tissue. MUC1, membrane-bound mucin, is expressed in normal pancreatic tissue, but there is no detectable MUC2, MUC4 and MUC5AC[6,7].

Secretion of MUC1 is associated with adenocarcinoma and high grade dysplasia in pancreatic intraepithelial neoplasia (PanIN)[8-10]. MUC1 is rarely expressed in IPMN.

Positive expression of MUC2 in IPMN (intestinal type) indicates progression to carcinoma with secretion of MUC1[8,11]. Absence of MUC2 expression (gastric type) implies benign phenotype. MUC1 is rarely expressed in mucinous cyst in one study, while in another study mucinous cysts were found positive for MUC1/DF3[12,13].

MUC4 secretion correlates to the severity of dysplasia in PanIN and a poor prognosis in patients with adenocarcinomas, but results are somewhat inconsistent in different studies[14-17]. Expression of MUC4 in pancreatic cancer cell line was associated with increased proliferation, motility, adhesion, aggregation and metastasis[18].

The 2015 American Gastroenterological Association guidelines define 3 high-risk features of pancreatic cyst for developing cancer: Cyst size > 3 cm, dilated pancreatic duct and mural nodule[19]. There are no characteristics of mucin expression in the cyst fluid or the epithelial lining, as a marker for carcinogenesis.

The aim of this metaanalysis and systematic review is to assess the knowledge about mucin expression in pancreatic premalignant and malignant states, and to understand the possible role of mucin expressions as prognostic markers.

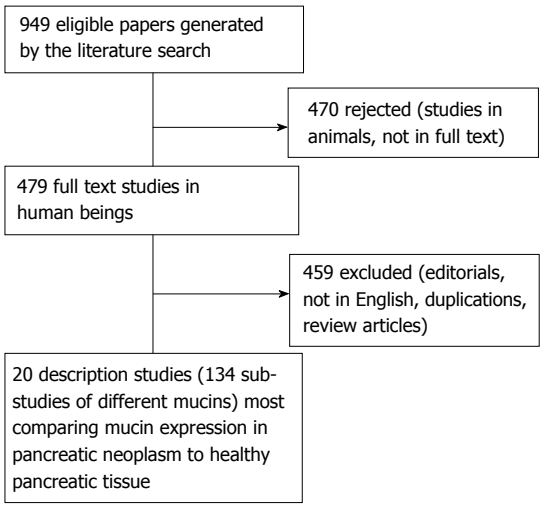


Figure 1 Flow chart of the articles identified for the meta-analysis.

MATERIALS AND METHODS

Search strategy

Searches were conducted for "mucin" and "pancreas" through May 31, 2016, using MEDLINE, PubMed, Scopus, EMBASE, and CENTRAL. Hand searches of articles references were also performed. Only fully published human studies in English were included (Figure 1).

Study selection

Observational studies about mucin expression in pancreatic tissue of cysts and adenocarcinoma were included. PRISMA guidelines for systematic reviews were strictly followed.

Data extraction

Author, country, year of publication, number of patients, and the number of positive staining were extracted. Data was stratified according to lesions (ductal adenocarcinoma, IPMN, mucinous cyst) and according to the mucin expressed (Table 1).

Statistical analysis

Metaanalysis was performed by using Comprehensive metaanalysis software (Version 3, Biostat Inc., Englewood, NJ, United States). Pooled odds ratios and 95%CIs were calculated for mucin expression in pre-malignant and malignant pancreatic lesions. In all methods used (IMH, ISH or RT-PCR) OR represents quantitatively the number of patients with higher expression.

Heterogeneity was evaluated by Cochran *Q*-test, and considered to be present when *Q*-test $P < 0.10$. I^2 statistic was used to measure the proportion of inconsistency. We calculated publication bias using funnel plot of standard error by log odds ratio. Even distribution of the studies denied significant publication bias.

RESULTS

Out of 949 eligible papers we found 20 according to

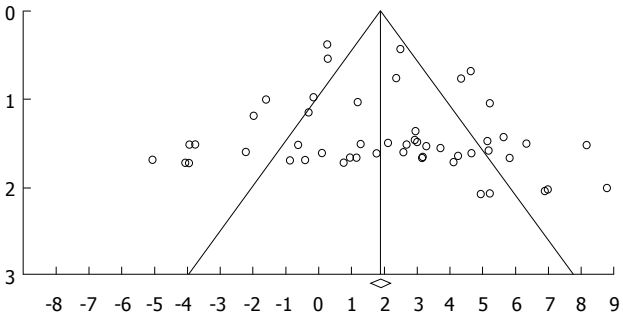


Figure 2 Funnel plot for publication bias.

Table 1 Summary of mucin expression in pancreatic lesions

Mucin gene	OR of mucin expression	*P*
MUC1	3.64	0.09
MUC2	13.39	0.05
MUC3	14.33	0.08
MUC4	118.43	< 0.001
MUC5AC	13.91	< 0.001
MUC5B	0.08	< 0.001
MUC6	0.52	0.41
MUC7	0	NA
Total mucin	9.99-21.72	< 0.001

OR: Odds ratio; NA: Not applicable.

the inclusion criteria, including 4262 patients, published till May 31, 2016 from 4 countries (Japan 10, United States 9, France 1, Norway 1)[6,8,9,11-15,20-32] (Figure 1). There are 134 sub-studies (stratifying data according to mucin types and lesions). In 104 sub-studies immunohistochemistry (IMH) has been used, in 20 sub-studies RT-PCR for RNA, and in10 histochemistry. Eleven studies and 84 sub-studies had also results of normal pancreatic tissue for comparison with the neoplastic lesion. Ductal adenocarcinoma was examined in 14 studies and 60 sub-studies (2206 cases); IPMN was examined in 12 studies and 46 sub-studies (1691 cases). There were 365 cases of mucinous or colloid carcinoma, mucinous cystic neoplasm, hyperplastic pancreatic lesion, chronic pancreatitis and pseudo cysts. Funnel plot denies a significant publication bias (Figure 2).

In the random-effect model, mucin expression was significantly higher in pancreatic lesions than in normal pancreatic tissue with OR 10.206 (95%CI: 4.781-21.781, $P < 0.0001$) (Figure 3). Measure of heterogeneity was high, demonstrated in the included studies: Q = 296.973, df (Q) = 55.00, I^2= 81.48%. OR for mucin expression in pancreatic ductal adenocarcinoma and IPMN was 9.99 with 95%CI: 3.68-27.15, $P < 0.001$, and 21.72 with 95%CI: 4.01-117.55, $P < 0.001$, respectively (Figure 4). OR for expression in pancreatic lesion of MUC1- 4, MUC5AC, MUC5B, MUC6 and MUC7, was 3.64 with 95%CI: 0.80-16.49, $P = 0.09$; 13.39 with 95%CI: 1.03-173.43, $P = 0.05$; 14.33 with 95%CI: 0.742-95.97, $P = 0.08$; 118.43 with 95%CI: 19.39-723.48, $P < 0.001$; 13.91 with 95%CI: 2.35-82.14, $P < 0.001$; 0.08 with 95%CI: 0.02-0.36, $P < 0.001$; 0.52 with 95%CI: 0.11-2.47, $P = 0.41$; respectively (Figure 5). MUC7 was never expressed in pancreatic lesion or normal tissue (Table 1).

Studies description

Yamada *et al*[20] using histochemical methods compared the mucin expression between malignant and benign tumors of the pancreas. They found significant higher expression of sialomucin (> 50% of glands) in malignant tumors and higher expression of neutral mucin (> 50% of glands) in benign tumors. Osako *et al*[21] demonstrated a significant contrast between expression of mammary type mucin and intestinal type mucin in carcinomas and intraductal papillary tumor. The oncogenic mucin antigens, Tn and sialyl Tn (STn), were expressed in malignant and premalignant states but not in normal pancreatic mucosa. Incomplete glycosylation of mucins that results in expression of T, Tn, and sialyl-Tn antigens in pancreatic adenocarcinoma was described by Terada *et al*[13,32]. They found increased expression of Tn antigen and STn antigen in comparison with normal pancreatic tissue, but the same expression of *MUC1* and T antigen. Similar findings were described for IPMN, which support the sequence of events from IPMN to adenocarcinoma. Yonezawa *et al*[8] found higher expression of *MUC1* in ductal adenocarcinoma than IPMN, and lower expression of *MUC2*. Invasive growth areas of IPMN had *MUC1* expression similar to adenocarcinoma. The same group demonstrated up regulation of *MUC5AC* mRNA in IPMN cases with a favorable prognosis, whereas such expression was not found in ductal adenocarcinoma cases with a poor prognosis[22].

Andrianifahanana *et al*[23] described a significant higher *MUC4* expression in adenocarcinoma tissue than in chronic pancreatitis or normal pancreatic tissue. Lüttges *et al*[9] found expression of *MUC2* in all IPMN and mucinous carcinoma cases of the pancreas but in only one of 35 of ductular adenocarcinoma cases. *MUC1* expression was only demonstrated in ductular adenocarcinoma tissue. The same group also found strong expression of *MUC5AC* and *MUC2* in mucinous cystic neoplasms of the pancreas, but no such expression of *MUC1* and *MUC6*[12]. Kim *et al*[24] found a significant higher expression of *MUC1, MUC5AC*, Md2, STn antigen and sulpho Lewis a antigen in ductal adenocarcinoma of the pancreas than in normal pancreatic tissue. Swartz *et al*[14] found higher expression of *MUC4* in invasive ductal adenocarcinoma of the pancreas than in PanIN. Expression was not demonstrated in normal pancreatic tissue. Nakamura *et al*[11] described 2 kinds of IPMN, according to *MUC2* expression with higher invasive property for *MUC2* positive than negative tumors. Terris *et al*[25] found increased expression of *MUC5AC* and *MUC2* in IPMN, similar to colloid carcinoma, and different from ductal adenocarcinoma where *MUC1* expression was increased. Horinouchi *et al*[6] found higher expression of *MUC1* and *MUC5AC* in ductal adenocarcinoma than in IPMN. *MUC2* was only expressed in IPMN of "dark phenotype". Saitou *et al*[15] found a

Study name	Subgroup within study	Comparison	Time point	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Osaka M	DF3 IMH ductal adenocarcinoma	Japan	1993	19.00	1.07	338.67	2.00	0.05
Osaka M	DF4 IMH IPMN	Japan	1993	0.02	0.00	0.47	-2.46	0.01
Osaka M	MRP IMH IPMN	Japan	1993	1001.00	18.00	55675.78	3.37	0.00
Osaka M	STn antigen IMH ductal adenocarcinoma	Japan	1993	6643.00	128.67	342958.99	4.37	0.00
Osaka M	STn antigen IPMN	Japan	1993	1001.00	18.00	55675.78	3.37	0.00
Osaka M	T antigen IMH ductal adenocarcinoma	Japan	1993	1.34	0.46	3.90	0.54	0.59
Osaka M	T antigen IMH IPMN	Japan	1993	3.67	0.19	71.54	0.86	0.39
Osaka M	Tn antigen IMH ductal adenocarcinoma	Japan	1993	6643.00	128.67	342958.99	4.37	0.00
Osaka M	Tn antigen IMH IPMN	Japan	1993	1001.00	18.00	55675.78	3.37	0.00
Terada T	MUC1 IMH SP IPMN	Japan	1996	0.11	0.00	2.60	-1.37	0.17
Terada T	STn antigen IMH SP ductal adenocarcinoma	Japan	1996	143.00	2.42	8467.01	2.38	0.02
Terada T	STn antigen IMH SP IPMN	Japan	1996	24.20	0.93	629.32	1.92	0.06
Terada T	Tn antigen IMH SP ductal adenocarcinoma	Japan	1996	143.00	2.42	8467.01	2.38	0.02
Terada T	Tn antigen IMH SP IPMN	Japan	1996	13.44	0.58	314.29	1.62	0.11
Yonezawa S	MUC2 RT-PCR IPMN	Japan	1999	172.62	9.56	3118.40	3.49	0.00
Yonezawa S	MUC5AC RT-PCR ductal adenocarcinoma	Japan	1999	20.52	1.10	382.54	2.02	0.04
Yonezawa S	MUC5AC RT-PCR IPMN	Japan	1999	569.44	29.39	11033.41	4.20	0.00
Andrianifanana M	MUC4 RT-PCR ductal adenocarcinoma	United States	2001	41.67	1.96	887.56	2.39	0.02
Andrianifanana M	MUC5AC RT-PCR chronic pancreatitis	United States	2001	0.42	0.01	11.92	-0.51	0.61
Andrianifanana M	MUC5AC RT-PCR ductal adenocarcinoma	United States	2001	0.01	0.00	0.18	-2.98	0.00
Andrianifanana M	MUC5B RT-PCR chronic pancreatitis	United States	2001	0.42	0.01	11.92	-0.51	0.61
Kim GE	MUC1 IMH ductal adenocarcinoma	United States	2002	12.33	5.24	29.02	5.75	0.00
Kim GE	MUC2 IMH ductal adenocarcinoma	United States	2002	8.42	0.44	159.89	1.42	0.16
Kim GE	MUC5AC IMH ductal adenocarcinoma	United States	2002	104.50	27.30	400.02	6.79	0.00
Kim GE	MUC6 IMH ductal adenocarcinoma	United States	2002	1.32	0.62	2.79	0.71	0.48
Kim GE	Nd2 IMH ductal adenocarcinoma	United States	2002	77.78	17.18	352.02	5.65	0.00
Kim GE	Sialyl Tn antigen IMH ductal adenocarcinoma	United States	2002	186.20	23.73	1460.83	4.97	0.00
Kim GE	Sulpho Lewis a IMH ductal adenocarcinoma	United States	2002	10.86	2.41	48.98	3.10	0.00
Swartz MJ	MUC4 IMH ductal adenocarcinoma	United States	2002	3591.86	180.43	71505.47	5.36	0.00
Swartz MJ	MUC4 IMH PanIN	United States	2002	287.13	17.19	4796.26	3.94	0.00
Terris B	MUC1 IMH colloid carcinoma	France	2002	2.20	0.07	64.90	0.46	0.65
Terris B	MUC1 IMH ductal adenocarcinoma	France	2002	62.33	2.13	1822.63	2.40	0.02
Terris B	MUC1 IMH IPMN	France	2002	1.12	0.05	26.83	0.07	0.94
Terris B	MUC2 IMH colloid carcinoma	France	2002	187.00	3.21	10884.81	2.52	0.01
Terris B	MUC2 IMH IPMN	France	2002	107.80	4.51	2576.92	2.89	0.00
Terris B	MUC3 IMH IPMN	France	2002	14.83	0.74	295.97	1.77	0.08
Terris B	MUC4 IMH ductal adenocarcinoma	France	2002	5.92	0.25	141.48	1.10	0.27
Terris B	MUC4 IMH IPMN	France	2002	27.13	1.33	554.23	2.14	0.03
Terris B	MUC5AC IMH colloid carcinoma	France	2002	23.80	0.89	633.53	1.89	0.06
Terris B	MUC5AC IMH ductal adenocarcinoma	France	2002	0.75	0.08	7.21	-0.25	0.80
Terris B	MUC5AC IMH IPMN	France	2002	71.40	2.81	1814.71	2.59	0.01
Terris B	MUC5B IMH ductal adenocarcinoma	France	2002	0.02	0.00	0.52	-2.34	0.02
Terris B	MUC5B IMH colloid carcinoma	France	2002	0.02	0.00	0.59	-2.27	0.02
Terris B	MUC5B IMH IPMN	France	2002	0.14	0.01	1.46	-1.64	0.10
Terris B	MUC6 IMH IPMN	France	2002	0.67	0.02	18.84	-0.23	0.82
Kanno A	MUC4 IHC IPMN	Japan	2006	341.00	12.90	9015.65	3.49	0.00
Kanno A	MUC5AC IHC hyperplastic tissue	Japan	2006	3.19	0.12	84.43	0.69	0.49
Kanno A	MUC5AC IHC IPMN	Japan	2006	1089.00	20.37	58214.67	3.44	0.00
Giorgadze TA	MUC1 IMH EUS-S ductal adenocarcinoma	United States	2006	3.33	0.44	25.39	1.16	0.25
Giorgadze TA	MUC2 IMH EUS-S ductal adenocarcinoma	United States	2006	0.20	0.03	1.47	-1.58	0.11
Giorgadze TA	MUC2 IMH SP ductal adenocarcinoma	United States	2006	2.64	0.10	69.88	0.58	0.56
Giorgadze TA	MUC5AC IMH EUS-S ductal adenocarcinoma	United States	2006	19.33	1.33	281.60	2.17	0.03
Giorgadze TA	MUC5AC IMH SP ductal adenocarcinoma	United States	2006	179.80	7.94	4070.43	3.26	0.00
Giorgadze TA	MUC6AC IMH EUS-S ductal adenocarcinoma	United States	2006	0.87	0.13	6.03	-0.14	0.89
Giorgadze TA	MUC6AC IMH SP ductal adenocarcinoma	United States	2006	0.02	0.00	0.38	-2.59	0.01
Streppel MM	MUC16 IMH PanIN	United States	2012	0.54	0.03	10.84	-0.40	0.69
				10.21	4.78	21.79	6.00	0.00

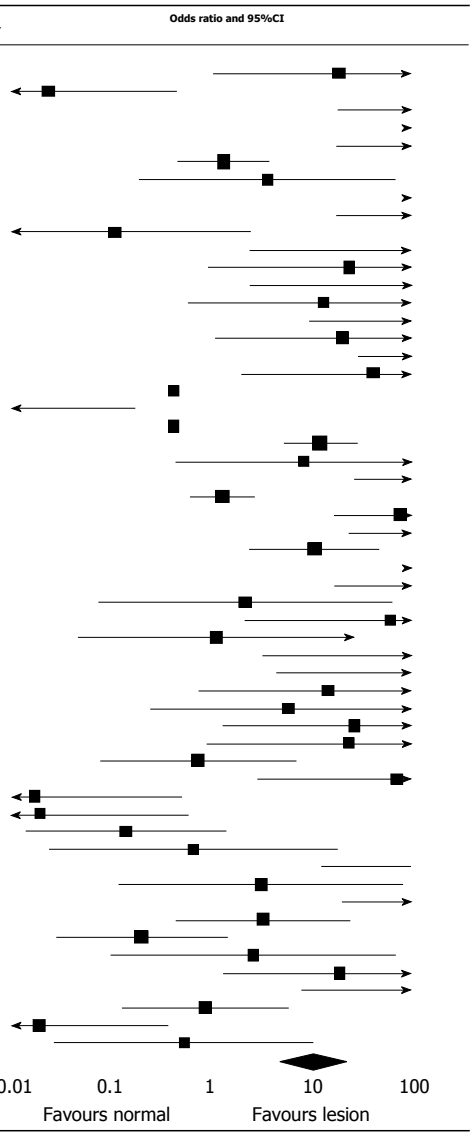
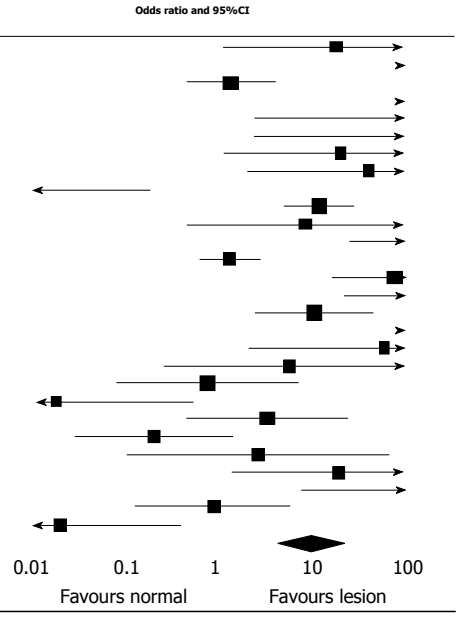


Figure 3 Metaanalysis of mucin expression in pancreatic lesions (20 studies, 134 sub-studies). PanIN: Pancreatic intraepithelial neoplasia; IPMN: Intraductal papillary mucinous neoplasms; STn: Sialyl Tn.

positive correlation between the strength of *MUC4* expression in ductal adenocarcinoma of the pancreas and aggressive behavior. Such a correlation could not be demonstrated for *MUC1*. Kanno *et al*[26] found *MUC4* and *MUC5AC* expression in adenoma and IPMN but not in normal or hyperplastic pancreatic tissue. Giorgadze *et al*[27] reviewed pancreatic 56 EUS-FNA specimens and 26 pancreatectomy specimens for expression profiles of *MUC1, MUC2, MUC5AC* and *MUC6*. *MUC5AC* expression was significantly higher in adenocarcinoma than in normal tissue both in EUS-FNA specimens and surgical specimens. Westgaard *et al*[28] found that in adenocarcinoma *MUC1* and *MUC4* expression was associated with a poor prognosis. Gonzalez Obeso *et al*[29] used alcian blue and mucicarmine stains in 11 pseudo cysts and 42 IPMNs or mucinous cysts aspirates. They could not demonstrate a significant difference in mucin staining between the various types of cysts. Streppel *et al*[30] found *MUC16* (CA125) expression in 81.5% of 200 pancreatic adenocarcinoma tissues, in comparison with none of 29 IPMN cases and in 2% of normal pancreatic tissues. Kitazono *et al*[31] looked at the expression rates of *MUC4* in intestinal-type IPMNs and gastric-type IPMNs using monoclonal antibodies 8G7 and 1G8. The expression rate of *MUC4* in the intestinal-type IPMNs was higher than in the gastric-type IPMNs. Maker *et al*[33] examined 40 cases of pancreatic IPMN comparing mucin expression in cases with high risk IPMN (with high grade dysplasia or carcinoma) and cases with low risk IPMN (with low grade dysplasia). They found a significant increase in *MUC2* and *MUC4* expression (10.0 ± 3.0 ng/mL and 20.6 ± 10.6 ng/mL *vs* 4.4 ± 1.2 ng/mL and 4.5 ± 1.4 ng/mL, $P = 0.03$, respectively). No change was demonstrated for *MUC1* and *MUC5AC*. This study is not included in the metaanalysis since numerical data is absent and only means of mucin expression are given.

A

Study name	Subgroup within study	Comparison	Time point	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Osaka M	DF3 IMH ductal adenocarcinoma	Japan	1993	19.00	1.07	338.67	2.00	0.05
Osaka M	STn antigen IMH ductal adenocarcinoma	Japan	1993	6643.00	128.67	342958.99	4.37	0.00
Osaka M	T antigen IMH ductal adenocarcinoma	Japan	1993	1.34	0.46	3.90	0.54	0.59
Osaka M	Tn antigen IMH ductal adenocarcinoma	Japan	1993	6643.00	128.67	342958.99	4.37	0.00
Terada T	STn antigen IMH SP ductal adenocarcinoma	Japan	1996	143.00	2.42	8467.01	2.38	0.02
Terada T	Tn antigen IMH SP ductal adenocarcinoma	Japan	1996	143.00	2.42	8467.01	2.38	0.02
Yonezawa S	MUC5AC RT-PCR ductal adenocarcinoma	Japan	1999	20.52	1.10	382.54	2.02	0.04
Andrianifanana M	MUC4 RT-PCR ductal adenocarcinoma	United States	2001	41.67	1.96	887.56	2.39	0.02
Andrianifanana M	MUC5AC RT-PCR ductal adenocarcinoma	United States	2001	0.01	0.00	0.18	-2.98	0.00
Kim GE	MUC1 IMH ductal adenocarcinoma	United States	2002	12.33	5.24	29.02	5.75	0.00
Kim GE	MUC2 IMH ductal adenocarcinoma	United States	2002	8.42	0.44	159.89	1.42	0.16
Kim GE	MUC5AC IMH ductal adenocarcinoma	United States	2002	104.50	27.30	400.02	6.79	0.00
Kim GE	MUC6 IMH ductal adenocarcinoma	United States	2002	1.32	0.62	2.79	0.71	0.48
Kim GE	Nd2 IMH ductal adenocarcinoma	United States	2002	77.78	17.18	352.02	5.65	0.00
Kim GE	Sialyl Tn antigen IMH ductal adenocarcinoma	United States	2002	186.20	23.73	1460.83	4.97	0.00
Kim GE	Sulpho Lewis a IMH ductal adenocarcinoma	United States	2002	10.86	2.41	48.98	3.10	0.00
Swartz MJ	MUC4 IMH ductal adenocarcinoma	United States	2002	3591.86	180.43	71505.47	5.36	0.00
Terris B	MUC1 IMH ductal adenocarcinoma	France	2002	62.33	2.13	1822.63	2.40	0.02
Terris B	MUC4 IMH ductal adenocarcinoma	France	2002	5.92	0.25	141.48	1.10	0.27
Terris B	MUC5AC IMH ductal adenocarcinoma	France	2002	0.75	0.08	7.21	-0.25	0.80
Terris B	MUC5B IMH ductal adenocarcinoma	France	2002	0.02	0.00	0.52	-2.34	0.02
Giorgadze TA	MUC1 IMH EUS-S ductal adenocarcinoma	United States	2006	3.33	0.44	25.39	1.16	0.25
Giorgadze TA	MUC2 IMH EUS-S ductal adenocarcinoma	United States	2006	0.20	0.03	1.47	-1.58	0.11
Giorgadze TA	MUC2 IMH SP ductal adenocarcinoma	United States	2006	2.64	0.10	69.88	0.58	0.56
Giorgadze TA	MUC5AC IMH EUS-S ductal adenocarcinoma	United States	2006	19.33	1.33	281.60	2.17	0.03
Giorgadze TA	MUC5AC IMH SP ductal adenocarcinoma	United States	2006	179.80	7.94	4070.43	3.26	0.00
Giorgadze TA	MUC6AC IMH EUS-S ductal adenocarcinoma	United States	2006	0.87	0.13	6.03	-0.14	0.89
Giorgadze TA	MUC6AC IMH SP ductal adenocarcinoma	United States	2006	0.02	0.00	0.38	-2.59	0.01
				9.99	3.68	27.15	4.51	0.00



B

Study name	Subgroup within study	Comparison	Time point	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Osaka M	DF3 IMH IPMN	Japan	1993	0.02	0.00	0.47	-2.46	0.01
Osaka M	MRP IMH IPMN	Japan	1993	1001.00	18.00	55675.78	3.37	0.00
Osaka M	STn antigen IMH IPMN	Japan	1993	1001.00	18.00	55675.78	3.37	0.00
Osaka M	T antigen IMH IPMN	Japan	1993	3.67	0.19	71.54	0.86	0.39
Osaka M	Tn antigen IMH IPMN	Japan	1993	1001.00	18.00	55675.78	3.37	0.00
Yonezawa S	MUC2 RT-PCR IPMN	Japan	1999	172.62	9.56	3118.40	3.49	0.00
Yonezawa S	MUC5AC RT-PCR IPMN	Japan	1999	569.44	29.39	11033.41	4.20	0.00
Terris B	MUC1 IMH IPMN	France	2002	1.12	0.05	26.83	0.07	0.94
Terris B	MUC2 IMH IPMN	France	2002	107.80	4.51	2576.92	2.89	0.00
Terris B	MUC3 IMH IPMN	France	2002	14.83	0.74	295.97	1.77	0.08
Terris B	MUC4 IMH IPMN	France	2002	27.13	1.33	554.23	2.14	0.03
Terris B	MUC5AC IMH IPMN	France	2002	71.40	2.81	1814.71	2.59	0.01
Terris B	MUC5B IMH IPMN	France	2002	0.14	0.01	1.46	-1.64	0.10
Terris B	MUC6 IMH IPMN	France	2002	0.67	0.02	18.84	-0.23	0.82
Kanno A	MUC4 IHC IPMN	Japan	2006	341.00	12.90	9015.65	3.49	0.00
Kanno A	MUC5AC IHC IPMN	Japan	2006	1089.00	20.37	58214.67	3.44	0.00
Streppel MM	MUC16 IMH PanIN	United States	2012	0.54	0.03	10.84	-0.40	0.69
				21.72	4.01	117.55	3.57	0.00

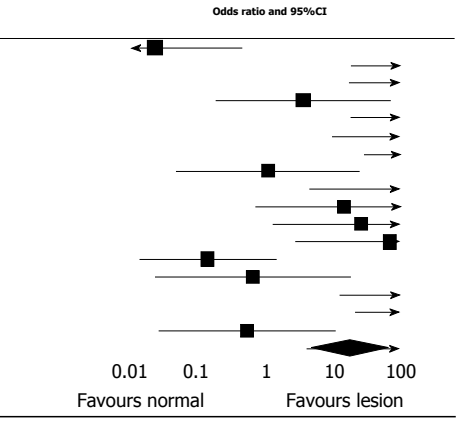


Figure 4 Meta-analysis of mucin expression in pancreatic lesions, sub-studies of different lesions. A: Ductal adenocarcinoma; B: Intraductal papillary mucinous neoplasm (20 studies, 102 sub-studies). PanIN: Pancreatic intraepithelial neoplasia; IPMN: Intraductal papillary mucinous neoplasms; STn: Sialyl Tn.

DISCUSSION

Mucin is an important component of the mucus layers protecting epithelial surfaces of the respiratory, digestive, urinary and reproductive organs, and as such was studied intensively. The role of mucin in exocrine/endocrine gland such as the pancreas is less understood. Most of the studies about pancreatic mucin expression involved malignant transformation and characteristics of pancreatic cysts. In Table 1 we summarized the knowledge about mucin expression in the pancreas, including the findings of our metaanalysis.

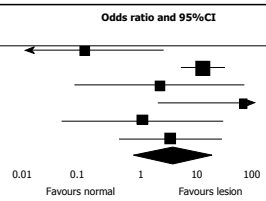
In our metaanalysis we found a significant increase in the expression of *MUC2*, *MUC4*, and *MUC5AC*, 13.39, 118.43 and 13.91 times respectively, in pancreatic lesion in comparison with normal pancreatic tissue (Table 1), and decreased expression of MUC5B. The results for *MUC1*, *MUC3*, *MUC6*, Tn and STn were not statistically significant.

Exploring individual studies some different and inconsistent finding are presented, but it is obvious that higher malignant behavior of IPMN and transfer into ductal adenocarcinoma is characterized by increased expression of *MUC2*, *MUC4* and *MUC5AC*[9,12-15,20,21,23,26-28,33]. The expression of these mucins in the ductal adenocarcinoma implied a bad prognosis. *MUC1* expression, even though did not reach significance in the metaanalysis, was also a marker for bad prognosis in ductal adenocarcinoma[8,24,28].

IPMN could be originates from the pancreatic main duct, or side-branches, being of gastric type (*MUC5AC* is expressed in dark cells) or of intestinal type (*MUC2* is expressed in clear cells). Gastric IPMNs are *MUC1* and *MUC2* negative, usually located in the branch small ducts, and rarely develop into cancer. Intestinal IPMNs are *MUC1* negative but *MUC2* positive. However, when they transform into cancer, the *MUC1* becomes positive. They are mostly located in the main duct. *MUC4* expression in IPMNs may help to distinguish intestinal

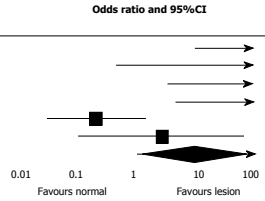
A

Study name	Subgroup within study	Comparison	Time point	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Terada T	MUC1 IMH SP IPMN	Japan	1996	0.11	0.00	2.60	-1.37	0.17
Kim GE	MUC1 IMH ductal adenocarcinoma	United States	2002	12.33	5.24	29.02	5.75	0.00
Terris B	MUC1 IMH colloid carcinoma	France	2002	2.20	0.07	64.90	0.46	0.65
Terris B	MUC1 IMH ductal adenocarcinoma	France	2002	62.33	2.13	1822.63	2.40	0.02
Terris B	MUC1 IMH IPMN	France	2002	1.12	0.05	26.83	0.07	0.94
Giorgadze TA	MUC1 IMH EUS-S ductal adenocarcinoma	United States	2006	3.33	0.44	25.39	1.16	0.25
				3.64	0.80	16.49	1.68	0.09



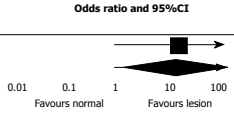
B

Study name	Subgroup within study	Comparison	Time point	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Yonezawa S	MUC2 RT-PCR IPMN	Japan	1999	172.62	9.56	3118.40	3.49	0.00
Kim GE	MUC2 IMH ductal adenocarcinoma	United States	2002	8.42	0.44	159.89	1.42	0.16
Terris B	MUC2 IMH colloid carcinoma	France	2002	187.00	3.21	10884.81	2.52	0.01
Terris B	MUC2 IMH IPMN	France	2002	107.80	4.51	2576.92	2.89	0.00
Giorgadze TA	MUC2 IMH EUS-S ductal adenocarcinoma	United States	2006	0.20	0.03	1.47	-1.58	0.11
Giorgadze TA	MUC2 IMH SP ductal adenocarcinoma	United States	2006	2.64	0.10	69.88	0.58	0.56
				13.39	1.03	173.43	1.98	0.05



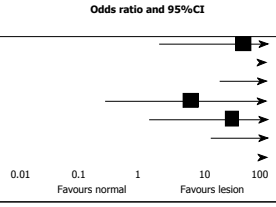
C

Study name	Subgroup within study	Comparison	Time point	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Terris B	MUC3 IMH IPMN	France	2002	14.83	0.74	295.97	1.77	0.08
				14.83	0.74	295.97	1.77	0.08



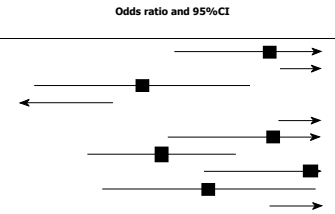
D

Study name	Subgroup within study	Comparison	Time point	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Andrianifanana M	MUC4 RT-PCR ductal adenocarcinoma	United States	2001	41.67	1.96	887.56	2.39	0.02
Swartz MJ	MUC4 IMH ductal adenocarcinoma	United States	2002	3591.86	180.43	71505.47	5.36	0.00
Swartz MJ	MUC4 IMH PanIN	United States	2002	287.13	17.19	4796.26	3.94	0.00
Terris B	MUC4 IMH ductal adenocarcinoma	France	2002	5.92	0.25	141.48	1.10	0.27
Terris B	MUC4 IMH IPMN	France	2002	27.13	1.33	554.23	2.14	0.03
Kanno A	MUC4 IHC IPMN	Japan	2006	341.00	12.90	9015.65	3.49	0.00
				118.43	19.39	723.48	5.17	0.00



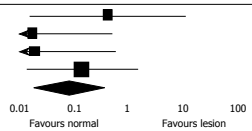
E

Study name	Subgroup within study	Comparison	Time point	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Yonezawa S	MUC5AC RT-PCR ductal adenocarcinoma	Japan	1999	20.52	1.10	382.54	2.02	0.04
Yonezawa S	MUC5AC RT-PCR IPMN	Japan	1999	569.44	29.39	11033.41	4.20	0.00
Andrianifanana M	MUC5AC RT-PCR chronic pancreatitis	United States	2001	0.42	0.01	11.92	-0.51	0.61
Andrianifanana M	MUC5AC RT-PCR ductal adenocarcinoma	United States	2001	0.01	0.00	0.18	-2.98	0.00
Kim GE	MUC5AC IMH ductal adenocarcinoma	United States	2002	104.50	27.30	400.02	6.79	0.00
Terris B	MUC5AC IMH colloid carcinoma	France	2002	23.80	0.89	633.53	1.89	0.06
Terris B	MUC5AC IMH ductal adenocarcinoma	France	2002	0.75	0.08	7.21	-0.25	0.80
Terris B	MUC5AC IMH IPMN	France	2002	71.40	2.81	1814.71	2.59	0.01
Kanno A	MUC5AC IHC hyperplastic tissue	Japan	2006	3.19	0.12	84.43	0.69	0.49
Kanno A	MUC5AC IHC IPMN	Japan	2006	1089.00	20.37	58214.67	3.44	0.00
Giorgadze TA	MUC5AC IMH EUS-S ductal adenocarcinoma	United States	2006	19.33	1.33	281.60	2.17	0.03
Giorgadze TA	MUC5AC IMH SP ductal adenocarcinoma	United States	2006	179.80	7.94	4070.43	3.26	0.00
				13.91	2.35	82.14	2.91	0.00



F

Study name	Subgroup within study	Comparison	Time point	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Andrianifanana M	MUC5B RT-PCR chronic pancreatitis	United States	2001	0.42	0.01	11.92	-0.51	0.61
Terris B	MUC5B IMH ductal adenocarcinoma	France	2002	0.02	0.00	0.52	-2.34	0.02
Terris B	MUC5B IMH colloid carcinoma	France	2002	0.02	0.00	0.59	-2.27	0.02
Terris B	MUC5B IMH IPMN	France	2002	0.14	0.01	1.46	-1.64	0.10
				0.08	0.02	0.36	-3.31	0.00



G

Study name	Subgroup within study	Comparison	Time point	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	*Z*-value	*P*-value
Kim GE	MUC6 IMH ductal adenocarcinoma	United States	2002	1.32	0.62	2.79	0.71	0.48
Terris B	MUC6 IMH IPMN	France	2002	0.67	0.02	18.84	-0.23	0.82
Giorgadze TA	MUC6AC IMH EUS-S ductal adenocarcinoma	United States	2006	0.87	0.13	6.03	-0.14	0.89
Giorgadze TA	MUC6AC IMH SP ductal adenocarcinoma	United States	2006	0.02	0.00	0.38	-2.59	0.01
				0.52	0.11	2.47	-0.83	0.41

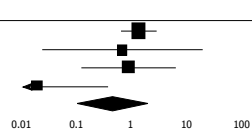


Figure 5 Meta-analysis of mucin expression in pancreatic lesions, sub-studies of different mucins. A: MUC1; B: MUC2; C: MUC3; D: MUC4; E: MUC5AC; F: MUC5B; G: MUC6 (17 studies, 104 sub-studies). PanIN: Pancreatic intraepithelial neoplasia; IPMN: Intraductal papillary mucinous neoplasms; STn: Sialyl Tn.

IPMNs from the safer gastric-type IPMNs.

Our meta-analysis has some limitations, since the methods of mucin expression measurement, and the definition of the pancreatic lesion may be inaccurate. There is heterogeneity regarding detection of mucin expression and disease classification. In some studies

immunohistochemistry was used for protein detection and in other RT-PCR or *in situ* hybridization for RNA detection. The definition of pancreatic mucinous cyst and side-branch or main-duct IPMN (Previously IPMT) also was changed during the last decade, and the results of different mucins expression in different lesions should be taken with caution. Also PanIN (pancreatic intra epithelial neoplasia), the pancreatic gland equivalent of adenomatous change or dysplasia, has been never studied in the context or mucin genes expression.

In conclusion, expression of *MUC2*, *MUC4*, *MUC5AC* and probably *MUC1*, may serve as prognostic marker for transformation of IPMN to ductal adenocarcinoma, for aggressiveness of the pancreatic tumor, and as targets for potential therapy. Further studies are needed to establish these observations.

COMMENTS

Background

Pancreatic carcinogenesis is associated with genetic and epigenetic changes, that may affect mucin genes. Certain mucins are expressed during carcinogenesis, while specific patterns have been recognized in pre-malignant and malignant lesions.

Research frontiers

Assessing mucin expression in pancreatic premalignant and malignant states, and to establish its role as a prognostic marker.

Innovations and breakthroughs

Mucin expression was higher in pancreatic lesions than in healthy pancreatic tissue: OR 10.206 (95%CI: 4.781-21.781, $P < 0.0001$).

Applications

The author found a significant increase in the expression of *MUC2*, *MUC4* and *MUC5AC*, 13.39, 118.43 and 13.91 times respectively, in pancreatic lesion in comparison with normal pancreatic tissue, and decrease expression of MUC5B.

Peer-review

This is a very good paper, with a large amount of interesting data and work. The analysis is conducted respecting the protocols of meta-analysis.

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Contents

Bimonthly Volume 5 Number 3 June 26, 2017

MINIREVIEWS

71 Diffusion tensor imaging beyond brains: Applications in abdominal and pelvic organs

Wang YT, Li YC, Kong WF, Yin LL, Pu H

World Journal of Meta-Analysis
Volume 5 Number 3 June 26, 2017

Contents

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MINIREVIEWS

Diffusion tensor imaging beyond brains: Applications in abdominal and pelvic organs

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Abstract

Functional magnetic resonance imaging (MRI) provided critical functional information in addition to the anatomic profiles offered by conventional MRI, and has been enormously used in the initial diagnosis and followed evaluation of various diseases. Diffusion tensor imaging (DTI) is a newly developed and advanced technique that measures the diffusion properties including both diffusion motion and its direction *in situ*, and has been extensively applied in central nerve system with acknowledged success. Technical advances have enabled DTI in abdominal and pelvic organs. Its application is increasing, yet remains less understood. A systematic overview of clinical application of DTI in abdominal and pelvic organs such as liver, pancreas, kidneys, prostate, uterus, *etc*., is therefore presented. Exploration of techniques with less artifacts and more normative post-processing enabled generally satisfactory image quality and repeatability of measurement. DTI appears to be more valuable in the evaluation of diffused diseases of organs with highly directionally arranged structures, such as the assessment of function impairment of native and transplanted kidneys. However, the utility of DTI to diagnose focal lesions, such as liver mass, pancreatic and prostate tumor, remains limited. Besides, diffusion of different layers of the uterus and the fiber structure disruption can be depicted by DTI. Finally, a discussion of future directions of research is given. The underlying heterogeneous pathologic conditions of certain diseases need to be further differentiated, and it is suggested that DTI parameters might potentially depict certain pathologic characterization such as cell density. Nevertheless, DTI should be better integrated into the current multi-modality evaluation in clinical practice.

Key words: Functional magnetic resonance imaging; Diffusion tensor imaging; Abdomen; Pelvis; Kidney

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Core tip: As a newly developed and advanced technique of functional magnetic resonance imaging, diffusion tensor imaging (DTI) measures the diffusion properties

including anisotropy. After its successful application in brains, technical advances have now enabled DTI in abdominal and pelvic organs. We herein give a systematic overview of clinical application of DTI in abdominal and pelvic organs such as liver, pancreas, kidneys, prostate, uterus, *etc*. DTI appears to be more valuable in the evaluation of diffused diseases of organs with highly directionally arranged structures, such as the assessment of function impairment of native and transplanted kidneys. However, the utility of DTI to diagnose focal lesions remains limited. It is suggested that DTI parameters might potentially depict certain pathologic characterization such as cell density.

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INTRODUCTION

As conventional magnetic resonance imaging (MRI) offers excellent anatomic information and has gained considerable success in the disease diagnosis throughout the body, functional assessment becomes available with the rapid development of related techniques. Considering the radiation caused by nuclear medicine examinations and the risk of nephrogenic systemic fibrosis in enhanced MRI scans, unenhanced MRI techniques have gained special clinic interest[1]. Diffusion-weighted imaging (DWI), which uses motion of intrinsic water molecules as genuine contrast was explored, then diffusion tensor imaging (DTI) made a step further and detects diffusion properties along at least six different directions, from which the main diffusion direction and the degree of diffusion anisotropy can be calculated[2]. A frequently used index to measure diffusion anisotropy is the fractional anisotropy (FA), ranges from 0 (isotropic: No preferred direction) to 1 (full anisotropy: Only one direction)[3]. The collected data can be converted to gray-scaled FA-maps, color-coded orientation image, and furthermore, tractography that enables 3D reconstruction[4]. Such data provided unique insight into the tissue microstructure, especially those with highly direction preference.

DTI has been traditionally applied to the brain, where tractography was developed to visualize white matter fiber bundles, and microstructural injuries of white matter fiber tracts were quantified[5]. It has been extensively used in the evaluation of brain tumor, injury, degeneration, *etc*.[5-7]. Although abdominal and pelvic MRI encountered some problems such as motion artifacts when first introduced, various techniques such as respiratory triggering and breath-hold imaging have sufficiently improved the image quality[8,9]. Accordingly, the utility of DTI is rapidly extending. However, DTI of abdomen and pelvis was relatively inadequately understood. Furthermore, DTI of various organs may have different clinical emphasis and challenges due to these distinct structures and physiologies. This review aims to give a systematic overview of clinical application of DTI in abdominal and pelvic organs such as liver, pancreas, kidneys, uterus, prostate, *etc.*, and discuss potential future research directions of the above-mentioned issues.

DTI OF THE LIVER

Technical perspectives

Both 1.5T and 3T MRI devices have been used in liver DTI. Usually, a preliminary T2-weighted single-shot turbo spin echo sequence was required for anatomical localization. The coronal DTI was then acquired using the in-built single-shot echo planar imaging (EPI) sequence. Fat-saturation with the spectral adiabatic inversion recovery approach can be employed to avoid chemical-shift artefacts. Li *et al*[10] reported that good image quality, acceptable scan time and reasonable FA/ADC values were acquired using diffusion-encoding directions of 9 with *b*-value of 0.300 s/mm^2. The effect of respiratory and cardiac motion in liver DTI was assessed[11]. Although some study reported that respiratory motion tended to increase DTI metrics (mainly mean diffusivity), some researchers also suggest to acquire DTI during free breathing and to adjust respiratory mismatch by post-processing[12,13]. The left lobe appeared to present increased FA and mean diffusivity during systole, but the right lobe was less affected by cardiac motion[12]. Regarding the repeatability of diffusion-related parameters, both apparent diffusion coefficient (ADC, measured in DWI) and FA had relatively low degrees of variation on both intra-session and inter-session basis in general, but the right lobe values were considered more reliable than left lobes[11]. The normal images of hepatic DTI are presented in Figure 1.

DTI findings in livers with various pathologies

Diffusion studies in liver have been advocated as a tool to stage liver fibrosis, based on the assumption that fibrosis can be reflected by changes of diffusion properties. Whereas DWI is commonly used for such purposes, few studies reported DTI results. Two studies performed liver DTI on a 1.5T and a 3T scanner respectively, and both reported that conventional DWI performed better than DTI for the diagnosis of fibrosis and inflammation, and concluded that ADC values measured on DWI had the potential for fibrotic and inflammatory grading. The FA showed a trend toward higher levels with increasing inflammatory grade and fibrotic stage, but was of less diagnostic value. It was explained that many other non-specific pathologic processes could lead to FA elevation as well[14,15].

For focal mass-like lesions assessment, the literature is sparse. Erturk *et al*[16] reported that metastases tended to have low ADCs and high FA values, cysts had high

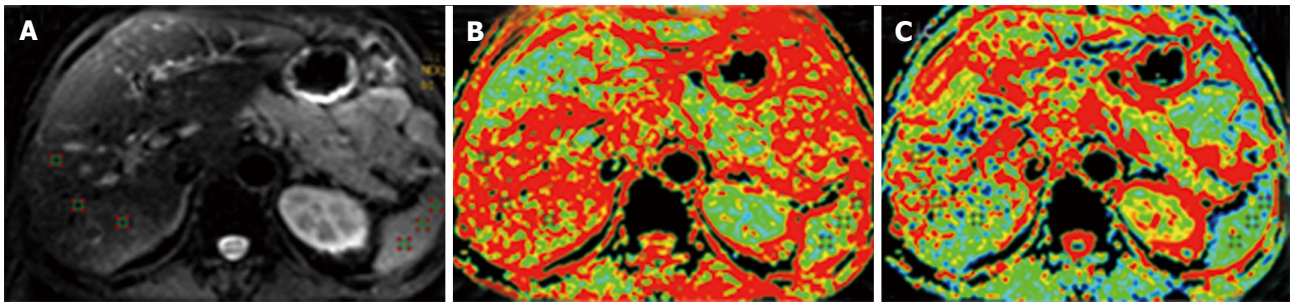


Figure 1 Normal images of hepatic diffusion tensor imaging. A: Diffusion image (*b* value of 0), mainly presenting the anatomic profiles; B: Fractional anisotropy map of the liver, presenting as the pseudo-colored image; C: Apparent diffusion coefficient map of the liver, presenting as the pseudo-colored image as well (Li *et al*[10], 2015; open access from *PlosOne*, permission confirmed).

ADCs and low FA values, and hemangiomas had high ADCs and high FA values. ADC had a better diagnostic performance for discriminating metastases from benign hepatic lesions than FA values (areas under the curve (Az values): 0.88 for ADC and 0.73 for FA), but FA had excellent ability to discriminate cysts from hemangiomas (Az value: 0.96)[16]. Another study revealed that hepatocellular carcinomas presented significantly lower ADC and higher mean FA value than normal liver regions, but diagnostic cutoff values, diagnostic accuracy and the comparison between ADC and FA were not given[10]. In general, DTI can play a supportive role in definition of focal liver lesion pathology.

DTI OF THE PANCREAS

The pancreas is a glandular organ with complex exocrine microstructure and endocrine microvascular physiology, and very few studies reported pancreatic DTI results. The normal images of pancreatic DTI are presented in Figure 2. A small sampled trial by Nissan *et al*[17] compared pancreatic DTI scans between healthy volunteers and patients with pancreatic-ductal-adenocacinoma. Fat-suppressed, respiratory triggered twice refocused spin-echo sequence, and *b*-values of 0, 100 and 500 s/mm^2 were used. They found a significant reduction in the directional diffusion coefficients and a lower contribution of fast intra-voxel-incoherent-motion (IVIM) component at $b \leqslant 100$ s/mm^2 in the malignant lesion[17].

Another larger sampled study focused on patients with acute pancreatitis (AP). It reported that both FA and ADC value from DTI could be employed to differentiate AP from normal pancreas, and also differentiate edema AP from necrosis AP. Furthermore, both ADC and FA value of pancreas had a negative correlation with the severity of AP (measured by MRI severity index). The authors discussed that the aggravation of pancreatic microcirculation ischemia, which played a key role in the transition from pancreatic edema to necrosis, could be detected by ADC and FA decreases[18]. DTI may spare the patients from radiation exposure of commonly used CT, and showed the potential to offer additional pathologic information to conventional MRI.

DTI OF THE KIDNEYS

Technical perspectives

Usually, a rapid T2-weighted sequence axial and coronal to the body axis were obtained for morphological evaluation. Then, coronal DTI were obtained with EPI. Several studies explored the optimal imaging parameters for anisotropy measurement. In the study of Kataoka *et al*[19], five different sequences with different parameters including respiration-triggered acquisition or multiple breath-holding, different slice thicknesses and different numbers of signal averaging and *b*-values were compared. It determined that the optimal sequence used respiratory triggering including a 3-mm slice thickness, three signal averages, and *b*-values of 0, 200 or 400 s/mm^2, which allowed the largest cortex–medulla difference of FA. Another study reported to have achieved high-resolution scans by free-breathing approaches, using a navigator-triggered sequence[20]. A later study registered DTI images of native and transplanted kidneys, using a multimodal nonrigid registration algorithm, and revealed that respiratory triggering was not necessary to measure diffusion parameters in transplanted kidneys, but still appeared advantageous in native kidneys[21]. However, these studies were small sampled, and based on the strategy to increase acquisition time, which lasted for 6 to 8 min and therefore the effect of respiratory motion needed to be properly handled. But some trials adopting shorter acquisition time appears reasonable to use breath-held, or even free-breathing approaches as well[22-24]. The influence of the number of encoding directions on image quality was explored; a preliminary study reported that the best image quality was visually assessed for images acquired with 15 and 32 encoding directions[25]. DTI at 1.5T and 3T were compared, researchers showed renal DTI with a 3T scanner had significant better signal to noise ratio (SNR) than that with a 1.5T scanner, although FA and ADCs at 3T did not significantly differ from that at 1.5T[26,27]. Indeed, increasing studies are using 3T systems to perform renal DTI.

Normal values and repeatability of renal DTI

In the renal structures, especially in the renal medulla,

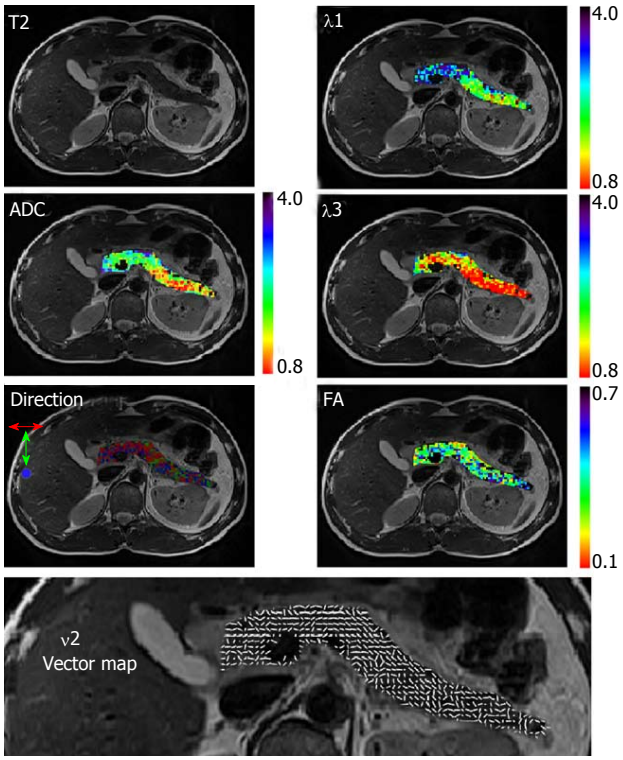


Figure 2 Normal images of pancreatic diffusion tensor imaging. Maps were overlaid on the corresponding T2 weighted image. The direction map presents in three colors the direction of the 1st principal eigenvector; red: Left to right direction; green: Head to feet direction; and blue: Anterior to posterior direction. Vector map presents in white sticks the direction of the 1st principal eigenvector (Nissan *et al*[17], 2014; open access from *PlosOne*, permission confirmed). FA: Fractional anisotropy; ADC: Apparent diffusion coefficient.

diffusion properties are expected to be anisotropic as a consequence of the radial orientation of tubules, collecting ducts, and blood vessels, which are the basis for the application of DTI[28]. Indeed, kidney becomes the most explored organ to perform DTI among abdominal and pelvic structures up to date. The normal images of renal DTI are presented in Figure 3.

The medullary FA value (ranged from 0.32 to 0.45) was reported to be higher than the cortical FA value (ranged from 0.24 to 0.28), whereas the cortical ADC (ranged from 2.21 to 2.39 × 10^{-3} mm^2/s) was higher than the medullary ADC (ranged from 1.87 to 1.99 × 10^{-3} mm^2/s)[24,29,30]. This can be attributed to a more orientated architecture of the renal medulla than the cortex. One study reported that medullary FA values in women were lower than those in men, and medullary FA positively correlated with estimated glomerular filtration rate (eGFR)[29].

Repeatability is another issue concerned in clinical practice. Studies exhibited that the intra- and inter-observer measurements correlated well: No significant difference was noted between different observers, and the within-subject coefficient of variation obtained for both the ADC and FA values were less than 10% in the analyses[9,20,24]. Factors that may potentially influence the diffusion parameters include hydration status and renal blood flow, *etc.* The study by Müller *et al*[31] showed significantly decreased ADC values in the kidneys of dehydrated healthy volunteers that increased upon rehydration, which could be attributed to the increase in GFR and osmotically driven water motion in the kidney. To reduce the inter-individual variation, fluid intake was suggested to be restricted prior to the scans. It has also been reported that ADC of the renal cortex and FA values of the renal medulla tended to elevate as the blood flow increased, which should be considered when interpreting DTI data[9].

DTI findings in kidneys with various pathologies

Diffused renal diseases such as chronic kidney disease usually lead to renal function impairment. Studies showed the feasibility of DTI to assess such conditions, inferring that the reduction of diffusion parameters was possibly caused by tubular atrophy, interstitial fibrosis, cellular infiltration, and the scarring of glomeruli. The parenchymal ADC and FA of kidneys was showed significantly lower in patients than healthy controls, regardless of whether eGFR was reduced. Both the renal ADC and FA values (both cortical and medullary) correlated with eGFR, and inversely correlated with serum creatinine and blood urea nitrogen[22,32]. Another article proposed the medullary FA value to be the main parameter for assessing renal function damage[33]. Relations between diffusion property changes and specific pathologic processes were investigated. The study of Liu *et al*[32] found that renal FA values (both cortical and medullary) negatively correlated with glomerular lesion and tubulointerstitial injury. Whereas another study investigating chronic glomerulonephritis concluded that cortical FA negatively correlated with the percentage of glomerulosclerosis, and medullary FA negatively correlated with tubulointerstitial fibrosis[34]. Some studies employed DTI to assess diabetic nephropathy (DN), reporting that both mean medullary FA and ADC were significantly lower in diabetics (even with eGFR > 60 mL/min per 1.73 m^2) than in controls, indicating the possibility of early identification of diabetics at risk of DN progression by DTI[35]. More recently, DTI was used to evaluate renal function in the follow-up of patients with autosomal dominant polycystic kidney disease[36].

For focal lesions in kidneys, the literature is sparse. A recent study used DTI to differentiate clear-cell renal cell carcinoma from low-fat renal angiomyolipomas (RAML). With the *b*-value of 0, 800 s/mm^2 and the cutoff FA value of 0.254, DTI reached a sensitivity of 100%, and a specificity of 73.3% for the differentiation[37]. However, other tumors were poorly reported so far.

DTI for the evaluation of transplanted kidneys

Renal transplantation has been established as the widely-accepted treatment for patients with end-stage renal diseases. Given the shortage of clinically available donor kidneys and the significant incidence of allograft dysfunction, noninvasive and accurate assessment of

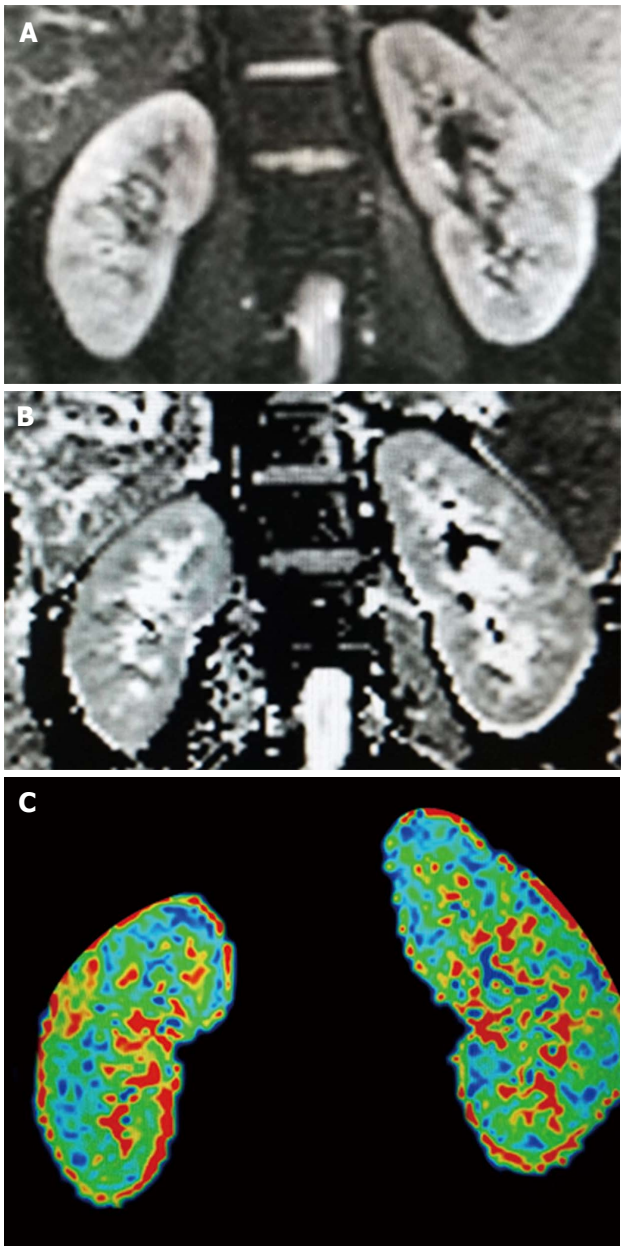


Figure 3 Normal images of renal diffusion tensor imaging. A: Diffusion image (*b*-value of 0), mainly presenting the anatomic profiles; B: Apparent diffusion coefficient map of the kidneys; C: Fractional anisotropy map of the kidneys, presenting as the pseudo-colored image.

the allograft renal function becomes critical to ensure the success of transplantation. Several studies explored the utility of DTI for the functional assessment. The medullary FA exhibited a high correlation with eGFR, and was proposed as a valuable indicator of allograft function[38,39]. Lanzman *et al*[38] also found that the corticomedullary difference in FA values was lower in functionally impaired renal allografts. Hueper *et al*[40] compared the DTI parameters between allografts with initial graft function and delayed graft function, and both FA and ADC exhibited an inverse correlation with the amount of renal fibrosis. These results indicated that DTI might become a sensitive biomarker of allograft function with the information of anisotropy.

DTI OF THE PROSTATE

Technical perspectives

The introduction of ultra-fast EPI sequences and parallel imaging techniques enabled the application of DTI to the prostate[41]. Both 1.5T and 3T scanners were used to perform prostatic DTI, but it is commonly accepted that 3T or even higher magnetic field systems can lead to higher SNR, improved spatial and temporal resolution[42]. Several different numbers of diffusion-encoding directions were tested, and all resulted satisfactory imaging quality in the study by Kim *et al*[43]. Reduced field-of-view acquisition was attempted in another study, generating high-resolution DTI of the prostate, which could potentially enable a more accurate detection of focal tumors[44].

Normal values of prostatic DTI

Prostate gland consists of various vascular, neural, and other anisotropic water paths, and there are distinct structural arrangements among central gland (CG), peripheral zone (PZ) and periprostatic neurovascular tracts, which make the DTI potentially applicable. Besides, the prostate is also an organ under the effect of the hormones and has dynamic changes as the age grows. In 2004, *in vivo* prostatic DTI were performed on six subjects, reporting a relatively high FA value of the PZ and CG of around 0.4. Later studies recorded lower FA values, and observed significant differences in the FA value between PZ (ranged from 0.16 to 0.21) and CZ (ranged from 0.26 to 0.37)[44,45]. Age-related changes of normal prostate were also assessed. The FA and ADC values in the normal prostatic PZ showed an age-dependent pattern, as FA decreases and ADC increases with age. Whereas the FA and ADC in CZ did not appear to be significantly age-related[46].

DTI for the diagnosis of prostate cancer and evaluation of periprostatic neurovascular bundles

Despite recent advances in MRI, the extent and aggressiveness of prostate cancer remain diagnostic challenges for radiologists. As the reliance on DWI increases in the clinical practice, DTI with additional anisotropic information was explored. An earlier study observed decreased FA values in the peripheral cancerous tissues compared with the normal peripheral portion[47]. Whereas no significant differences between the FA values for cancerous and normal PZ tissues in the study by Xu *et al*[48]. By contrast, later studies mostly reported increased FA values in cancerous tissues (ranged from 0.29 to 0.38) compared with non-cancerous tissues (ranged from 0.15 to 0.31), regardless of the location of the neoplastic tissue (either in PZ or CZ)[41,49,50]. Another study investigated the relation between gleason scores (GS) and DTI parameters in prostate cancer in PZ, revealing that FA values in the cancerous tissues were positively correlated with the GS (r = 0.48; P < 0.001), while the ADC values were negatively correlated with the GS (r = -0.54; P < 0.001)[51]. The authors claimed that increased FA were compatible with the hypercellular nature of prostate

tumors[52]. The variation in the FA values reported by the above-mentioned studies may be related to the different grades of malignant changes, as each study included relatively small sample with various cancer grades. In addition, Xu *et al*[48] discussed that the measured anisotropy could be biased with the increased image noise in the cancerous region where shorter T2 led to more significantly lowered SNR than in the normal regions. In general, the reliability of FA measurement still need to be improved, and DTI needs to be better integrated to multi-modality assessment of prostatic lesions.

Several studies investigated the evaluation of peri-prostatic neurovascular bundles by DTI, but the results varied. Some studies optimistically showed that 3D-DTI allowed effective description of the entire plexus of the periprostatic fibers in all directions[53,54]. But 3 of 8 subjects had no tracts detected with conventional DTI acquisition in another small-sampled study, in which zoomed DTI improved the detection rate[55]. A recent study even doubted whether the visualized DTI tracts really represent nerve tracts or neurovascular bundles, because DTI tract profiles were significantly dependent on FA thresholds and tended to present non-specificity[56]. Therefore, the utility of DTI for this indication remains controversial.

DTI OF THE UTERUS

The uterus is a fibromuscular organ with layered structures. The overall arrangement of muscle fibers is highly directional, which is the basis of DTI application. Specially, this organ is under the effect of hormones and has physiological (menstrual cycle, menopausal period) fluctuations, which may influence the diffusion properties. In 2006, three-dimensional fiber architecture of the normal human uterus based on DTI was evaluated in five samples *ex vivo*, revealing two basic fiber directions: Circular and longitudinal oriented[57]. The study by Fiocchi *et al*[58] confirmed such results *in vivo*, and showed that two third of the Caesarean-scarred uteri had altered fiber structure (lower fiber number and density) in the scarred anterior isthmus. They inferred that DTI may detect significant caesarean scars which may lead to subsequent placental complications. Diffusion of different layers were measured in the study by Fujimoto *et al*[59], showing that FA was the highest for junctional zone (0.297), followed by outer myometrium (0.257) and endometrium (0.186); fibers were the longest in outer myometrium (42.0 mm), followed by junctional zone (34.2 mm) and endometrium (20.0 mm). This presented detailed and quantified data for the understanding of the layered structure of uterus. The study by He *et al*[60] revealed that uterine FA and ADC values had dynamic changes during menstrual cycle, which includes several different phases: Menstrual phase (MP), follicular phase (FP), ovulatory phase (OP) and luteal phase (LP). Specifically, endometrial FA values significantly declined, whereas ADC values increased during MP, and ADC values of myometrium significantly increased from MP to LP. Variation of FA values between MP-FP, MP-OP was found correlated moderately with serum oestradiol levels, and the authors inferred that higher serum oestradiol levels were accompanied by larger increase of the endometrium with higher isotropy of water diffusion directionality[60].

The DTI data of diseased uterus is quite scarce. Toba *et al*[61] investigated the feasibility of DTI for evaluating the myometrial invasion of endometrial cancer *ex vivo*. Myometrial infiltration of endometrial tumor may be detected with the disruption of the anisotropic layer, as the FA values of the tumors (0.21 ± 0.05) were significantly lower than the inner layer of the myometrial zone (0.44 ± 0.01) and exterior myometrium (0.32 ± 0.08)[61]. More pathologies need to be included to expand the understanding of DTI in uterus with abnormality.

DTI OF OTHER PELVIC STRUCTURES

DTI, especially with tractography, has been used to depict the fiber orientation of skeletal muscles to some extent. The female pelvic floor, which has a multilayered complex anatomy and includes several closely aligned muscles, were investigated by Zijta *et al*[62,63] with small samples. The assumption was to use DTI with fiber tractography to depict normal pelvic floor anatomy, and to further evaluate pelvic organ prolapse. Several clinically relevant pelvic structures (including the perineal body, anal sphincter complex, internal obturator muscle and the puboperineal muscle) were satisfactorily and reliably identified, but no significant differences in DTI parameters were found between the prolapse group and the asymptomatic group overall[62,63].

One study has investigated the anal canal structures by DTI so far. FA values of various layers of normal anal canal were measured, and good inter-rater agreement and test reproducibility were achieved[64]. However, further data remains lacked.

FUTURE DIRECTIONS OF RESEARCH

DTI scans of abdominal and pelvic organs still confront with technical limitations: Not only common issues related to abdominal and pelvic MRI such as motional artifacts due to breathing and peristalsis, but also additional problems related to DTI such as the low SNR of EPI sequence due to gradient eddy currents, B0 field inhomogeneity and susceptibility difference[17]. It seems state of art to balance the longer acquisition time and less motional artifacts by either improved sequence or motional triggering protocols. Further studies can explore better techniques to increase SNR, reduce geometrical distortions and assess the contribution of IVIM.

Another issue is the methodology of post-processing and parameter measurements, which would influence the reliability and repeatability of scan results. Factors influencing the DTI parameter measurements, such as

hydration state and blood flow of targeted organs, should be further understood in order to standardize patient conditions[24,65]. Besides, consensus is needed on the placement of regions of interest (ROIs), where mean FA was calculated, since ROIs were manually delineated along the outlines of the targeted organs in some studies, but were placed in representative regions of the organ or tissue in other studies[17,22].

In general, DTI is more applied in diffused diseases of solid organs than in focal lesions. Organs with more directionally arranged structures have been explored to a greater extent, such as the kidney. In the circumstances that DTI parameters such as FA was reported of less diagnostic value, it should be noted that the underlying pathologic conditions that led to a final presentation of disease (such as renal function impairment or liver fibrosis) can be heterogeneous[14,38]. Future studies can explore the potential of DTI to differentiate between these pathologic conditions.

In focal lesion assessment, it is suggested that FA might reflect the histology of tumors, in particular of tumor cell density, and it is expected that locations with higher FA would have higher tumor cellularity, as well as a relatively higher Ki-67 labeling index, and therefore a higher malignant potential[16,52,66]. Future studies could apply DTI in lesions with prominent cellularity changes. For example, it is known that the density of gastrointestinal stromal tumor metastases decrease after cytostatic chemotherapy, and FA might be shown of value in these group of patients[67].

The last but not the least, DTI scan should be further integrated into the current multi-modality evaluation in clinical practice. For instance, it is mentioned that the differentiation of hepatic masses such as cysts, hemangiomas, and metastases can be performed easily by well-established imaging criteria. In this regard, performing DTI might seem unnecessary[16]. Another example is the diagnosis of prostate cancer, where multi-modality functional imaging has been researched extensively. Combined algorithm can be designed in future studies with the purpose of a more precise and full-scaled assessment.

CONCLUSION

In conclusion, DTI has been explored and applied in abdominal and pelvic organs such as liver, pancreas, kidneys, prostate, uterus, *etc.* Technical advances enabled generally satisfactory image quality and measurement repeatability. DTI appears to be more valuable in the evaluation of diffused diseases of organs with highly directionally arranged structures, such as the assessment of function impairment of native and transplanted kidneys. However, the utility of DTI to diagnose focal lesions remains limited. It is suggested that DTI parameters might potentially depict certain pathologic characterization such as cell density. Furthermore, DTI should be better integrated into the current multi-modality evaluation in clinical practice.

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WJMA World Journal of Meta-Analysis

Contents

Bimonthly Volume 5 Number 4 August 26, 2017

MINIREVIEWS

80 Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale

Luchini C, Stubbs B, Solmi M, Veronese N

SYSTEMATIC REVIEWS

85 Remission endpoints in ulcerative colitis: A systematic review

Jitsumura M, Kokelaar RF, Harris DA

103 Medication non-adherence in bipolar disorder: Review of rates, demographic and clinical predictors

Chakrabarti S

Contents

World Journal of Meta-Analysis
Volume 5 Number 4 August 26, 2017

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MINIREVIEWS

Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale

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Abstract

One of the most important points in the meta-analyses is certainly represented by the assessment of the quality of the studies included in such research. The meta-analyses are considered the highest level of evidence in science. Also for this reason, the quality of the studies included should be accurately evaluated by standardized tools. The overall results of the meta-analysis depend indeed also on a rigorous evaluation of the studies quality. Among all the possible tools for this complex evaluation, the Newcastle Ottawa Scale (NOS) is one of the most used worldwide, above all for observational studies. In this review, we will discuss the strengths and limitation of the NOS, also on the basis of the branch of science in which it has been applied.

Key words: Quality; Meta-analysis; Newcastle Ottawa Scale

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Core tip: To assess the quality of a meta-analysis is a remarkable point. In this review, we summarize the current evidence regarding the use of the Newcastle Ottawa Scale, one of the most used tool for evaluating

quality in meta-analyses of observational studies. Taking also our works as example, we found that, even standardized and quick in its application, it suffers from some limitations, particularly when evaluating cross-sectional studies.

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INTRODUCTION

The quality assessment of studies included in systematic reviews and meta analyses is essential to enable a clear understanding of the evidence base. There are several sources of biases in meta-analyses including inaccurate selection of participants, data collection, analysis and selective reporting of study results[1]. Many of these biases derive directly from the studies which are included in the meta-analysis. However, since systematic reviews and meta-analyses are considered the highest level of evidence in science[2], the quality of the studies included should be accurately evaluated by validated and standardized tools.

For randomized controlled trials (RCTs), numerous tools are available to assess the risk of bias and methodological quality. Among the most commonly used, the Cochrane Collaboration's tool[3] seems one of the most accurate, since it accounts for the main features of the RCTs. However, other tools (such as the Jadad's scale[4]) are commonly used.

There are less methodological quality assessment tools available for the meta-analyses of observational studies. Some authors (including our group[5,6]) have used reporting checklists for detailing the quality of included studies (such as STROBE[7-9]). Whilst this method has several strengths, it may be seen as a simple reporting checklist. Such tools are not validated for assessing the quality of studies included in meta-analyses[1]. For this reason, other tools are commonly used for assessing quality and risk of bias in observational (both cross-sectional and longitudinal) studies. Among these, the Newcastle Ottawa Scale (NOS)[10] is one of the most used worldwide.

Given the rising number of meta analyses of observational studies in the scientific literature, it is mandatory that the tools used to assess study quality in such endeavors are appraised. In this review, we will discuss the strengths and limitation of the NOS and its application, taking as example the branches of pathology and psychiatry, also with reference to some meta-analyses from our group of research.

REVIEW AND DISCUSSION

NOS: Definition

The NOS can be used for both case-control and longitudinal (prospective studies). Typically, cross-sectional studies are evaluated as case control studies. The NOS evaluates three quality parameters (selection, comparability, and outcome) divided across eight specific items, which slightly differ when scoring case control and longitudinal studies[10]. Each item on the scale is scored from one point, except for comparability, which can be adapted to the specific topic of interest to score up to two points. Thus, the maximum for each study is 9, with studies having less than 5 points being identified as representing at high risk of bias[11].

In order to minimize the subjective interpretation of bias from scoring the NOS typically two independent authors should score each paper. However, in our opinion, the most important as well as critical point in the NOS scoring and filling in is certainly represented by the specific field in which the meta-analysis has been conducted. Each field of science has indeed intrinsic aspects with consequent implications: Here we present these differences and both the advantages and the limitations of NOS scale in some of the most important branches of science.

NOS for meta-analyses in pathology

The pathologists' role in the era of modern medicine is based on performing an accurate as well as precise diagnosis, using standardized parameters, fixed cut-offs and thresholds. This standard strategy should be applied from the gross sampling to the pathology report[12,13]. The perfect tool for modern surgical pathologists to reach a consensus on the parameters to be reported in the diagnosis (when, how and why) is certainly represented by meta-analysis. With this statistical method the best standard and significant parameters, that can guide the pathologists during the diagnostic activity, can be documented. The meta-analysis can be thus applied to three of the main aspects of surgical pathology: (1) the prognostic impact of the mutation status of particular genes in cancer[14,15]; (2) the prognostic role of macro- or microscopic features of cancers[16-25]; and (3) the diagnostic utility of some morphological, immunohistochemical and/or molecular parameters[26]. Regarding the specific points of NOS scale for pathologists, an important topic is represented by the selection of the right method for ascertainment of exposure. If the meta-analysis regards a morphological aspect or an immunohistochemical staining, the classical microscopic exam should be preferred. Conversely, if the investigation regards a molecular aspect, the best standard molecular approach for the specific parameter should be applied, knowing that two of the most important are Sanger Sequencing[27]

Table 1 Strengths and weaknesses of the Newcastle Ottawa Scale

Strengths	Weaknesses
Quick and adaptable	Not validation for cross-sectional studies
Validated	Poor agreement
Moderator	Lack of comprehensive manuals

and Next Generation Sequencing[28-30]. For the outcome of interest, it is important specifying that this point is very subjective and may vary more than other points among different meta-analyses. In prognostic meta-analyses, however, we suggest to consider the disease-specific survival or the recurrence-free survival as the right parameter, being the overall survival the most common parameter in prognostic studies and thus not an index of quality. The point of NOS scale represented by the control for important factor or additional factor is obviously very important, since it can give two stars, determining a significant part of the quality's evaluation. In this case the choice of the right parameters it is even more important. Knowing that data from multivariate analysis are more reliable, this merit should be acknowledge using this index, for example giving a star to a study that presents hazard ratios and an additional star if this data are obtained considering at least two or more potential confounders. For meta-analysis in pathology, at last, it has to be highlighted that a standard length for the follow-up of patients is 60 mo (5 years). A point of strength of this scale is that these parameters are not fixed and adaptable on the basis of the specific analysis. For example, a meta-analysis on the survival of patients with glioblastomas, a tumor with a very poor prognosis generally no longer than 2 years, will reach a star for smaller period (18 mo for example) than the classical 60 mo. The adaptability of NOS scale in this sense represents surely a point of strength. A limitation of this scale in pathology is that it may be very difficult, or even impossible, considering every possible source of bias in this scale, or highlighting every point of strength of the analyzed studies with this multi-stars system. The expertise and a consensus meeting among the authors is the best way to choose the right parameters for this scale.

NOS for meta-analyses in psychiatry

Psychiatry is different from pathology and other branches of medicine, since diagnoses, response, and remission are defined exclusively on clinical evaluation. Thus, the selection and exposure or outcome NOS items, which assess whether cases are diagnosed through reliable and independent validation or through self-report instead, is fundamental in establishing research quality. Moreover, among the main diagnostic systems, namely DSM-V[31] and ICD, some differences are evident[32] and there remains a great debate about diagnosis in general. Also, a control group defined as free from a specific mental disease in the general population, has a lower odds of having other psychiatric comorbidity compared to a control population of inpatients, due to frequent medical comorbidity among patients with severe psychiatric conditions[33,34]. Furthermore, remission and response definitions need specific psychopathologic scales' cut-offs to be defined, and self-report or no description of such criteria need to be accounted for from a quality assessment scale, which is the case of NOS. Finally, treatment adherence is a substantial problem in psychiatry, and results are often affected by rates of completers and subjects lost at follow-up; again outcome NOS items account for such a variable. Thus authors encourage the use of NOS scale in the field of psychiatry, as has already been done in both observational[35,36] and interventional[37] studies' meta-analyses.

Strengths of the NOS

The NOS is one of the most known scale for assessing quality and risk of bias in observational studies for several reasons[38], as reported in Table 1. The first one is that this tool is relatively quick to do, although it requires the right attention. Second, as already explained, the adaptability of its indexes on the basis of the investigated topic is very important. Furthermore, differently from other checklists and tools, it is validated for case-control and longitudinal studies[10]. Finally, differently from other tools, NOS gives a score between 0 and 9 and so it is possible to use it as potential moderator in meta-regression analyses[11,39].

Weaknesses of the NOS

The NOS suffers from several weaknesses, however (Table 1). First, some domains are not univocal and one author should usually adapt this scale modifying some items. It is particularly true for cross-sectional studies for which the NOS should be adapted from the scheme of the case-control studies. Regarding the longitudinal investigations, the points usually adapted by the authors are the number and type of adjustments in the multivariate analyses, the duration of follow-up (not univocal follow-up is in fact given) and the outcome of interest not present at the baseline.

Another point of weakness is the low agreement between two independent reviewers in making the NOS. In the work proposed by Hartling *et al*[40], the agreement between the two reviewers was moderate/poor as shown by the *k*-value (< 0.50 for eight of the nine questions on the NOS). This is particularly true in case of low experience by the authors in meta-analysis/systematic reviews[41] suggesting that a training with a more expert author is needed.

Finally, the lack of comprehensive manuals could be interpreted as another limitation[42].

CONCLUSION

The NOS is a tool commonly used in medicine for

the assessment of quality. Although it is a validated instrument and with a long history of reliability it suffers from several limitations. Other tools (tailored for cross-sectional studies and with more univocal items for other observational studies) are probably needed.

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SYSTEMATIC REVIEWS

Remission endpoints in ulcerative colitis: A systematic review

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Abstract

AIM

To summarize the current consensus on the definition of remission and the endpoints employed in clinical trials.

METHODS

A bibliograraphic search was performed from 1946 to 2016 sing online databases (National Library of Medicine's PubMed Central Medline, OVID SP MEDLINE, OVID EMBASE, the Cochrane Library and Conference Abstracts) with key words: ("ulcerative colitis") AND ("ulcerative colitis endoscopic index of severity" OR "UCEIS") AND ("remission") as well as ("ulcerative colitis") AND ("ulcerative colitis disease activity index") OR "UCDAI" OR "UC disease activity index" OR "Sutherland index") AND ("remission").

RESULTS

The search returned 37 and 116 articles for the UCEIS and UCDAI respectively. For the UCEIS, 12 articles were cited in the final analysis of which 9 validation studies have been identified. Despite the UCEIS has been more extensively validated in all three aspects (validity, responsiveness and reliability), it has been little employed to monitor disease in randomised clinical trials. For the UCDAI, 37 articles were considered for the final analysis. Although the UCDAI is only partially validated, 29 randomised clinical trials were acknowledged to use the UCDAI to determine endpoints and disease remission, though no clear protocol was identified.

CONCLUSION

Although the UCEIS has been more widely validated than the UCDAI, it has not been reflected in the monitoring of disease activity in clinical trials. Conversely, the UCDAI has been used in numerous large clinical trials to define their endpoints and disease remission, however, it is challenging to determine the best possible outcomes due to a lack of homogeneity of the clinical

trial protocols. Before determining a gold standard index, international agreement on remission is urgently needed to advance patient care.

Key words: Ulcerative colitis; Remission; Ulcerative colitis endoscopic index of severity; Ulcerative disease activity index

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Core tip: Despite the decades of discussion, disease remission for ulcerative colitis has yet to be fully defined. Instead, numerous indices that measure a large variety of endpoints had been developed, each claiming to be accurate and informative. This systematic review aimed to summarise the issues related to the uncertain definition of disease remissions in clinical trial studies by focusing on two indices ulcerative colitis endoscopic index of severity and ulcerative disease activity index. We recommend that an international consensus of remission should be sought before establishing a gold standard outcome measurement to untangle this confusion.

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INTRODUCTION

How do we determine remission as an endpoint in ulcerative colitis (UC) clinical trials when we design a study? There is no universally agreed definition of remission as an endpoint in UC clinical trials as of date, despite much discussion and urge for the standardisation. Currently, it is chosen to reflect the purpose of the studies, rather than long-term clinical outcomes or controlling bothersome symptoms that patients often suffer from. Furthermore, a lack of homogeneity of the clinical trial protocols makes comparison of such studies more difficult to comprehend.

UC is a chronic relapsing-remitting inflammatory bowel disease, affecting mucosa of the large bowel. Patients with UC often present with debilitating symptoms such as abdominal pain and rectal bleeding. Although the aetiology of UC is believed to be multifactorial involving dysregulated immune system, intestinal mucosal disturbance and genetic predisposition, natural history of the disease is poorly understood[1]. There is no curative treatment at present, thus the aim of management is induction and maintenance of remission with immunosuppressive agents, permitting individuals to carry on their daily life. The failure of medical therapy or refractory disease often require colorectal surgery, and there is an increased risk of colorectal cancer[2].

Since the first disease activity outcome measurement was developed in 1955, the Truelove and Witts Index, numerous outcome measure instruments have been developed[3]. Not only has the number of these instruments been growing, but also the assessed disease components have been expanding. Traditionally, disease activity has been assessed by a clinical and symptom scoring system, with or without a combined endoscopic assessment. A recent review counted seventeen clinical disease activity indices which evaluate symptoms, of which eight do so without endoscopic or biomarker assessment[4]. The purpose of these disease activity indices is to provide an objective measurement of the disease activity by employing typical symptoms such as stool frequency and rectal bleeding. Endoscopic assessment is another dimension of the disease that is mandated by the Food and Drug Administration (FDA)[5] and at least thirty-one instruments were proposed[6]. Many of these endoscopic indices, such as Mayo score and ulcerative colitis disease activity index (UCDAI), evaluate the macroscopic appearance of large bowel, together with symptomatic disease activity. Recently, the prognostic potential of histological assessment in UC has been highlighted in several studies[7-9], although histological remission has yet to be proposed as a therapeutic endpoint for clinical trials or practice, twenty-six histological activity indices have been developed thus far. It is important to note that there is considerable disparity between visual endoscopic assessment and histological disease activity[9], although confusingly these terms are used interchangeably[9]. In addition to symptomatology, endoscopic, and histological scoring systems, radiological outcome instruments as well as new biochemical markers are an additional developing dimension of disease assessment[4].

In addition to these objective indices, we cannot neglect patient subjective outcome measurement tools and quality of life (QoL) questionnaires. The aim of these tools is to evaluate the patients' emotional, social or professional well-being so that their ideas, concerns, and expectations can be a part of the objective medical decision-making process. Patients often have different expectations of treatment and remission from those of physicians, and symptoms used in established scoring tools may be of relatively little concerns to some individuals. Establishing an understanding of chronicity is also important in assessing a patient's disease, especially when reconciling the long term treatment goals with a patients' concerns regarding how quickly embarrassing, troublesome and physical symptoms can be resolved with minimal side effects[10]. Furthermore, we cannot underestimate the power of the internet and smartphone use in medicine; many patients often seek online diagnosis of their symptoms before they are formally assessed by a clinician, and may already be either well informed or misguided when discussing management. Patients often use "remission" and "flare-ups" informally to describe their disease activity without reference to formal assessments of such, and

thus misunderstandings may occur when discussing assessment and treatment. A few self-reporting assessment tools (smartphone apps) are available, allowing patients to monitor their disease activity on daily basis in a more objective manner[11]. Whether these patient-reported measurement instruments show a good correlation with true disease activity by other measures appears to be almost irrelevant. Many patients with asymptomatic UC do not feel the need of continuing medications in the absence of discernible symptoms, especially when they give side effects, making the negotiation more challenging for clinicians. A good rapport and the ability to reach negotiated consensus with patients is an integral skill for clinicians managing complex UC patients.

The overall picture is that there are numerous indices that measure a large variety of endpoints, each claiming to be accurate and informative regarding one or other management goal. Confusingly, these indices share similar names or are often referred to by multiple names or abbreviations, such as the UCDAI which is also referred to as the Sutherland Index. Unfortunately, no single scoring system provides comprehensive assessment of disease activity, and the majority of these indices lack robust clinical validation. Most clinical trials, from which the scoring systems are derived, choose disease outcome measures and endpoints reflecting the purpose of the studies, rather than long-term clinical outcomes or real-world symptom control for patients. Furthermore, each clinical trial defines remission differently, making comparison between different trials difficult.

The consequence of the complexity in UC outcome measurements and the huge variety in competing scoring systems is that many patients with UC may receive suboptimal therapy and poor long-term disease control.

This systematic review will reassess and summarise the current consensus on the definition of remission and the endpoints employed in clinical trials by focusing on two most validated and well-used indices, the ulcerative colitis endoscopic index of severity (UCEIS) and UCDAI, in order to address the issues with the standardisation of clinical trial protocols.

The current target of disease remission endoscopically is mucosal healing although it has not been fully validated or no standardised definition of mucosal healing[12,13]. Yet, this appears to be the goal for many clinical practice as well as drug trials.

The recent draft guideline released by the FDA[5] states the ideal primary efficacy assessment instrument in clinical trials should consist of (1) a signs and symptoms assessment scale - best measured by a patient-reported outcome instrument. If not, an observer-reported outcome instrument; and (2) an endoscopic and histological assessment scale.

Thus, endoscopic assessment tools with comprehensive clinical symptom assessment components that come from patients would be a reasonable choice to argue remission and endpoints employed in clinical trials.

Amongst numerous endoscopic indices claiming to measure disease activity, the UCEIS is one of the most widely validated indices to date. It would be interesting to see any impact of the quality of validation for defining remission and endpoints compared with the index, such as the UCDAI, that has not been fully validated yet being widely employed in clinical trials. For these reasons, these two indices were chosen for this systematic review.

UCEIS

The UCEIS proposed by Travis *et al*[14] in 2012 is the only validated endoscopic index in ulcerative colitis to date[15]. It was developed to minimise variation in endoscopic assessment, thus it could be widely applied as a reliable outcome measure in clinical trials as well as clinical settings.

The first stage of development of the UCEIS demonstrated the significant inconsistency in endoscopic assessment amongst specialists by 10 specialists scoring the severity of UC using the Baron score[16] in colonoscopy videos. The greatest correlation was found in the "severe" level of the Baron score, demonstrating a 76% agreement, however, only 27% agreement was achieved for a normal mucosa (Baron score 0) and 37% agreement for moderate friability (Baron score 2).

The second part of the study further quantifies intra- and inter-observer variation on common descriptors on endoscopic assessments (Table 1). For intra-observer variation, 60 repeat pair assessment of 36 different videos were scored and assessed by κ statistics. For inter-observer variation, 30 new investigators were randomly allocated to score 25 videos, thus each video was assessed by 10-12 investigators.

Both intra- and inter-observer variation showed good agreement to assess erosions and ulcers, vascular pattern and bleeding, which were subsequently chosen for descriptors of a newly developed endoscopic assessment tool, the UCEIS (Table 2).

The authors also proposes definition of remission using the UCEIS, which is when all three descriptors were level 1 (no visible bleeding or erosions or ulceration, but some blurring or loss of capillary margins with a recognisable vascular pattern is allowed).

UCDAI

The UCDAI (also called UC Disease Activity Index, and Sutherland Index) was introduced by Sutherland *et al*[17] to assess efficacy of 5-aminosalicylic acid enema in the treatment of distal UC in its randomized, double-blind clinical trial in 1987.

The index was used for objective assessment during this drug trial and considers four variables of UC - stool frequency, rectal bleeding, mucosal appearance and physician's rating of disease activity (Table 3). Unlike the UCEIS, the UCDAI was developed without any validated study. Although the authors described that the index incorporates many of the subscales used by

Table 1 Descriptors and intra- and inter-observer variation

Descriptor	Likert scale anchor points	Intra-observer variation (a weighted *k*)	Inter-observer variation (a weighted *k*)
Vascular pattern	Normal (1) Patchy loss (3) Obliterated (5)	0.61	0.42
Mucosal erythema	None (1) Light red (3) Dark red (5)	0.43	0.35
Mucosal surface (Granularity)	Normal (1) Granular (3) Nodular (5)	0.45	0.34
Mucosal oedema	None (1) Probable (3) Definite (5)	0.43	0.31
Mucopus	None (1) Some (3) Lots (5)	0.47	0.4
Bleeding	None (1) Mucosal (2) Luminal mild (3) Luminal moderate (4) Luminal severe (5)	0.57	0.37
Incidental friability	None (1) Mild (2) Moderate (3) Severe (4) Very severe (5)	0.49	0.4
Contact friability	None (1) Probable (3) Definite (5)	0.34	0.3
Erosions and ulcers	None (1) Erosions (2) Superficial ulcer (3) Deep ulcer (4)	0.65	0.45
Extent of erosions or ulcers	None (1) Limited (2) Substantial (3) Extensive (4)	0.6	0.42

other investigators and demonstrated efficacy as an overall index and individual component subscale, they failed to demonstrate this with any form of statistical assessment. Furthermore, they also compared between the overall index and the physician's global assessment by this drug trial study physician and concluded that the UCDAI demonstrates good correlation with the physician's assessment (P = 0.0001). This conclusion fails to demonstrate objectivity although the authors' fundamental aim of designing this index was to provide objective assessment.

The UCEIS was developed based on components to minimise the variation identified in previous endoscopic assessment instruments. It has been validated from various angles at the time of designing, making it more reliable than traditional instruments. Conversely, the UCDAI was designed without any validated evidence to assess efficacy of a drug for treatment of UC. Yet, it has been widely used in numerous clinical trials for decades and even recommended by the FDA as one of the endoscopic assessment tools.

Table 2 The ulcerative colitis endoscopic index of severity descriptors (maximum score = 8, Scoring is based on the most severe area)

Descriptors	Likert Scale anchor point	Definition
Vascular pattern	0: Normal	Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	1: Patchy obliteration	
	2: Complete obliteration	Complete obliteration
Bleeding	0: None	
	1: Mucosa	Some spots or streaks of coagulated blood on the surface of the mucosa
	2: Luminal mild	Some free liquid blood in the lumen
	3: Luminal moderate or severe	Frank blood in the lumen ahead of endoscope or visible oozing from a haemorrhagic mucosa
Erosions and Ulcers	0: None	None
	1: Erosions	Tiny < 5 mm defects in the mucosa, of white or yellow colour with a flat edge
	2: Superficial ulcer	Larger > 5 mm defect in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial
	3: Deep ulcer	Deeper excavated defects in the mucosa, with a slightly raised edge

Table 3 Ulcerative colitis disease activity index (maximum score = 12)

Variables	Score	Items
Stool frequency	0	Normal
	1	1-2 stools/d more than normal
	2	3-4 stools/d more than normal
	3	> 4 stools/d more than normal
Rectal bleeding	0	None
	1	Streaks of blood
	2	Obvious blood
	3	Mostly blood
Endoscopic appearance	0	Normal
	1	Mild friability
	2	Moderate friability
	3	Exudation, spontaneous bleeding
Physician global assessment	0	Normal
	1	Mild
	2	Moderate
	3	Severe

MATERIALS AND METHODS

A systematic bibliographic search was performed between 10th and 14th November 2016 of the following online databases: OVID SP MEDLINE (1946 to present),

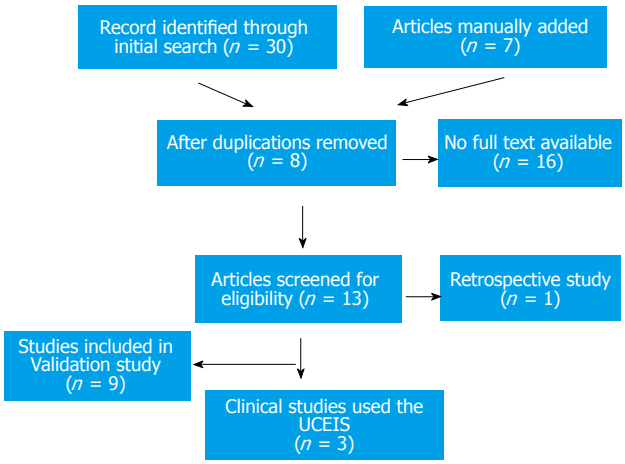


Figure 1 PRISMA flow diagram for ulcerative colitis endoscopic index of severity. UCEIS: Ulcerative colitis endoscopic index of severity.

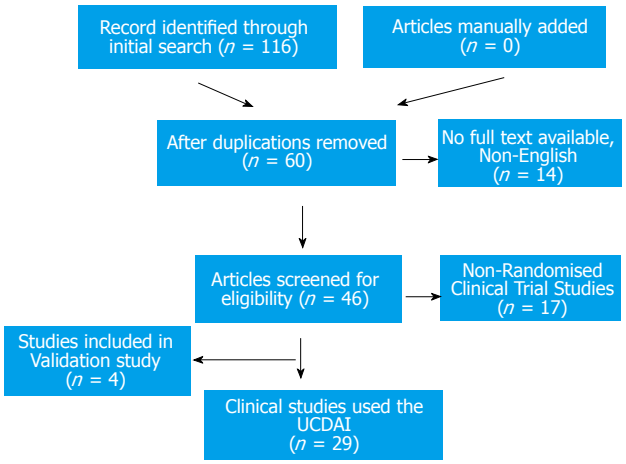


Figure 2 PRISMA flow diagram for ulcerative colitis disease activity index. UCDAI: Ulcerative colitis disease activity index.

OVID EMBASE (1974 to present), National Library of Medicine's PubMed Central MEDLINE (1950 to present), the Cochrane Library, using the key heading-words strategy set below and the medial subject heading. The bibliographies of recovered systematic review, meta-analysis, and review articles were also searched for additional articles.

Each database was searched for the following headings: (1) Ulcerative colitis endoscopic index of severity: ("ulcerative colitis") AND ("ulcerative colitis endoscopic index of severity" OR "UCEIS") AND ("remission"); and (2) Ulcerative Colitis Disease Activity Index: ("ulcerative colitis") AND ("Ulcerative colitis disease activity index" OR "UC disease activity index" OR "UCDAI" OR "Sutherland index") AND ("remission")

Non-English articles, studies pertaining to paediatric subjects, and non-human subjects were excluded. Studies presenting data of patient populations already included in other publication (duplicates) were excluded. No abstract publications without subsequent full-text published data were used. Disagreements about inclusion were resolved in a consensus meeting.

RESULTS

Ulcerative colitis endoscopic index of severity

A total of 37 articles were returned using the initial search. After applying exclusion criteria and eliminating duplication, 12 articles screened for relevance and manual search of articles referenced in the retrieved articles was performed. Nine articles were included in the final analysis for validation assessment of UCEIS and 3 articles were evaluated for the UCEIS use in clinical trials (Figure 1).

UCDAI

A total of 116 articles were returned using the initial search, which was down to 37 articles after considering exclusion criteria and duplication. Four articles were identified for the final analysis of validation assessment and 29 articles were included to evaluate defining remission and endpoints of clinical trials (Figure 2).

What do we need in outcome measurement instruments?

The definition of disease remission has not yet been validated or standardised. Inevitably, implementing clinical scoring tools based on a broad definition of remission results in inaccuracy of outcomes, and a reduction in the utility of a derived tool. The gold standard for disease activity in UC must be a diagnostic tool that truly quantifies the disease activity and can accurately assess and therefore guide future disease managements and outcome. A robust and standardised outcome measurement instrument is vital for clinical trials and establishment of medical therapy, although many instruments are not fully validated.

In this systematic review, validation of UCEIS and UCDAI studies were described by dividing into validity, reproducibility and responsiveness (Table 4).

Validity: The diagnostic and prognostic validity of an assessment tool is defined as evidence that variations in UC disease activity causally produce variations in the measurement outcomes. This must be demonstrated by qualitative assessment and evidence of indices measuring disease activity adequately and sufficient reflection of true disease. The development of these indices should be supported by a robust systematic review of literature. Statistical studies of agreement between the indices and disease activity should be assessed including sensitivity and specificity. Validity of the correlation between an index score and objective assessment score including clinical disease activity index scores or physician global assessment of severity should be measured. Although there are many indices have been proposed the degree of validity for these indices vary, and many indices are not fully validated. In this study, UCEIS and UCDAI, one of the best validated indices and most widely used indices in drug trials

Table 4 Validation studies of ulcerative colitis endoscopic index of severity and ul-cerative colitis disease activity index

	Ref.	Patient number	Outcomes
UCEIS			
Validity	Corte *et al*[18]	89	Correlation between UCEIS and outcomes The UCEIS score was directly proportional to requirement of rescue therapy UCEIS ⩾ 5 was significantly linked to requiring colectomy 18/54 (33%) patients with UCEIS ⩾ 5 compared to 3/33 (9%) with UCEIS ⩽ 4 No definition of remission
	Fernandes *et al*[19]	108	Prediction of outcomes in acute severe colitis UCEIS was applied to score of the rectum and sigmoid, seg-UCEIS Seg-UCEIS predicted to develop steroid-refractory disease and the likelihood of colectomy (seg-UCEIS = 14 had a 17 times higher risk of steroid-refractory disease and a 25 times higher risk of requiring colectomy) Every 1 point increase in the UCEIS or Seg-UCEIS increased the need of colectomy by 2.78 and 1.79 respectively Mayo score did not predict these No definition of remission
	Arai *et al*[20]	285	Reflection of true UC activity and remission The recurrence rate was directly proportional to the UCEIS score (5.0% for UCEIS = 0, 22.4% for UCEIS = 1, 27.0% for UCEIS = 2, 35.7% for UCEIS = 3, 75% for UCEIS = 4-5) The absence of bleeding and mucosal damage were independent factors for continued clinical remission UCEIS ranged from 0 to 5 when clinical remission, Mayo ⩽ 1 UCEIS ⩽ 1 for clinical remission, which showed sensitivity of 68% and specificity 57% The expected duration of recurrence is also prolonged when UCEIS ⩽ 1
	Kucharski *et al*[21]	49	Assessment of 9 endoscopic indices correlate well with (1) clinical indices; and (2) histological Geboes Index[22] The UCEIS showed the strongest correlation with the Geboes Index (the coefficient: 0.434 to 0.629) Recommends the UCEIS for the best overall correlations with both clinical and histological indices
Responsiveness	Ikeya *et al*[23]	41	The ability to detect to change after Tacrolimus remission induction treatment for moderate to severe UC Although Mayo endoscopic score is easy to use, it does not distinguish depth of ulcers unlike UCEIS Despite UCEIS score improved from 7 to 4, Mayo endoscopic score remained at 3 (severe) An improvement of UCEIS ⩾ 3 showed close correlation with clinical remission, colectomy-free and relapse free rates Proposed remission (score 0-1), mild (2-4), moderate (5-6), severe (7-8) UCEIS 1 in remission is only from vascular pattern
	Menasci *et al*[24]	80	Comparison of the global UCEIS score from 5 segments and a traditional method of UCEIS score The regular method of the UCEIS is to score the most inflamed segment of the bowel This was compared with the sum of the score of five colonic segments A very good correlation (Spearman's r = 0.86, P < 0.0001) for disease with UCEIS score ⩽ 5 Less correlation (r = 0.48, P < 0.01) for disease with UCEIS > 5
Reliability	Travis *et al*[15]		Investigation of intra- and inter-observer consistency assessment 25 readers evaluated 28 videos including 4 duplicates to assess intra-reader reliability The intra and inter-reader reliability ratios for the UCEIS were 0.96 and 0.88 respectively The USCEI revealed a strong correlation with overall assessment of severity without being influenced by knowledge of clinical information No definition of remission
	Feagan *et al*[25]	281	The effect of centralized review of images on inter-observer variations Patients with UCDAI ⩾ 2 were randomised to evaluate the efficacy of delayed mesalamine treatment (4.8 g/d for 10 wk)
	Travis *et al*[26]		UCEIS was used as a part of inter-observer agreement study and showed interclass correlation coefficient of 0.83 amongst 7 central readers, which is superior to UCDAI Clinical information influences UCEIS score 40 readers evaluated 28 of 44 videos No discrepancy between blinded and unblended readers Intra- and inter-reader variability demonstrated moderate to substantial agreement (κ = 0.47 to 0.74 and κ = 0.40 to 0.50 respectively) UCEIS correlated well with patient-reported symptoms - rectal bleeding, stool frequency and patient functional assessment (rank correlation = 0.76 to 0.82)
UCDAI			
Validity	Higgins *et al*[27]	66	Finding endpoints in disease activity indices for remission and improvement in UC UCDAI < 2.5 for remission, which had a sensitivity and specificity of 0.82 and 0.89 Remission in this study was defined by patients
	Poole *et al*[28]	126	Establish the relationship between the UCDAI and patient reported EQ-5D The UCDAI with or without endoscopy assessment demonstrated a good correlation with EQ-5D Endoscopy assessment may not link with the disease activity

	Kucharski *et al*[21]	49	Assessment of 9 endoscopic indices correlate well with (1) clinical indices; and (2) histological Geboes Index (22) The UCDAI showed strong correlations with all 9 endoscopic indices (the coefficient in a range of 0.712 to 0.790) The UCDAI showed the highest correlation amongst clinical activity indices with the Geboes Index (the Spearman's coefficient 0.478) Compared to UCEIS, the UCDAI is less correlated with the Geboes Index
Reliability	Feagan *et al*[25]	281	The effect of centralized review of images on inter-observer variations Patients with UCDAI ⩾ 2 were randomised to evaluate the efficacy of delayed mesalamine treatment (4.8 g/d for 10 wk) 31% of patients with UCDAI ⩾ 2 enrolled in the RCT initially were considered ineligible by the central readers Inter-observer agreement amongst 7 central readers was good (interclass correlation coefficient: 0.78)

UC: Ulcerative colitis; UCEIS: Ulcerative colitis endoscopic index of severity; Seg-UCEIS: The sum of the rectal and sigmoid segmental UCEIS score; UCDAI: Ulcerative colitis disease activity index; EQ-5D: EuroQol Five Dimensions Questionnaire; RCT: Randomised control trial.

respectively, were studied for their evidence of validity.

The UCEIS is one of the well validated indices in many aspects. The authors have studied difficulties in standardisation of the disease activity indices and defining remission in systematic reviews as well as reviews of literature prior to the development of the UCEIS[29,30]. The authors attempted to develop an index that minimises this variation by validating variation in endoscopic assessment of disease activity, which was described in 2.1. The study also suggested remission might be defined as no obliteration of vascular pattern, no rectal bleeding and no erosion or ulceration, although this has not been fully validated.

Since the UCEIS was published in 2012, there are nine studies attempted to validate the UCEIS, of which four studies are focusing on validity.

Corte *et al*[18] validated whether the UCEIS predicts clinical outcomes of acute severe colitis. 98 Patients with the UCEIS score from 3 to 8 were included in this study. It showed when UCEIS ⩾ 5, 33% (18/54) of acute colitis patients required colectomy 18/54 (33%) whereas only 9% (3/33) of patients with UCEIS ⩽ 4 required surgical interventions. When the UCEIS score is above 7 at the time of admission, almost all patients required medical therapy more than hydrocortisone, such as infliximab or ciclosporin. It concluded that the higher UCEIS score is associated with higher requirement of rescue therapy, surgical intervention and readmission.

Fernandes *et al*[19] identified patients with poor response to optimal therapy with 108 patients who are defined as acute severe colitis based on the Truelove and Witts criteria (the score ⩾ 2). All the patients received intravenous prednisolone 40-60 mg/d, methylprednisolone 60 mg or hydrocortisone 400 mg/d. Patients who had not responded to the initial therapy within 3 d received salvage therapy, and their UCEIS scores ranged from 2 to 8. The study also divided the UCEIS scoring system to segmental bowel - rectum and sigmoid, which demonstrated a strong correlation between higher UCEIS score and unfavourable outcomes especially the UCEIS-segmental score predicted refractoriness to steroid therapy. The UCEIS was significantly better at predicting clinical outcomes than the Mayo endoscopic sub-score.

Arai *et al*[20] attempted to foresee the prognosis of patients with UC who are in clinical remission. 285 patients who are in clinical remission (partial Mayo score of ⩽ 1) were included in the study. The UCEIS score of these patients with clinical remission ranged from 0 to 5, of which 92% received a UCEIS score of 2 or 3. These scores are higher than a suggested score for clinical remission. The study demonstrated the recurrence risk is direct proportional to the UCEIS score - the recurrence rate of 5.0% for UCEIS = 0, 22.4% for UCEIS = 1, 27.0% for UCEIS = 2, 35.7% for UCEIS = 3, 75% for UCEIS = 4-5. The study also highlighted the absence of bleeding and mucosal damage being independent factors for clinical remission. The duration of recurrence was also significantly prolonged in patients with lower UCEIS score. The study presented validity of the UCEIS with its predictability of clinical outcomes. Furthermore, it suggests UCEIS ⩽ 1 for clinical remission based on the direct correlation between the recurrence rate and the UCEIS, which showed sensitivity of 68% and specificity 57%.

Kucharski *et al*[21] assessed correlations between 9 endoscopic indices and 11 clinical activity indices. The author also assessed correlations between those endoscopic indices and the histological Geboes index[22]. Nine endoscopic indices used are Baron score[16], Powell-Tuck Score[31], Schroeder Score[32], UCDAI, Rachmilewitz Endoscopic Index[33], LÖtberg Score[34], Lemann Endoscopic Index[35], Feagan Score[36] and UCEIS. Eleven clinical activity indices are Truelove and Witts Severity Index[3], Powell-Tuck Index[31], Schroeder Score[32], UCDAI, Rachmilewitz Index[33], Lichtiger Index[37], Seo Score[38], Walmsley Index[39], Improvement Based on Individual Symptom Scores (IBOISS)[40], Feagan Score[36] and Montreal Classification of Severity of Ulcerative Colitis[41].

The correlations between clinical and endoscopic indices were evaluated using Spearman's ranking correlation coefficient. The Rachmilewitz Index showed strong correlations with 5 clinical activity indices (UCDAI,

Truelove and Witts, Schroeder Score, IBOISS and Feagan Index) with the correlation coefficient ranging in 0.710-0.788. The UCEIS also showed high correlations with the UCDAI, Schroeder Score, IBOISS and Feagan Index, the coefficient ranging from 0.722 to 0.761. When the correlations between clinical indices and the Geboes Index were assessed, all clinical indices showed low correlations, whereas all endoscopic indices showed better correlations with the histological Geboes Index. To evaluate correlations with endoscopic indices, all endoscopic indices were scored at four colonic segments right colon, transverse colon, left colon and rectum. The highest correlations were seen with the UCEIS at all four segments (the coefficient ranging from 0.434 to 0.629). The authors conclude that the UCEIS is the most effective endoscopic outcome measure instrument when considering correlations of both clinical and histological indices. In contrast, the UCDAI showed moderate correlations with rectal and transverse colonic segment with the Geboes Index with 0.651 and 0.534 respectively, though the correlations with other two segments were low with 0.428 for left colon and 0.459 for right colon.

Although the UCDAI has been widely used especially in multiple and large clinical trials, the study focused on validation of this index is much less compared to the UCEIS. The UCDAI was developed to assess the efficacy and safety of 5-aminosalicylic acid enema use for patients with UC[17]. The UCDAI claim to assess disease activity from four descriptors - stool frequency, rectal bleeding, mucosal appearance and physician's global assessment of the disease. Although the description of each scoring system is simple to understand, it cannot avoid subjectivity without clear definition of each item. In particular, physician's global assessment is far from being objective. Furthermore, the supposedly objective endoscopic assessment is scored based on severity of "friability". Yet again, this friability without clear definition cannot avoid subjectivity, meaning it is exposed to greater inter- and intra-observer variability.

Higgins *et al*[27] defined objective end points in disease activity indices including UCDAI for remission and improvement in UC. This study was conducted on 66 patients with UC and their subjective dichotomous assessment of remission and regulatory remission were compared with the UCDAI. Regulatory remission was defined as (1) no more than grade Ⅰ or Ⅱ changes on a Feagan endoscopic score; and (2) absence of visible rectal bleeding in this study. It suggests the cut off point for clinical remission of the UCDAI is below 2.5, offering good statistical power - sensitivity and specificity is 0.82 and 0.89 for patient defined remission and 0.92 and 0.93 for regulatory remission. Patient-defined dichotomous end points may be over-simplification, however, as it is clinically significant outcomes that determines if therapies are perceived as beneficial by patients. Regardless of physicians' objective assessment, patients with the disease are those that must agree with it in order to gain benefit in receiving therapies.

Poole *et al*[28] designed a new patient-reported disease assessment instrument, EuroQoI Five Dimensions Questionnaire (EQ-5D), for which the UCDAI was used to validate the instrument. Although validation of the UCDAI was not the aim of this study, the correlation between physician-rated and patient-rated instruments was elaborated. The study concluded that the abbreviated UCDAI (without endoscopic assessment component) and EQ-5D showed reasonable consistency when severity of the disease was measured in two randomised studies (PINCE[42] and PODIUM[43]). Goodness of fit was verified by the mean square error for mean predicted utility score. This showed patients in remission was 0.939, 0.944 and 0.940 mean utility units for estimated-PINCE, observed-PINCE and PODIUM.

Comparison of these two very different outcome measure instruments highlighted two incomparable benefits when they are chosen for clinical trials. The UCEIS is extensively validated and development of the index is based on robust studies, whereas the UCDAI is deigned based on expert opinion on the disease. However, the UCDAI is more widely used in clinical trials. This makes the choice of an index for future clinical trial studies more difficult when the clinical benefit was considered. In this systematic review, only two indices are compared. With current inconsistent use of measurement instruments and non-standardised definition of remission, the choice is almost impossible.

Responsiveness: Responsiveness is assessed in this systematic review as the ability to detect changes after a treatment that has known efficacy.

Ikeya *et al*[23] investigated true evaluation of UC severity and outcome after Tacrolimus remission induction therapy using the UCEIS as well as Mayo endoscopic subscore (Mayo ES) with 41 patients who are known to have moderate to severe disease.

In this study, clinical remission was defined as clinical activity index (CAI) $\leqslant$ 4 and a reduction of CAI score more than 4 was defined as clinical response. On the contrary, an increase of CAI score more than 4 was defined as relapse.

After 12 wk from the treatment, 31 patients (75.6%) successfully achieved clinical remission [defined as clinical activity index (CAI) $\leqslant$ 4] and 3 patients did not respond. Overall the UCEIS and Mayo ES showed close correlations, however, when the Mayo ES was 3, there was prominent discrepancy between the two indices. The UCEIS score equivalent to Mayo ES 3 ranged from 5 to 8 pre-treatments and 3 to 7 post-treatments. This was believed to be due to a lack of ability to distinguish characteristics of ulcers, vascular patterns or bleeding with the Mayo ES. For instance, ulcers and erosions often become smaller and shallower in the early phases of mucosal healing. Since the Mayo ES does not distinguish the size and depth of ulcers, it tends to stay with the same score, meaning the Mayo ES score is 3 for all types of ulcers. Furthermore, the Mayo ES combine all those macroscopic findings of ulcers,

vascular pattern and bleeding into four different overall grades. This means if there are ulcerations of any shape, the Mayo ES score becomes 3, even if vascular pattern disturbance is resolved.

The study also demonstrated significantly better relapse-free and colectomy-free rates when the UCEIS score was improved by more than 3. In addition, improvement by a UCEIS score of more than 3 was strongly associated with achieving clinical remission group (23 out of 41 patients).

Menasci *et al*[24] evaluated to see whether the global score of the sum of 5 colonic segments (rectum, sigmoid, descending, transverse, and ascending colon), abbreviated as tU score, would alter the outcome score when it is compared with the regular method of UCEIS scoring, which is to score the most inflamed colonic segment. The two scores showed a good correlation with Spearman's $r = 0.86$ and P value less than 0.0001 for less severe disease UCEIS $\leqslant 5$. However, correlation is substantially decreased for severe disease (UCEIS > 5) with Spearman's $r = 0.48$ and $P < 0.01$. Moreover, when these two scoring methods were applied to assess patients with a flare-up at 1 year, *tU* score was more sensitive than the regular UCEIS score with area under ROC curve = 0.688 ± 0.06 *vs* 0.60 ± 0.07 and $P < 0.01$. The tU score was also significantly higher when patients with and without a flare-up at 1 year were assessed, whereas the regular UCEIS score did not differ (25.3 ± 8.2 *vs* 20.1 ± 6, $P < 0.005$). This concluded that the evaluation of disease by full colonoscopy with multiple segments may provide the more accurate method to evaluate disease activity.

Overall, the study concluded that the UCEIS confirmed better responsiveness than the UCDAI, and it is superior to describe accurate endoscopic findings in patients with severe UC. This responsiveness can be crucial in clinical trials since duration of primary endpoints in many clinical trials is approximately 12 wk[44]. Thus, indices that allow to capture small but vital improvement that reflects on disease outcome is essential to clinical trials.

Reliability: Despite mucosal healing becoming the goal for management for UC, the most critical limitation of endoscopic assessment is its inherent intra- and inter-observer variations[6,45-47]. Reliability is evaluated with inter- and intra-observer reliability as well as internal consistency. The leading author of the UCEIS led another study to investigate reliability in different aspects.

The first study published in 2013 investigated intra- and inter-observation reliability[15]. Twenty-five readers from 14 countries were recruited in this study, who evaluated 28 videos. To quantify intra-observer reliability, 4 duplicated videos were included. For inter-observer reliability, all readers were trained to ensure consistent understanding and use of the scoring system. Internal consistency was measured using the Cronbach's coefficient alpha, which was 0.863 for the overall UCEIS - bleeding 0.80, vascular pattern 0.83, and ulcers and erosions 0.79.

The study found that the intra and inter-observer reliability ratios for the UCEIS were 0.96 and 0.88 respectively. Intra-observer agreement static was calculated with kappa, which was 0.72, with individual descriptors ranging from 0.47 (for bleeding) to 0.87 (for vascular pattern). Inter-observer agreement statistic was slightly lower at 0.50, with individual descriptors ranging from 0.48 (bleeding) to 0.54 (vascular pattern). Additionally, these observer reliabilities were compared with readers who were given clinical information at the time of the video readings, which determined no apparent bias by clinical information.

To evaluate the impact of clinical information on UCEIS scores, the author also undertook another study in 2015[26]. The study invited 40 readers from various countries who were experienced with endoscopic assessment. Each reader was divided into two groups (with and without clinical information) and conducted evaluation of a random 28 from 44 videos, which had not been used in the previous study. Furthermore, 4 videos included misleading information in order to ensure disparity between endoscopic assessment and clinical information.

This study showed there is no impact of clinical information on mean UCEIS scores. They were almost identical whether readers had knowledge of patient's clinical information and the median SD was 0.94 for blinded and 0.93 for unblinded. The SD was low for videos with severe disease.

Intra- and inter-observer agreement of the blinded and unblinded readers was also evaluated. Intra-observer agreements for bleeding and vascular pattern were very similar for the two groups, whereas that for erosions and ulcers just reached to statistical significance with kappa of 0.47 for blinded and 0.74 for unblinded.

The study also extended to compare the UCEIS with other indices and patient-reported symptom scoring systems. The full Mayo Clinic Score (MC)[32], partial MC (excluding endoscopic subscore)[48], patient-reported stool frequency and rectal bleeding subscore, patient functional assessment score and Feagan score were compared with the UCEIS as well as Feagan Score[36]. This showed the UCEIS is significantly superior to the Feagan Score including patient-reported symptom subscore. This implies that the UCEIS alone may be sufficient for outcome measurement in clinical trials.

The only inter-observer and central reader variations study on UCDAI also referred to UCEIS[25]. The authors investigated the role of central readers to minimise inter-observer variations, which may contribute to false responses to placebo in UC trials. They conducted a 10-wk randomised double-blinded placebo-controlled study on patients with UC who scored UCDAI $\geqslant 2$.

Three hundreds and forty-three patients, who were initially assessed by site investigators, were enrolled to the randomised clinical trials. Clinical remission (UCDAI,

Table 5 Definitions of remission in ulcerative colitis

Guidelines	Definition
FDA[5]	Clinical remission
	Mayo score of ⩽ 2 with no individual subscore > 1
	Rectal Bleeding subscore = 0
	Stool Frequency subscore = 0 (at least one point decrease in Stool Frequency subscore from baseline and achieved 1 is considered)
	Endoscopy subscore = (Mayo score: 0 or 1, UCDAI = 0)
	Clinical response
	Reduction in Mayo score ⩾ 3 and ⩾ 30% from baseline with Rectal Bleeding subscore ⩽ 1
	Corticosteroid-free remission
	Clinical remission in patients using oral corticosteroids at baseline who have discontinued them and are in clinical remission at the end of the study
World Gastroenterology Organisation	Clinical remission
	UCDAI ⩽ 2 (2010 World Gastroenterology Organisation Practice Guideline)[50]
	Corticosteroid-free remission
	Decreasing the frequency and severity of recurrence and reliance on corticosteroids
International Organisation for the Study of IBD	End points = induction of remission = mucosal healing[12]
	The absence of friability, blood, erosions and ulcers in all visible segments
	No mention of clinical symptoms
American College of Gastroenterology	No clear definition[51]
British Society of Gastroenterology	No clear definition[52]
European Crohn's and Colitis Organisation	Remission[53]
	A complete resolution of symptoms and endoscopic mucosal healing
	Not been a fully validated definition of remission
	Suggest the best way forward is a combination of
	Stool Frequency ⩽ 3
	No rectal bleeding
	Normal or quiescence mucosa at endoscopy
	Clinical response
	Clinical and endoscopic response depending on the activity index
	Generally, a decrease in the activity index > 30% plus a decrease in the rectal bleeding and endoscopic subscores

UCDAI: Ulcerative colitis disease activity index; IBD: Inflammatory bowel disease; FDA: Food and Drug Administration.

stool frequency and bleeding scores of 0) was achieved by 30.0% of patients treated with mesalamine and 20.6% of those with placebo. However, when those 343 were re-assessed by 7 central-readers, 31% of those patients were in fact ineligible as they scored lower than 2. Furthermore, this altered the remission rate to 29.0% and 13.8% in the mesalamine and placebo groups respectively. In conclusion, this study suggests robust methodology for future clinical trials in UC to avoid misleading results.

The authors also extended the study to quantify the inter-observer variation amongst 7 central readers using UCDAI, UCEIS, Feagan score, visual analogue scale. Of those indices, UCEIS demonstrated the highest interclass correlation coefficient with 0.83 and UCDAI was 0.79. The authors concluded that this might be attributed to no friability assessment in UCEIS, which is the commonest source of disagreement between central and site readers in this study.

What is remission in UC?

Definition of remission: Remission rates can vary by more than two-fold depending on the definition of remission used for data analysis[49]. In addition to uncertainty about standardisation of disease activity measurement, disease remission has also never been conclusively defined or validated. Defining disease remission should be the fundamental starting point of studying therapeutic efficacy and disease monitoring, before standardising how to measure disease activity.

Definitions of remission in UC vary depending on users, settings and the purpose of monitoring the disease activity. The definition of remission used in clinical practice and by the patient is often different from that used in clinical trials. Remission, clinical remission, complete remission, partial remission, clinical response, mucosal healing or remission, corticosteroid-free remission, registration remission are frequently employed terms used in clinical practice by healthcare professionals and patients, although these terms are used interchangeably and variably without strict definition, including in clinical trials.

Table 5 is a summary of definitions of remissions in UC defined by large regulatory bodies and guidelines. All guidelines mention remission to manage disease, however, few guidelines explicitly define remission. The American College of Gastroenterology is no exception, though it controversially states that, "practical therapeutic end point, endoscopic demonstration of mucosal healing is not usually necessary for a patient who achieves clinical remission". The FDA recommends a primary endpoint of clinical remission, and clinical remission is defined

Table 6 Clinical studies measured with the ulcerative colitis endoscopic index of severity

Ref.	Year	Type of study	Drug/subject of study	Entry criteria	Primary endpoint	Secondary endpoint	Remission/clinical improvement	Length of study
Hartman *et al*[54]	2016	Randomised, double-blind, placebo-controlled study	AVX-470, oral	36 patients with Mayo score 5-12 and Mayo ES ⩾ 2	Not set, but implies clinical response at week 4	Not set	Remission was not defined. Clinical response Mayo reduction ⩾ 3	4 wk
Lin *et al*[55]	2015	Prospective, multi-centre study	Faecal calprotectin	52 patients with UC	N/A	N/A	Endoscopic remission: UCEIS < 3	N/A
Magro *et al*[56] ACERTIVE study	2016	Cross-sectional multi-centre study	Faecal calprotectin/ lipocalin	371 patients Mayo partial score < 2, montreal classification < 2			Remission: UCEIS ⩽ 1 Mucosal healing: Mayo ES = 0	

UCEIS: Ulcerative colitis endoscopic index of severity; UC: Ulcerative colitis; ES: Endoscopic subscore; N/A: Not available.

as follows[5]: Rectal Bleeding subscore = 0: (1) Stool Frequency subscore = 0 (or stool frequency subscore 1 is considered if at least one point improvement in Stool Frequency subscore from baseline); and (2) Endoscopy subscore 0 on UCDAI.

It also describes mucosal healing should not be supported from macroscopic appearance of the mucosa through endoscopy. However, the FDA further describes that there are no criteria for histological assessment of mucosal healing due to a lack of validated gold standard histological scoring systems.

The European Crohn's and Colitis Organisation (ECCO) more realistically states in their guidelines for patients in UC that there is no fully validated definition of remission.

How indices are used in clinical trials and defining remission endpoints: Since there is no gold-standard outcome measurement instruments in UC, many clinical trials have employed instruments depending on its application. Classic disease activity measurement instruments have been recently challenged by the FDA because of the significant effect of their subjective components affecting reproducibility. Even the traditionally promoted indices used by the FDA (Mayo Score and UCDAI) contain physician global assessment, which is highly sensitive to bias. The FDA suggests the primary endpoint should be achieved by endoscopic as well as clinical outcome, however, the difficulty in this is that these symptoms do not necessarily occur simultaneously with symptom control, especially where stool frequency and abdominal pain are considered. Nevertheless, these symptoms affect patients' quality of life. There are therefore further hurdles to overcome before standardisation of endpoint definition in UC[44].

In this systematic review, remission endpoints were investigated by studying the application of the UCEIS and UCDAI in clinical research and therapeutic trials (Tables 6 and 7). There are only three clinical research identified which applied the UCEIS for disease outcome measure and defined remission. Furthermore, only one randomised clinical trial has chosen the index for its outcome measurement instrument so far[54].

The trial was the first-in-human trial of AVX-470, which is a bovine-derived, orally-administered, anti-tumour necrosis factor (TNF) antibody, that works to intestinal mucosal tissue with minimal systematic effects. TNF is upregulated in the colonic mucosa in UC and believed to play a pathological role by loss of mucosal barrier integrity[57]. AVX-470 reduces levels of TNF protein in mice models, thus correcting immune dysregulation. In this study, the UCEIS was used to assess endoscopic response to treatment along with the total Mayo score and sub-scores.

This study successfully correlates between UCEIS scores and TNF immunohistochemistry scores at baseline. Further, it found that TNF staining was significantly reduced in proximal and distal segments of bowel, whereas the UCEIS changes were more apparent in proximal segments than distal ones. Although the study described achieving clinical remission, this was never defined.

The UCEIS was used for endoscopic assessment in a prospective study to quantify faecal calprotectin in patients with UC[55]. The authors used Quantum Blue Calprotectin High Range Rapid Test (Buhlmann laboratories AG, Schonenbuch, Switzerland) for faecal calprotectin measurement tools in this study. Interestingly, the authors defined endoscopic remission when the UCEIS < 3. They also concluded that faecal calprotectin and CRP were both well correlated with the UCEIS (the Spearman correlation coefficient is 0.696 and 0.581 respectively). Moreover, they concluded that when a cut-off faecal calprotectin of 191 μg/g is set, this could predict endoscopic remission and mucosal remission (UCEIS < 3) with 88% sensitivity and 75% specificity. However, when UCEIS < 1 clinical remission proposed by other authors[14,23] is applied, faecal calprotectin would be lower than 191 μg/g. This could lead to underestimate patients who should be treated.

The largest patient population study that used the UCEIS is a cross-sectional, multi-centre study, ACERTIVE study[56]. The aim of this study was to evaluate potential applications of biomarkers (faecal calprotectin and neutrophil gelatinase B-associated lipocalin) as disease activity measuring instrument

Table 7 Randomised clinical trials measured with the ulcerative colitis disease activity index

Ref.	Year	Drug	Entry criteria	Primary endpoint	Secondary endpoint	Remission/clinical improvement	Length of study
Randomised clinical trials - to induce remission Mesalazine (5-ASA)							
Marteau *et al*[58]	2005	Pentasa (PR + PO *vs* PO alone)	UCDAI: 3-8	Remission at week 4	Remission rate at week 8 Improvement at week 4 and 8	Remission: UCDAI ⩽ 1 Clinical improvement: A decrease of UCDAI ⩾ 2	8 wk
D'Haens *et al*[59]	2006	SPD476 - MMX mesalazine	UCDAI: 4-10 + endoscopic score ⩾1 PGA score ⩽ 2	Remission	Change in UCDAI, FS, histology at week 8 Change in symptoms	Remission: UCDAI ⩽ 1 (with RB 0, SF ⩽ 1) at week 8	8 wk
Sandborn *et al*[60]	2007	MMX Multi Matrix System mesalazine	UCDAI: 4-10 + endoscopic score ⩾1 PGA score ⩽ 2	Clinical/endoscopic remission at 8 wk	Proportion of clinical improvement Proportion of patients as treatment failure Change in: RB, SF, FS	Clinical remission: UCDAI ⩽ 1 Endoscopic remission: UCDAI endoscopic subscore ⩽ 1 Clinical improvement: A decrease of UCDAI ⩾ 3 Treatment failure: Unchanged or worsened UCDAI	8 wk
Lichtenstein *et al*[61]	2007	SPD476 - MMX mesalazine OD *vs* BD	UCDAI: 4-10	Clinical and endoscopic remission at week 8	Comparison of remission rate at week 8	Clinical remission: UCDAI ⩽ 1 with RB/SF/EI = 0	8 wk
Kamm *et al*[62,63] MEZAVANT study	2007 2009	MEZAVANT MMX Mesalamine	Mild - mod UC: UCDAI 4-10 + endoscopic subscore ⩾ 1, PGA ⩽ 2	Clinical + Endoscopic remission at week 8	Clinical remission Clinical improvement Change in UCDAI	Clinical + endoscopic remission: UCDAI ⩽ 1 + subscore RB/SF = 0, No mucosal friability + a ⩾ 1 reduction in EI Clinical improvement: Decrease in UCDAI ⩾ 3	8 wk
Ito *et al*[64]	2010	Asacol *vs* PentasaTime-dependent *vs* pH dependent Mesalamine	UCDAI: 3-8 and blood stool score ⩾ 1	To demonstrate Asacol over Pentasa AND the decrease in UCDAI	Macroscopic changes	Remission: UCDAI ⩽ 2 and no blood diarrhoea Clinical improvement: UCDAI decreased by ⩾ 2	8 wk
Hiwatashi *et al*[65]	2010	Mesalazine - dose study	UCDAI: 6-8	Change in UCDAI at week 8	Remission, improvement, efficacy	Remission: UCDAI ⩽ 1 Efficacy: Decrease of UCDAI ⩾ 2	8 wk
Flourié *et al*[66] MOTUS study	2013	Mesalazine, Pentasa OD or BD in total of 4 g/d	UCDAI: 3-8	UCDAI ⩽ 1 after 8 wk	Complete remission (UCDAI = 0) at 8 wk UCDAI decreased by ⩾ 2 at 8 wk Clinical remission at week 4, 8, 12 Mucosal healing at 8 wk	Complete remission: UCDAI = 0 Endoscopic remission: UCDAI endoscopic subscore: 0 or 1 Clinical remission: UCDAI ⩽ 1	12 wk
Probert *et al*[42] PINCE study	2013	Mesalazine (pentasa) enema	UCDAI: 3-8	Remission rate (UCDAI < 2) at 4 wk	Remission rate at 8 wk, improvement at week 2, 4 and 8 Time to cessation of RB QoL (EQ-5D)	Remission: UCDAI ⩽ 1 Clinical improvement: UCDAI decreased by ⩾ 2	8 wk
Sun *et al*[67]	2016	Mesalazine (modified-release *vs* enteric-coated tablets)	UCDAI: 3-8 + bloody stool score > 1	The decrease in UCDAI	Remission rate Efficacy rate	Remission: UCDAI ⩽ 2 + bloody stool 0 Clinical improvement: A decrease of UCDAI ⩾ 2	8 wk
Suzuki *et al*[68]	2016	pH dependent release mesalamine, asacol dose	UCDAI: 6 - 10 Rectal bleeding score ⩾ 1	Decrease in UCDAI		Remission: UCDAI ⩽ 2 Rectal bleeding score: 0 Improvement UCDAI decreased by ⩾ 2	8 wk
Thiazole compounds							
Mantzaris *et al*[69]	2004	Azathioprine alone (2.2 mg/kg) *vs* combination with olsalazine (0.5 g TID)	Steroid-dependent remission	Relapse rate	Time to relapse Time to discontinuation Severity of relapse	Remission: UCDAI ⩽ 1 Relapse: New symptoms + UCDAI > 3	2 yr

Schreiber *et al*[70]	2007	Tetomilast - Thiazole compound	UCDAI: 4-11	Clinical improvement: UCDAI decreased by ⩾ 3 at 8 wk	Remission Clinical improvement at week 4 IBDQ-32 score Proportion of pts with improved Flexible Sigmoidscopy score Time to clinical improvement Time to remission	Clinical improvement: UCDAI decreased by ⩾ 3 Remission: UCDAI ⩽ 1	8 wk
Steroids							
Travis *et al*[71] CORE Ⅱ study	2012	Budesonide MMX	UCDAI: 4-10	Clinical/endoscopic remission at week 8	Clinical improvement Endoscopic improvement at week 8	Clinical/endoscopic Remission: UCDAI ⩽ 1 + RB/SF/EI = 0 Clinical improvement: A decrease of UCDAI ⩾ 3 Endoscopic improvement: A decrease of EI ⩾ 1	8 wk
Probiotics							
Vernia *et al*[72]	2000	Sodium Butyrate	Mild-moderate UC	Remission or marked improvement		Remission: UCDAI ⩽ 2 Positive response: Decrease of UCDAI ⩾ 2	6 wk
Mahmood *et al*[73]	2005	Human recombinant trefoil factor 3 enema	UCDAI: >3	Remission at week 2	Clinical significant improvement in clinical and histological scores at 2 and 4 wk	Remission: UCDAI ⩽ 1 without RB Clinical improvement: A decrease of UCDAI >3	4 wk
Lichtenstein *et al*[74]	2007	Bowman-Birk inhibitor concentrate - soy extract with high protease inhibitor activity	UCDAI: 4-10	Remission at week 8		Remission: UCDAI ⩽ 1 + no RB or SF Clinical improvement: UCDAI decrease ⩾ 1	
Tursi *et al*[75]	2009	VSL #3 (probiotic)	UCDAI 3-8, endoscopic subscore ⩾ 3	Decrease in UCDAI of ⩾ 50%	Activity of relapsing UC Remission Improvement Change in objective and subjective symptoms	Remission: UCDAI ⩽ 2	8 wk
Sood *et al*[76]	2009	VSL #3 probiotic	UCDAI 3-9 with endoscopic subscore ⩾ 2	Clinical improvement at week 6	Clinical remission	Clinical remission: UCDAI ⩽ 2 Clinical improvement: A decrease UCDAI by 50%	12 wk
Tamaki *et al*[77]	2016	Bifidobacterium longum 536 (probiotic)	UCDAI 3-9	Change in UCDAI	Remission Improvement of Objective and subjective symptoms Endoscopic improvement in Mayo subscore	Remission: UCDAI ⩽ 2	8 wk
Helminth therapy Garg *et al*[78]	2014	Helminth Trichuris suis ova	UCDAI of ⩾ 4	Clinical improvement	Clinical remission	Clinical improvement: Decrease in the UCDAI of ⩾ 4 Clinical remission: UCDAI of ⩽ 2	12 wk
Nicotine therapy							
Ingram *et al*[79]	2005	Nicotine enema 6 mg/d	Confirmed UC with inflamed mucosa grade > 2	Clinical remission	Improvement in the UCDAI	Clinical remission: UCDAI EI ⩽ 1 and No RB for 1 wk	6 wk
Randomised clinical trials - to maintain remission							
Lichtenstein *et al*[80-82] and Zakko *et al*[83]	2010 2012 2015 2016	Mesalamine granules 1.5 g/d, OD	Previously achieved remission with steroids for > 1 mo and < 12 mo	Percentage of patients relapse-free at 6 mo	Mean changes from baseline at month 6	Relapse: UCDAI RB ⩾ 1 and EI ⩾ 2 Remission: UCDAI RB = 0, EI < 2	6 mo
Bokemeyer *et al*[43] and Dignass *et al*[84]	2009 2011	Mesalazine, Pentasa OD or BD in total of 2 g/d	Clinical remission: UCDAI < 2	To demonstrate OD is not inferior to BD	Time to relapse between 2 groups UC-DAI total and subscores between 2 groups	Remain in remission UCDAI ⩽ 2	12 mo

RB: Rectal bleeding; SF: Stool frequency; EI: Endoscopic index/subscore; OD: Once daily; BD: Twice daily; TID: Three times daily; UCDAI: Ulcerative colitis disease activity index; QoL: Quality of life.

in patients with asymptomatic UC. The UCEIS and Geboes index[22] were applied for macroscopic and

microscopic assessment respectively. Nine percent of the asymptomatic patients had active disease with UCEIS > 2. Twenty-one percent of the asymptomatic patients presented with Geboes index > 3. One point fifteen percent and 5% of the patients presented with focal and diffuse basal plasmacytosis, respectively. Patients with asymptomatic disease indeed showed presence of macroscopic as well as microscopic disease. Furthermore, 50% of patients who scored a UCEIS < 2 and 15% of patients who were considered to have achieved mucosal healing (Mayo ES = 0) had diffuse basal plasmacytosis. These results support the previous published notion that macroscopic findings are not sufficient to define remission or endpoint[9].

Both biomarkers predicted mucosal healing as well as histological remission with satisfactory probability of 75%-93%. The authors proposed a cut-off figures of 150-250 μg/g for faecal calprotectin and 12 μg/g for lipocalin. This range of cut-off level for faecal calprotectin is due to the application of two faecal calprotectin measurement tools (Quantum Blue Calprotectin High Range Rapid Test and Automated Fluroimmunoassay-EliA Test) from stool samples. Although this proposed cut-off point for faecal calprotectin for clinical remission is a similar value with the Taiwan group[55], the defined remission show variance as the Taiwan group set UCEIS < 3 for remission whereas ACERTIVE study used UCEIS $\leqslant$ 1. Although it is only one score difference, this can be of significance for disease outcome. As Arai *et al*[20] concluded, the recurrence rate was directly proportional to the UCEIS score. The recurrence rate for UCEIS 1 disease is 22.4%, whereas UCEIS 2 disease increases to 27.0%. As the authors state validation of the proposed cut-off values is required before introducing them in clinical setting. Moreover, caution should be applied when introducing biomarkers especially when their intention is to replace endoscopic assessment.

Table 6 shows the summary of the randomised clinical trials that utilised the UCDAI for disease activity assessment, defining remission and endpoints. The studies were divided into introduction and maintenance of disease remission.

Most of the studies investigated the efficacy of introducing remission set clinical remission as UCDAI $\leqslant$ 1, however some studies defined as UCDAI $\leqslant$ 2 for remission. It appears that many studies have taken advantage of defining their own remission, clinical response and endpoints with the UCDAI as it is not clearly defined in previous guidelines. The studies with probiotics appear to choose higher remission cut-off point, which could interpret that it is undemanding to achieve clinical remission so that it would satisfy requirements of regulatory bodies such as the FDA. The previous validation study suggested UCDAI score < 2.5 for clinical remission[65], meaning UCDAI $\leqslant$ 2 is still within the range of remission.

Another point to note is that many studies have their own additional criteria with a specific patient-reported symptom scoring system to measure rectal bleeding and stool frequency to define remission or clinical response. This is likely attributed to the guideline published by the FDA, which encourages to assess patient-reported outcome measurement on rectal bleeding and stool frequency in addition to the macroscopic assessment with endoscopy as an endpoint for clinical trials. This is also reflected on their definition of clinical remission on Table 5.

If a more stringent primary endpoint is enforced the clinical utility of therapeutics may be harder to demonstrate, potentially limiting the number of agents available in the marketplace. Furthermore, drug development for UC faces bigger challenge due to the unknown natural history of UC, unpredictable relapse and remission patterns as well as response to medications with known efficacy. If the stringent remission and endpoint was forced by regulatory bodies, the pharmaceutical industry may choose drugs that have cheaper development cost.

Although the FDA supports the use of UCDAI for measuring primary endpoints, UCDAI has limitations. As it is highlighted in the previous section, one of the weakness is a lack of validation and vulnerability to observer bias. Adding inconsistent definition of remission and endpoint for each clinical trial hinders providing optimal management to patients with the disease.

DISCUSSION

Homogeneity of the clinical trials in UC has been discussed amongst experts for decades. Despite a desire for a single gold-standard disease activity index, the number of indices has been steadily increasing. Disease remission is yet to be fully defined, thus trial outcomes vary and limit the utility of these studies depending on the purpose of its clinical use. Most trials chose individual endpoints which are not necessarily clinically pertinent. Clinicians, on the other hand are constantly negotiating with patients to provide the best possible management for this chronic condition, regardless of an index score. This variation makes the comparison amongst clinical trials extremely difficult, hindering drug development.

So far, many review studies summarised and evaluated currently available indices on different assessments. The majority of these studies highlighted the wide variation of endpoints by different indices and emphasised the importance of having a gold-standard index to assess the efficacy of the interventions. This has led to development of more indices rather than choosing a gold-standard index, adding more choices and fuelling confusion amongst researchers and clinicians. This systematic review proposes to emphasise on a universal consensus on UC remission before developing any more indices. Futher more this systematic review would assist scientists and clinicians to have a better understanding of confusing definitions and disease activity indices that have been used interchangeably.

This systematic review was conducted to evaluate the definition and evidence for remission endpoints in ulcerative colitis from the point of view of two particular indices. The UCDAI has been widely used in clinical studies compared to the UCEIS. Although the UCEIS has been extensively validated, only one randomised clinical trial has employed the UCEIS as their outcome measurement instrument of date. The reason may be threefold. Firstly, other traditional disease activity measurement instruments have been widely used in previous clinical trials, making comparison with those trials more straightforward, although less robust. Secondary, if clinical trials were conducted for drug development, they would more likely choose the disease activity indices as recommended by regulatory bodies such as the FDA or equivalent. Finally, the UCEIS was recently developed thus there is no surprise that the number of clinical trials using this scoring system is still low.

The other two studies that used the UCEIS are not randomised clinical trials, though they demonstrated how multiple definitions of remission used in the evaluation of biomarker, calprotectin, to monitor disease activity could alter the outcomes. Without a universal definition of remission, researchers can freely define the UCEIS score for a remission endpoint, making evaluation of calprotectin use in clinical practice very difficult.

Furthermore, regulatory bodies such as the FDA recommend measuring endpoints in terms of clinical remission with particular indices, although they still do not convey the ideal length of clinical trial to achieve a primary endpoint or the duration of clinical remission before relapsing. This diversity of clinical protocols was also emphasised in this systematic review.

One of the criticisms for traditional outcome measurement instruments has been insufficient validation. The UCEIS has designed to overcome from this problem and to take a step forward for establishing a gold standard outcome measurement instrument. Yet, this systematic review highlighted that validation is not necessarily an issue for employing an outcome measurement instrument for clinical trials. Although we focused on developing new ideal indices, a new index may not be a solution to establish a gold standard outcome measurement instrument.

A lack of understanding in aetiology and natural history of ulcerative colitis may contribute to this confusion. In order to untangle this confusion, we recommend that an international consensus of remission should be sought as a matter of urgency before establishing a gold standard outcome measurement. Once a universal consensus for remission is reached and defined, establishing a gold-standard index, which can measure true symptoms and is transferable and meaningful to clinical practice, can be determined. That would lead to standardisation of clinical trial protocols for advancing patient care.

COMMENTS

Background

The current target of disease remission endoscopically is mucosal healing although it has not been fully validated or no standardised definition of mucosal healing. Yet, this appears to be the goal for many clinical practice as well as drug trials. The recent draft guideline released by the FDA states the ideal primary efficacy assessment instrument in clinical trials should consist of (1) a signs and symptoms assessment scale - best measured by a patient-reported outcome instrument. If not, an observer-reported outcome instrument; and (2) an endoscopic and histological assessment scale. Thus, endoscopic assessment tools with comprehensive clinical symptom assessment components that come from patients would be a reasonable choice to argue remission and endpoints employed in clinical trials.

Research frontiers

The authors believe this has been mentioned everywhere in the paper that definition of ulcerative colitis endpoint has been introducing ambiguity especially when different clinical trial studies are compared. The authors also mentioned in the summary that a lack of understanding in aetiology and disease natural history may contribute to this confusion, which needs to be addressed in the future research.

Innovations and breakthroughs

The authors added to emphasize the differences from other similar studies.

Applications

The authors added "This systematic review would assist scientists and clinicians to have a better understanding of confusing definitions and disease activity indices that have been used interchangeably".

Peer-review

This is a comprehensive review of remission endpoints in ulcerative colitis, the paper is well written and is very useful for both clinical practice and teaching purposes.

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SYSTEMATIC REVIEWS

Medication non-adherence in bipolar disorder: Review of rates, demographic and clinical predictors

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Abstract

AIM

To conduct a systematic search for all studies examining rates and demographic and illness-related determinants of medication non-adherence in bipolar disorder (BD).

METHODS

A comprehensive literature search was undertaken of six English-language databases to identify published articles on medication non-adherence in BD from inception till December 2016. Any article, either a review or an original-research article was examined for its relevance to the subject. All such articles were manually searched to locate any further articles containing relevant information. Studies were included only if they had adequately described the patient sample, assessment methods and statistical procedures, presented their results systematically and their conclusions were congruent with the results.

RESULTS

The initial search yielded 249 articles on the subject; of these 198 articles were included. Of the 162 original-research studies, 132 had provided information on rates of medication non-adherence in BD. There was a wide variation in rates ranging from universal adherence (100%) to almost universal non-adherence (96%); this discrepancy was more due to methodological differences than true variations in rates. Notwithstanding the significant discrepancies in methodology, based on these 132 studies mean rates of 41.5%-43% and median rates of 40%-41% were obtained for medication non-adherence in BD. Rates of adherence with mood stabilizers were significantly lower than those for antipsychotics, or for medications of all classes. None of the demographic attributes were unequivocally linked to medication non-adherence in BD. Similarly, medication-related variables such as type of medications, doses, treatment regimens and side effects did not demonstrate consistent associations with non-adherence. Among clinical characteristics the presence of comorbid substance use disorder and absence of insight were the only two factors clearly linked to non-adherence in BD.

CONCLUSION

Medication non-adherence is prevalent in about a third

to half of patients with BD. Demographic, illness and treatment related factors do not predict non-adherence with certainty.

Key words: Medications; Demographics; Rates; Non-adherence; Illness characteristics; Treatment variables; Bipolar disorder

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Core tip: Based on existing reviews non-adherence is estimated to be present in 25%-42% of patients with bipolar disorder (BD). The present, more comprehensive review comprising of 198 studies found mean rates of 41.5%-43% and median rates of 40%-41% for medication non-adherence in BD. Neither demographic characteristics nor medication-related variables were unequivocally linked to medication non-adherence in BD, while comorbid substance use disorder and absence of insight were the only two clinical factors consistently associated with non-adherence in BD. The failure of clinical and demographic factors to predict non-adherence emphasizes the importance of other patient orientated factors in determining non-adherence in BD.

Chakrabarti S. Medication non-adherence in bipolar disorder: Review of rates, demographic and clinical predictors. *World J Meta-Anal* 2017; 5(4): 103-123 Available from: URL: http://www.wjgnet.com/2308-3840/full/v5/i4/103.htm DOI: http://dx.doi.org/10.13105/wjma.v5.i4.103

INTRODUCTION

Bipolar disorder (BD) is prototypical of all chronic medical conditions with enduring symptoms, residual disability and the need for long-term care[1,2]. Like other such conditions, non-adherence with treatment is very common among patients with BD and associated with a range of adverse consequences such as poor clinical outcomes, functional impairment, impaired quality of life, increased health-service utilization and higher costs of care[2-4].

Several reviews on the subject have estimated non-adherence rates in BD to range from around 8% to 68% with mean rates varying from 25% to 40% across these reviews[5-8]. Despite this wide variation in rates the median rate of non-adherence, which is probably a more true measure of non-adherence, has been fairly stable at 40% to 42% in different reviews. However, it is somewhat surprising that despite there being over 100 studies on treatment non-adherence in BD, most of these reviews have not included more than a handful of studies. Moreover, the majority of reviews are somewhat dated and have not systematically and comprehensively searched the existing literature to identify all possible studies relating to non-adherence in BD. Those that have systematically reviewed the existing literature (*e.g.*, Busby and Sajatovic[3]) appeared to have used very stringent selection criteria limiting the number of studies they have included.

The correlates of non-adherence in BD have been traditionally categorized into patient-related, illness-related, treatment-related and physician-related factors[9-12]. The majority of studies have, however, examined demographic correlates like age, gender, marital status, or clinical features such as age of onset, longitudinal course, symptom-severity, insight and comorbidity, or medication-related variables such as the class of medications, number and doses of medications and side effects associated with treatment[3,13,14]. However, results of these studies have been largely inconsistent, leading to considerable uncertainty regarding which of these factors truly influence non-adherence in BD[8,13]. Consequently, there is little consensus among reviews regarding the clinical, demographic and treatment-related determinants of medication non-adherence in BD. Moreover, similar to the reviews on the rates of non-adherence in BD, reviews examining correlates of non-adherence are based on a limited number of studies.

Given these drawbacks of existing reviews on rates and correlates of medication non-adherence in BD, the present review aimed to conduct a more comprehensive and systematic search for all possible studies of BD, which have investigated these aspects. The principal objective was to estimate rates of medication non-adherence in BD and examine its demographic, illness and medication related correlates based on a much wider selection and a larger number of studies than those that have been included as a part of earlier reviews.

MATERIALS AND METHODS

A comprehensive literature search was undertaken using the following six English-language databases: MEDLINE, PubMed, PsycINFO, EMBASE, Cochrane and Google to identify published articles on medication non-adherence in BD from inception till December 2016. Search terms included BD, bipolar depression or mania used in conjunction with other terms including adherence, compliance, concordance, non-adherence, non-compliance, determinants, predictors, treatment and medication. Any article, either a review or an original research article (based on clinical trials or observational studies) was examined for its relevance to the subject. All such articles were manually searched to locate any further articles, which were judged to be containing information pertaining to the topic. In an effort to identify and include as many studies as possible the initial criteria for selection were broad and inclusive. Any article that had provided information on rates and/or demographic, clinical or treatment correlates of medication non-adherence in BD was included. Articles dealing with other forms of adherence, *e.g.*, appointment adherence or attendance for psychosocial interventions were considered only if they had provided

Table 1 Rates of medication non-adherence in bipolar disorder: Reviews

Ref.	Review based on	Non-adherence rates
Van Putten[20], 1975	7 studies	20%-30% (only lithium)
Jamison and Akiskal[21], 1983	10 studies	33%-50% (only lithium)
Cochran[5], 1986	13 studies from 1966-1986	9%-57% (only lithium)
Goodwin and Jamison[22], 1990	50 studies	18%-53% (only lithium)
Lingam and Scott[6], 2002	3 studies and 1 review	20%-66%, median 41%
Perlick *et al*[7], 2004	25 papers from 1979-2004	23%-68%, median 42%
Colom *et al*[4], 2005	6 studies	20%-64%, mean 25%
Gaudiano *et al*[18], 2008	3 reviews	20%-60%, mean 40%
Basco and Smith[8], 2009	9 studies	8%-64%
Busby and Sajatovic[3], 2010	6 studies	20%-60%
Foster *et al*[23], 2011	7 studies	21%-50%
Leclerc *et al*[12], 2013	27 studies(rates derived from 6 studies)	12%-64%
García *et al*[16], 2016	9 studies	23%-60% (only antipsychotics)

Other reviews have also estimated non-adherence rates to be in the range of 20%-68% with a median rate of 41%-42% in BD including Schou[24] (1988), Guscott and Taylor[25] (1994), Scott[26] (1995), Schou[19] (1997), Berk *et al*[17] (2004), Sajatovic *et al*[27] (2004), Byrne *et al*[28] (2006), Depp and Lebowitz[29] (2007), Depp *et al*[14] (2008), Pompili *et al*[10] (2009), Crowe *et al*[15] (2011) and Rakofsky *et al*[11] (2011). BD: Bipolar disorder.

information on medication adherence. Both quantitative and qualitative studies were included. Final selection, however, also depended on the quality of studies, which was assessed partly based on criteria used in previous reviews[12,15]. Studies were included only if they had adequately described the source and nature of the patient sample, the methods of ascertaining relevant variables and the statistical procedures followed. Additionally, for any study to be incorporated its results should have been presented systematically and the conclusions should have been congruent with the results of the study.

Statistical analysis

Statistical analyses consisted mainly of estimation of mean and median rates. Student's *t* test was used to compare the non-adherence rates among different classes of medications. This was approved by the bio-statistics department of the institution.

RESULTS

The initial search yielded 249 articles on the subject; 43 of these were reviews and 206 were original research articles. Of these 51 articles (7 reviews and 44 original research articles) were excluded. Though these 51 articles did deal with some aspect of treatment adherence in BD the principal reason for excluding them was the lack of information either on rates of medication non-adherence or on demographic, illness or treatment related correlates of non-adherence in BD. Thus, the final list included 198 articles; 36 of these were reviews and 162 were original research articles.

Rates of medication non-adherence in BD

Reviews: Table 1 lists the reviews on rates of non-adherence in BD. The most commonly quoted reviews are the ones by Lingam and Scott[6] and Perlick *et al*[7], both of which have found rates ranging from about 20% to 68% with median rates of about 41% to 42% for non-adherence in BD. Other reviews included in the table also indicate that non-adherence rates vary from 8%-64% with mean rates of 25% to 40% and median rates of 40% to 41% for all classes of medications. Reviews on lithium estimate non-adherence rates to lie between 9% to 57%, while one review found the rates to vary from 23%-60% among patients on antipsychotics[16]. The wide variation in rates (from 8% to 68%) was most likely to be due to differences in methodology adopted by individual studies[4]. Moreover, the number of studies, from which these rates are derived was quite small in most reviews. Only Pompili *et al*[10] have included 104 articles on mood disorders from 1975 to 2009, but the number of studies from which the non-adherence rate for BD was derived was not clear. Despite these disparities and limitations it was evident that about a quarter to half of the patients with BD were fully or partially non-adherent[15,17]. This rate was similar to other chronic medical disorders including psychiatric and physical disorders[1,4,18]. There appeared to be no substantial differences between rates of non-adherence for mood stabilizers (principally lithium carbonate) and those for antipsychotics[4]. Similarly, no differences in rates between older or newer medications were noted. Indeed, studies conducted decades apart have revealed that rates of non-adherence have remained the same over the years despite the availability of many new types of medications[4,6,10,13,19].

Studies: Tables 2-4 list the 132 studies of this review providing an estimate of medication non-adherence in BD. Studies spanned exactly four decades with the first study conducted by Bech *et al*[30] among patients on lithium in 1976. The number of studies with patients on all classes of medications (n = 69) was the highest followed by studies of patients on mood stabilizers (n = 46). There were 15 studies of patients on antipsychotics and only two of patients on antidepressants. The majority of the studies were conducted in Western settings with barely 20 studies from non-Western countries. Not surprisingly, there was a wide variation in rates from universal adherence (100%) to almost universal non-adherence (96%). This was obviously more as a result of methodological differences across studies rather than a true variation in rates. Studies differed in the number of patients included, the duration during which adherence was assessed and the

Table 2 Rates of medication non-adherence in bipolar disorder: Studies of all classes of medications

Ref.	Study	Non-adherence rates
Keck *et al*[47], 1996a	*n* = 101; duration-past month; clinical interview and serum levels	64% fully or partially non-adherent
Keck *et al*[48], 1998	*n* = 134; duration - 12 mo; clinical interview	53% fully or partially non-adherent
Strakowski *et al*[49], 1998	*n* = 109 (83 with BD); duration - 12 mo; clinical interviews	59% fully or partially non-adherent
Weiss *et al*[50], 1998	*n* = 44 with BD and SUD; cross-sectional study; clinical interviews	79% fully or partially non-adherent (35% took medications less than 67% of the time)
Colom *et al*[51], 2000	*n* = 200; duration 2 yr; clinical interviews with patients and relatives and serum levels for mood stabilizers	40% fully or partially non-adherent
Svarstad *et al*[52], 2001	*n* = 67; duration 12 mo; retrospective claims data	33% irregular use
Calabrese *et al*[53], 2000	*n* = 324 with RCBD; duration - 6 mo; clinical interview	34%
Greenhouse *et al*[54], 2000	*n* = 32: duration - 1 wk; self-report	25%
Lam *et al*[55], 2003	*n* = 52; duration - 6 mo; serum levels and self-reports	Serum levels - 7%-22%; self-report - 12%-33%
Calabrese *et al*[56], 2005	*n* = 254 with RCBD; duration - 30 mo; clinical interview	20%-28%
Coletti *et al*[57], 2005	*n* = 38 adolescents; duration - 1 mo; parent reports	66% fully or partially non-adherent
Fleck *et al*[58], 2005	*n* = 50; cross-sectional study; visual analogue scale	52% fully or partially non-adherent
Roy *et al*[33], 2005	*n* = 100 (42 with BD); cross-sectional study; clinical interview	91%
Sajatovic *et al*[46], 2005	*n* = 52; duration - 3 mo; self-reports and DAI-10	12%
Sajatovic *et al*[59], 2006a	*n* = 323; cross-sectional study; clinical interview	36% partially or fully non-adherent
Clatworthy *et al*[36], 2007	*n* = 16; cross-sectional study; self-report-qualitative data	81%
DelBello *et al*[60], 2007	*n* = 71 adolescents; duration 12 mo; clinical interviews	65% fully or partially non-adherent
Johnson *et al*[61], 2007	*n* = 469; cross-sectional study; web-based survey; self-report	30%
Montoya *et al*[62], 2007	*n* = 312; cross-sectional study; clinical interviews	40% fully or partially non-adherent
Sajatovic *et al*[63], 2007c	*n* = 205 with RCBD; duration - 6 mo; clinical interview	20%
Shabani and Eftekhar[64], 2007	n = 22; duration - 17 mo; clinical interview	38%
Strakowski *et al*[65], 2007	*n* = 96 (United States) and 46 (Taiwan); duration – 1 yr (Taiwan) to 8 yr (United States); clinical interviews	21% (Taiwan) - 41% (United States) followed up without full treatment adherence
Baldessarini *et al*[66], 2008a	*n* = 429; duration -last 10 d; self-report	34% (psychiatrists rated 6%-18% as non-adherent)
Copeland *et al*[67], 2008	*n* = 435; duration - past 4 d; self-report of missed dose and self-report-MMAS	27% on missed dose and 46% on MMAS
Sajatovic *et al*[40], 2008	*n* = 302; duration - 3 yr; clinical interview	12%
Zeber *et al*[68], 2008	*n* = 435; cross-sectional study; self-report and MMAS	Overall 30%; 23% (self-report) to 46% (MMAS)
Taj *et al*[69], 2008	*n* = 23; cross-sectional study; clinical interviews	26%
Azorin *et al*[70], 2009	*n* = 766; duration 2 yr; clinical interview	At baseline - 44% (pure mania) - 50% (mixed mania); at 2 yr - 8% (pure mania) - 16% (mixed mania)
Clatworthy *et al*[71], 2009	*n* = 223; cross-sectional study; self-report - MARS	30%
Martinez-Aran *et al*[74], 2009	*n* = 103; cross-sectional study; clinical interviews with patients and relatives and serum levels for mood stabilizers	41%
Mazza *et al*[75], 2009	*n* = 131 (94 with BD); duration - 12 mo; serum levels and relatives' reports	22%
Sajatovic *et al*[72], 2009a	*n* = 140; cross-sectional study; self-report-TRQ	19%
Sajatovic *et al*[39], 2009b	*n* = 164; duration - 12 mo; self-report	19%
Sharifi *et al*[73], 2009	*n* = 76; duration - 8 wk; clinical interview	29%
Bates *et al*[76], 2010	*n* = 1052; cross-sectional study; web-based survey; self-report -MMAS	49.50%
Devulapalli *et al*[77], 2010	*n* = 140; duration - past month; self-report	19%
González-Pinto *et al*[78], 2010	*n* = 1831; duration - 24 mo; clinical interview	23%
Hou *et al*[79], 2010	*n* = 35; cross-sectional study; self-report -MMAS	54%
Jónsdóttir *et al*[80], 2010	*n* = 280 (114 with BD); duration- past week; self-report, MARS-5, serum levels	Serum levels - 34%; self-report - 16%
Gutiérrez-Rojas *et al*[81], 2010	*n* = 108; cross-sectional study; clinical interviews with patients and relatives and serum levels for mood stabilizers	17%
Perlis *et al*[82], 2010	*n* = 3640; duration - 12 mo; self-reports and clinical interviews	54% fully or partially non-adherent (24% non-adherent on 20% or more study visits)
Cely *et al*[83], 2011	*n* = 124; cross-sectional study; self-report-MMAS	30%
Cruz *et al*[35], 2011	*n* = 17 elderly subjects; cross-sectional study; self-report-MMAS	88%
Hong *et al*[84], 2011	*n* =1341; duration - 21 mo; clinical interview	24%
Savaş *et al*[85], 2011	*n* = 147; duration - 12 mo; self-report	27%
Sajatovic *et al*[86], 2011b	*n*= 140; duration - 1 mo; TRQ	18%
Mahmood *et al*[87], 2011	*n* = 40; duration - 1 mo; clinical interview	62%
Barraco *et al*[88], 2012	*n* = 650; duration - 12 mo; self-report-SMAQ and DAI-10	60% at baseline; 31% at 9 mo; 33% at 12 mo
Eker and Harkin[89], 2012	*n* = 71; duration - 6 wk; ANT, self-report-MARS, TOS	60%-61% at baseline; 13%-76% at 6wk
Murru *et al*[90], 2012	*n* = 76 schizoaffective disorder-bipolar type; duration - 10 yr; partly retrospective based on clinical interviews with patients and families and serum levels	41%
Miasso *et al*[91], 2012	*n* = 101; cross-sectional study; self-report-MMAS	63%
Sajatovic *et al*[92], 2012	*n* = 43; duration - 6 mo; self-report-TRQ, MMAS; Pill counts	TRQ - 48%-51% at baseline; 21%-25% at 6 mo - Pill counts - 58% at baseline

Vieta *et al*[93], 2012	*n* = 2448 psychiatrists; duration-3 mo; questionnaire survey	57% patients rated fully or partially non-adherent
Sharma *et al*[94], 2012	*n* = 127; cross-sectional study; self-report	40%
Belzeaux *et al*[95], 2013	*n* = 382; cross-sectional study; self-report - MARS and clinical interviews	25%
de Souza *et al*[96], 2013	*n* = 36 cross-sectional study; self-report - MMAS	78%
Gibson *et al*[97], 2013	*n* = 24; cross-sectional study; self-report	50%-77% fully or partially non adherent
Hibdye *et al*[98], 2013	*n* = 410; cross-sectional study; self-report - MMAS	51%
Jónsdóttir *et al*[99], 2013	*n* = 255 (109 with BD); duration - past week; self-report, serum levels	42% fully or partially non-adherent
Murru *et al*[100], 2013	schizoaffective disorder-bipolar type (*n* = 75) and BD (*n* = 151); duration - 10 yr; partly retrospective based on clinical interviews with patients and families and serum levels	BD - 33%; schizoaffective disorder-bipolar type - 44%
Arvilommi *et al*[101], 2014	*n* = 168; duration 18 mo; clinical interview	> 50% non-adherent
Kassis *et al*[102], 2014	*n* = 76; cross-sectional study; questionnaire based	55%
Ghaffari-Nejad *et al*[103], 2015	*n* = 123; duration-6 mo; DAI = 10	61% fully or partially non-adherent
Hajda *et al*[104], 2015	*n* = 33; cross-sectional study; self-report - DAI-10	58%
Ibrahim *et al*[105], 2015	*n* = 358 (177 with BD); cross-sectional study; self-report-MMAS-8	46%
Levin *et al*[106], 2015	*n* = 65; duration-3 mo; self-report-TRQ	32%-59% at baseline; 10%-40% at 3 mo
Mert *et al*[107], 2015	*n* = 68; duration - 6 mo; self-reports; relatives' reports, medical records	45%
Azadforouz *et al*[108], 2016	*n* = 47; duration-6 mo; clinical interview	36%
Mousavi *et al*[32], 2016	*n* = 73 with BD and psychotic symptoms; cross-sectional study; clinical interviews	96%

ANT: Attitudes towards neuroleptic treatment; BD: Bipolar disorder; CRS: Compliance rating scale; DAI-10: Drug Attitude Inventory-10 item version; MARS: Medication Adherence Report Scale (MARS-5-five item version); MMAS: Morisky Medication Adherence Scale (MMAS-8-8 item version); MPR: Medication possession ration; RBC: Red blood cells; RCBD: Rapid cycling bipolar disorder; RSM: Reasons for Stopping Medication' questionnaire; ROMI: Rating of Medication Influences Scale; SGA: Second generation antipsychotics; SMAQ: Simplified Medication Adherence Questionnaire; SUD: Substance use disorders; SRTAB: Self-reported Treatment Adherence Behaviours; TOS: Treatment Observation Form; TRQ: Tablet Routines Questionnaire.

techniques used to assess adherence. The majority of studies had sample sizes ranging from 100 to 500 patients (*n* = 51; 39%); but about a third had included 50 to 100 patients (*n* = 37; 28%), while 20% of the studies (*n* = 26) had less than 50 patients. Most studies were conducted over the period of 1 mo to 1 year (*n* = 56; 42%), but cross-sectional studies were also very common (*n* = 37; 28%), whereas about a quarter of the studies (*n* = 33; 25%) had extended beyond 1 year, often up to several years in some studies of mood stabilizers. About a third of the studies had used multiple measures to estimate adherence (*n* = 38; 29%), even as studies based only on self-reports (*n* = 37; 28%), or only on clinical interviews (*n* = 34; 26%) were equally common. Fifteen studies (11%) were based on analysis of claims data.

Rates were computed using the highest rate of non-adherence where multiple rates were mentioned and rates at baseline for longitudinal studies. Despite significant discrepancies in methodology across studies, when rates were computed from all the 132 studies the mean rate of non-adherence turned out to be 41.5% (41.52 ± 19.56) and the median rate was 40%. Rates of non-adherence were between 25% to 50% in 65 studies (49%) and greater than 50% in 42 of the 132 studies (32%).

Most studies with very high rates of non-adherence (> 80%) were either part of randomized-controlled trials[31], or had been conducted among inpatients or mental hospital populations[32-34], or were studies with qualitative designs[35,36]. Patient numbers were generally small in these studies. Similarly, studies with very low rates of non-adherence (< 20%) were either from specialized lithium clinics[37,38], or were derived from randomized-controlled trials[39-42]. Others studies with very low rates had relied either exclusively on patient reports to estimate non-adherence[43-45], or had used qualitative designs with small patient samples[46]. In contrast, the average rate of non-adherence in the 18 studies with large and more representative samples (naturalistic studies with > 500 patients) was higher at 49% (48.81 ± 14.13). The mean rate of adherence in the studies which had lasted more than 1 year was lower at 36% (36.36 ± 12.90). However, even after excluding the 21 studies with very high or very low rates, the mean rate of non-adherence in BD increased only to 43% (42.81 ± 14.66) and the median rate to 41%.

The average rate of non-adherence derived from studies where patients received all classes of medication was 45% (44.62 ± 19.61) with a median of 41%; after excluding 11 studies with very high or very low rates the mean rate was still 45% (44.94 ± 14.95), while the median rate increased to 43.5%. The mean rate of non-adherence among patients on mood stabilizers was 34% (34.16 ± 18.35) and the median rate was 31.5%. After excluding 9 studies with very high or very low rates the mean increased to 38% (37.82 ± 13.24) and the median to 34%. Rates derived from studies of antipsychotic medications were the highest with a mean of 51% (50.87 ± 15.87) and a median of 48%. After excluding one study with a very high rate the mean dropped to 48% (48.43 ± 13.44) and the median to 47%. Therefore, rates of non-adherence derived

Table 3 Rates of medication non-adherence in bipolar disorder: Studies of mood stabilizers

Ref.	Study	Non-adherence rates
Bech *et al*[30], 1976	*n* = 76 on lithium (49 with BD); duration - 2 yr; retrospective case record data and serum levels	24%
Jamison *et al*[9], 1979	*n* = 47 on lithium; cross-sectional study; self-report and psychiatrists' estimations	Patients - 47% non-adherent; psychiatrists - 35% non-adherent
Connelly *et al*[109], 1982	*n* = 48 on lithium; duration - 9 mo; serum levels and > 75% clinic attendance	25%
Connelly *et al*[110], 1984	*n* = 75 on lithium; duration - 6 mo; serum levels and > 75% clinic attendance	33%
Cochran[31], 1984	*n* = 28 on lithium; duration - 6 mo; self-report; case notes; clinical interview and serum levels	93% had major or minor non-adherence
Danion *et al*[111], 1987	*n* = 73 on lithium (36 with BD); duration - 2 yr; retrospective psychiatric assessments and serum levels	56% - subjective 19%; objective 56%
Aagaard *et al*[112], 1988 Maarbjerg *et al*[113], 1988	*n* =133 on lithium (47 with BD); duration - 6 mo; clinical interview	23%
Cochran and Gitlin[114], 1988	*n* = 48 on lithium (43 with BD); cross-sectional study; patient questionnaires	46% fully or partially non-adherent
Vestergaard and Schou[115], 1988	*n* = 480 on lithium (187 with BD); duration - 7 yr; medical records based on serum levels and clinical interviews	50% in first 6 mo; 25% per year during the first 2 yr; 10% per year after 4-5 yr
Lenzi *et al*[116], 1989	*n* = 67 women on lithium or carbamazepine; duration - 8 mo; self-report and serum levels	45%
Nilsson and Axelsson[117], 1989	*n* = 64 with mood disorders on lithium; duration - 7 yr; serum levels and medical records	25%
Aagaard and Vestergaard[118], 1990	*n* = 133 on lithium (61 with BD); duration - 2 yr; clinical interview	42%
Courtney *et al*[38], 1995	*n* = 15 on lithium; cross-sectional study; serum levels	0%
Lee *et al*[119], 1992	*n* = 50 on lithium; duration 12 mo; self-report; clinical interview; serum levels	30%
Berghöfer *et al*[120], 1996	*n* = 86 (55 with BD) on lithium; retrospective follow-up over a mean of 8.9 yr based on clinical interview and serum levels	24%
Keck *et al*[121], 1997	*n* = 140 on mood stabilizers; duration - 12 mo; clinical interview	51% fully or partially non-adherent
Maj *et al*[122], 1998	*n* = 402 on lithium; duration - 5 yr; clinical interview and serum levels	28%
Schumann *et al*[123], 1999	*n* = 75 (31 with BD) on lithium; duration-6 yr; retrospective medical records based on interviews and serum levels	55%
Wong *et al*[124], 1999	*n* = 80 with mood disorders on lithium (60 with BD cross-sectional study; self-reports; clinical interviews; serum levels	27.50%
Licht *et al*[125], 2001	*n* = 148 on mood stabilizers (132 on lithium): duration 24 mo; retrospective analysis of treatment charts, serum levels and clinical interviews	20%
McCleod and Sharp[37], 2001	*n* = 30 on lithium; cross-sectional study; self-reports, clinical ratings and serum levels	0%
Svarstad *et al*[52], 2001	*n* = 53 on lithium; duration 12 mo; retrospective claims data	26% irregular use
Scott[126], 2002	*n* = 98 (85 with BD) on mood stabilizers; cross-sectional study; self-reports-ROMI and TRQ	30% partially adherent
Scott and Pope[127], 2002a	*n* = 98 on mood stabilizers (78 with BD); duration- 24 mo; TRQ and serum levels	partial non-adherence - 47% over 2 yr; 32%over past month; 27% over past week; full non-adherence - 20% over 2 yr
Scott and Pope[128], 2002b	*n* = 98 on mood stabilizers (78 with BD); duration - 18 mo; TRQ and serum levels	TRQ - 32% partial adherence; serum levels - 36%
Dharmendra and Eagles[43], 2003	*n* = 411; duration - 3 yr; retrospective study based on self-reports and serum levels	15%
Pope and Scott[129], 2003	*n* = 72 on lithium (61 with BD); duration - 2 yr; self-report-RSM	46%
Bowden *et al*[130], 2005	*n* = 372 on lithium or valproate; duration - 52 wk; clinical interview	54%-75% premature discontinuations
Calabrese *et al*[56], 2005	*n* = 254 with RCBD on lithium or valproate; duration 20 mo; clinical interviews and serum levels	10%-28%
Patel *et al*[131], 2005	*n* = 32 adolescents on mood stabilizers; duration - 12 mo; clinical interviews and medical records	Treatment time without full adherence in 47%
Salloum *et al*[41], 2005	*n* = 59 with BD and alcohol dependence on lithium or lithium and valproate; duration - 24 wk; self-report and serum levels	13%-14%
Gonzalez-Pinto *et al*[132], 2006	*n* = 72; duration - 10 yr; clinical interviews and serum levels	22%
Drotar *et al*[133], 2007	*n* = 107 adolescents; on lithium and valproate; duration - 20 wk; serum levels, pill counts, self/parent report and clinical interview	16%-34% (average 17%) non-adherent on various measures
Kessing *et al*[134], 2007	*n* = 14277 on lithium; duration 6 yr; nation-wide register and pharmacy data	25% stopped lithium within 45 d
Manwani *et al*[135], 2007	*n* = 115 on mood stabilizers; duration - 10 mo; clinical interview	34% lifetime adherence in those with SUD 17% in those without SUD
Rosa *et al*[136], 2007	*n* = 106; cross-sectional study; self-report-MARS and serum and RBC levels	14% (based on levels) 33% (based on MARS)

Sajatovic *et al*[137], 2007a	*n* = 44637 on mood stabilizers; duration - 3 mo or more; retrospective claims data-MPR based	46% partially or fully non-adherent; took medications less than 50%-80% of the time
Baldessarini *et al*[138], 2008b	*n* = 2197 on single mood stabilizers; duration - 12 mo; national health plan claims data; MPR based	72% took medications less than 80% of the time
Vega *et al*[139], 2009	*n* = 72 on lithium; duration - 5 yr; clinical interviews and serum levels	8% (women)-39% (men)
Bauer *et al*[44], 2010	*n* = 312 on mood stabilizers; duration - 6 mo; self-report	11% partially or fully non-adherent
Sajatovic *et al*[86], 2011b	*n* = 136; duration - 1 mo; self-report-TRQ	18% in the past week or month
Scott *et al*[140], 2012	*n* = 81 on mood stabilizers; cross-sectional study; self-report -TRQ	26% - past month
Bauer *et al*[45], 2013a	*n* = 206 on mood stabilizers; duration 100 d; self-report	14% mean percent of days of missing doses
Arvilommi *et al*[101], 2014	*n* = 168 on mood stabilizers; duration 18 mo; clinical interview	40% fully or partially non-adherent
Sylvia *et al*[42], 2014	*n* = 283 on lithium; duration - 6 mo; self-report-TRQ	4.5%-7% reported missing at least 30% of their medications in the past week
Col *et al*[141], 2014	*n* = 78 on mood stabilizers; cross-sectional study; self-report-MARS	42%

ANT: Attitudes towards neuroleptic treatment; BD: Bipolar disorder; CRS: Compliance Rating Scale; DAI-10: Drug Attitude Inventory-10 item version; MARS: Medication Adherence Report Scale (MARS-5-five item version); MMAS: Morisky Medication Adherence Scale (MMAS-8-8 item version); MPR: Medication possession ration; RBC: Red blood cells; RCBD: Rapid cycling bipolar disorder; RSM: Reasons for Stopping Medication' questionnaire; ROMI: Rating of Medication Influences Scale; SGA: Second generation antipsychotics; SMAQ: Simplified Medication Adherence Questionnaire; SUD: Substance use disorders; SRTAB: Self-reported Treatment Adherence Behaviours; TOS: Treatment Observation Form; TRQ: Tablet Routines Questionnaire.

Table 4 Rates of medication non-adherence in bipolar disorder: studies of antipsychotics and antidepressants

Ref.	Study	Non-adherence rates
Antipsychotics		
Keck *et al*[142], 1996b	*n* = 77 on antipsychotics; duration - 6 mo; clinical interview	32%
Svarstad *et al*[52], 2001	*n* = 56 on antipsychotics; duration 12 mo; retrospective claims data	23% irregular use
Patel *et al*[131], 2005	*n* = 32 adolescents on antipsychotics; duration - 12 mo; clinical interviews and medical records	Treatment time without full adherence in 44%
Sajatovic *et al*[143], 2006b	*n* = 32993 on antipsychotics; duration - 3 mo or more; retrospective claims data-MPR based	48% partially or fully non-adherent; took antipsychotics less than 50%-80% of the time
Sajatovic *et al*[144], 2007b	*n* = 73964 on antipsychotics; duration - 3 mo or more; retrospective claims data-MPR based	39% among those > 60 yr and 50% in those < 60 yr took antipsychotics less than 50%-80% of the time
Hassan and Lage[145], 2009	*n* = 1973 on antipsychotics; duration - 12 mo; retrospective claims based data-MPR based	56% took antipsychotics less than 50% of the time and 73% less than 75% of the time
Lage and Hassan[146], 2009	*n* = 7,769 on antipsychotics; duration- 12 mo; retrospective claims data-MPR based	62% took antipsychotics less than 50% of the time and 79% less than 75% of the time
Lang *et al*[147], 2011	*n* = 9410 on antipsychotics; duration - 12 mo; retrospective claims data-MPR based	60% took antipsychotics less than 80% of the time
Rascati *et al*[148], 2011	*n* = 2446 on SGAs; duration - 18 mo; retrospective claims data-MPR based	42% took antipsychotics less than 80% of the time
Berger *et al*[34], 2012	*n* = 84 on SGAs: Duration-6 mo; retrospective claims data-MPR and CMG based	85% took antipsychotics less than 80% of times (50% according to CMGs)
Stephenson *et al*[149], 2012	*n* = 162 patients with BD on SGAs and 153 physicians; duration - 12 mo; retrospective claims data and physician survey	57% with low-moderate adherence; physicians overestimated adherence in 67% patients
Montes *et al*[150], 2013	*n* = 303; cross-sectional study; self-reports- DAI-10 and MMAS, CRS	69%
Kutzelnigg *et al*[151], 2014	Olanzapine alone or in combination with mood stabilizers; n = 891 at entry; 657 at 2 yr; clinical interview	33% at baseline; 20% at 2 yr
Arvilommi *et al*[101], 2014	*n* = 168 on SGAs; duration 18 mo; clinical interview	46% fully or partially non-adherent
Sajatovic *et al*[152], 2016	*n* = 1114 on lurasidone; duration- 27 mo; retrospective claims data-MPR based	67%took lurasidone less than 80% of the time
Antidepressants		
Svarstad *et al*[52], 2001	*n* = 22 on antidepressants; duration 12 mo; retrospective claims data	27% irregular use
Bauer *et al*[153], 2013b	*n* = 144 on antidepressants; duration - daily for 100 d; self-report	19% (missing/changing doses) to 41% (drug holidays)

ANT: Attitudes towards neuroleptic treatment; BD: Bipolar disorder; CMG: Cumulative medication gaps; CRS: Compliance Rating Scale; DAI-10: Drug Attitude Inventory-10 item version; MARS: Medication Adherence Report Scale (MARS-5-five item version); MMAS: Morisky Medication Adherence Scale (MMAS-8-8 item version); MPR: Medication possession ration; RBC: Red blood cells; RCBD: Rapid cycling bipolar disorder; RSM: Reasons for Stopping Medication' questionnaire; ROMI: Rating of Medication Influences Scale; SGA: Second generation antipsychotics; SMAQ: Simplified Medication Adherence Questionnaire; SUD: substance use disorders; SRTAB: Self-reported Treatment Adherence Behaviours; TOS: Treatment Observation Form; TRQ: Tablet Routines Questionnaire.

from studies of mood stabilizers were significantly lower than rates among patients on all three classes of medications, or among those on antipsychotics ($P < 0.05$ or $P < 0.01$), while there were no differences between rates among patients on all classes of medications and those on antipsychotics.

Demographic correlates of medication non-adherence in BD

Reviews: The evidence that socio-demographic characte-

ristics of patients influence their medication taking behaviour is largely inconsistent among patients with BD[154]. Accordingly, most reviews of the subject have concluded that there is no strong support for anassociation between demographic variables and medication non-adherence in BD[4,6,8,17,22,26]. Though certain demographic characteristics of patients have been associated with non-adherence in some studies of BD, such associations have not been found in others. There is also some discrepancy between reviews about which demographic parameters might be associated with non-adherence in BD; some reviews have concluded that younger age[12,14,22,27,29] and male gender[11,15,22,27] are more likely to be associated with non-adherence,while others have found that being single or living alone[2,3,7,11,15], being less educated[3,12,14,15,17] or belonging to ethnic minorities[3,10,11] were among the most consistent risk factors for non-adherence in BD.

Studies: Table 5 list the studies, which have examined the demographic correlates of medication non-adherence in BD. In keeping with the reviews on demographic variables influencing non-adherence in BD, these studies also demonstrate that there is very little to support the notion that demographic attributes of patients have a significant influence on their medication taking behaviour. Firstly, a large number of studies (*n* = 29) have been unable to find an association between medication non-adherence and any demographic variable. Among individual variables young age has often been cited as a correlate of non-adherence in BD[12,14,22,27,29], but the number of studies which have found an association with young age (*n* = 22) was almost similar to those that have been unable to demonstrate such an association (*n* = 19). Studies that have found associations with male gender, single marital status, lower levels of education, unemployment or low socioeconomic status or income were fewer than those unable to find such as association, or those that have found the obverse association. There appeared to be some link with a general "social disadvantage" factor including ethnic minority status, homelessness and dysfunctional family atmospheres, but the aggregate number of studies finding a positive association (*n* = 25) was not substantially different from those finding no such association (*n* = 16).

Clinical correlates of medication non-adherence in BD

Reviews: The relationship between several clinical features and medication non-adherence has been examined in a number of studies of BD. Clinical characteristics, which have been explored have included overall severity of the illness, severity of manic, depressive and psychotic symptoms as well as variables such as age of onset, duration of illness or episode-length, episode polarity and subtypes of BD. The impact of factors such as cognitive impairment, lack of insight and comorbidity on treatment-adherence has also been examined. The overall conclusion of reviews on the subject is that non-adherence in BD is a complex phenomenon and the association with clinical variables is ambiguous. Not only are the results of such associations inconsistent and equivocal, but the causal direction of any positive associations, *i.e.*, whether the clinical variable in question led to non-adherence or vice-versa, is often unclear[4,8,15,28]. Overall severity of illness in terms of number of episodes, number of hospitalizations or suicidality has been found to be associated with non-adherence in a few studies, but this is not a consistent finding[2-4,6,7,12]. Similarly, severity of manic symptoms have been found to impact adherence negatively quite commonly, though not all studies have found this association[2-4,6,15,22,23]. The influence of depressive or mixed symptoms and psychotic symptoms have not been examined often enough to reach any firm conclusions about their effect on non-adherence in BD[2-4,12,18,27,28]. It is postulated that cognitive impairment may adversely affect adherence in BD, but the evidence for this appears to be derived from only a few studies[2-4,8,14]. The evidence linking other clinical variables such as age of onset, duration of illness or episode-length, polarity and bipolar subtypes with non-adherence in BD is limited[3,8,12]. The adverse effects of comorbid personality disorders and anxiety disorders on adherence in BD has also found mention, though the evidence seems limited to a few studies[2-4,8,15]. In contrast, almost every review on the subject has concurred in finding that the presence of comorbid substance use disorders (SUD) has a significant negative impact on adherence in BD[6,8,12,14,23]. Current rather than past substance abuse is more likely to be associated with non-adherence in BD[3,163-166]. Finally, lack of insight and denial of illness has been consistently found to be associated with non-adherence in BD, though studies finding an association between insight and adherence in BD are still few in number[2,11,12,167,168].

Studies: Table 6 include studies examining the clinical correlates of medication non-adherence in BD. As is evident from the two tables there was no evidence of a consistent association with non-adherence for the majority of the clinical variables examined. Certain studies did find positive associations between non-adherence and clinical variables such as early age of onset, shorter durations of illness, greater number of hospitalizations, higher number of total, manic, depressive or mixed episodes, rapid cycling course, bipolar *vs* unipolar disorders and bipolar Ⅰ *vs* bipolar Ⅱ disorders, polarity of episodes, overall severity of illness and severity of depressive, mixed and psychotic symptoms, family history of psychiatric disorders, co-morbid personality disorders and comorbid anxiety or hyperkinetic disorders. However, the number of studies, which were unable to find such associations either equalled or outnumbered those with positive associations. The exceptions to this trend were associations of more severe manic symptoms (21 studies with positive associations and 16 without) and cognitive impairment

Table 5 Studies of demographic correlates of medication non-adherence in bipolar disorder

Demographic correlates	Studies with positive associations	Studies without positive associations	Others
Any demographic variable		Jamison *et al*[9], 1979; Aagaard and Vestergaard[118], 1990; Maj *et al*[122], 1998; Schumann *et al*[123], 1999; Colom *et al*[51], 2000; Licht *et al*[125], 2001; Scott [126], 2002; Scott and Pope[127], 2002a; Kliendienst and Griel[156], 2004; Revicki *et al*[155], 2005; Yen *et al*[157], 2005; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[40], 2008; Taj *et al*[69], 2008; Sajatovic *et al*[72], 2009a; Clatworthy *et al*[71], 2009; Martinez-Aran *et al*[74], 2009; Sharifi *et al*[73], 2009; González-Pinto *et al*[78], 2010; Cely *et al*[83], 2011; Murru *et al*[90], 2012; Bauer *et al*[45], 2013a; Bauer *et al*[153], 2013b; Jónsdóttir *et al*[99], 2013; Col *et al*[141], 2014; Sylvia *et al*[42], 2014; Ghaffari-Nejad *et al*[103], 2015; Levin *et al*[106], 2015; Mert *et al*[107], 2015	
Young age	Frank *et al*[158], 1985; Kleindienst and Greil[156], 2004; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b; Johnson *et al*[61], 2007; Baldessarini *et al*[66], 2008a; Baldessarini *et al*[138], 2008b; Copeland *et al*[67], 2008; Mazza *et al*[75], 2009; Bates *et al*[76], 2010; Bauer *et al*[44], 2010; Hou *et al*[79], 2010; Perlis *et al*[82], 2010; Lang *et al*[147], 2011; Savaş *et al*[85], 2011; Barraco *et al*[88], 2012; Montes *et al*[150], 2013; Hajda *et al*[104], 2015; Levin *et al*[106], 2015; Mousavi *et al*[32], 2016	Danion *et al*[111], 1987; Maarbjerg *et al*[113], 1988; Lenzi *et al*[116], 1989; Colom *et al*[51], 2000; Licht *et al*[125], 2001; Coletti *et al*[57], 2005; Gonzalez-Pinto *et al*[132], 2006; Drotar *et al*[133], 2007; Rosa *et al*[136], 2007; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[63], 2007 c; Zeber *et al*[68], 2008; Savaş *et al*[85], 2011; Belzeaux *et al*[95], 2013; Hibdye *et al*[98], 2013; Murru *et al*[100], 2013; Kutzelnigg *et al*[151], 2014; Azadforouz *et al*[108], 2016	Both young and old age- Kessing *et al*[134], 2007 Old age - Lehman and Rabins[159], 2006; Rascati *et al*[148], 2011; Sharma *et al*[94], 2012
Male gender	Frank *et al*[158], 1985; Aagaard *et al*[112], 1988; Vestergaard and Schou[115], 1988; McCleod and Sharp[37], 2001; Gonzalez-Pinto *et al*[132], 2006; Drotar *et al*[133], 2007; Vega *et al*[139], 2009; Savaş *et al*[85], 2011; Mousavi *et al*[32], 2016	Danion *et al*[111], 1987; Maarbjerg *et al*[113], 1988; Licht *et al*[125], 2001; Gonzalez-Pinto *et al*[132], 2006; Rosa *et al*[160], 2006; Rosa *et al*[136], 2007; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[63], 2007c; Johnson *et al*[61], 2007; Baldessarini *et al*[66], 2008a; Baldessarini *et al*[138], 2008b; Mazza *et al*[75], 2009; Bauer *et al*[44], 2010; Hou *et al*[79], 2010; Perlis *et al*[82], 2010; Rascati *et al*[148], 2011; Sajatovic *et al*[86], 2011b; Barraco *et al*[88], 2012; Sharma *et al*[94], 2012; Hibdye *et al*[98], 2013; Montes *et al*[150], 2013; Kutzelnigg *et al*[151], 2014; Hajda *et al*[104], 2015; Azadforouz *et al*[108], 2016	Female gender - Keck *et al*[142], 1996b; Keck *et al*[121], 1997; Jose *et al*[161], 2003; Sajatovic *et al*[46], 2005; Kessing *et al*[134], 2007; Copeland *et al*[67], 2008; Zeber *et al*[68], 2008; Bates *et al*[76], 2010; Belzeaux *et al*[95], 2013; Murru *et al*[100], 2013
Not married	Frank *et al*[158], 1985; Aagaard *et al*[112], 1988; Connelly *et al*[109], 1982; Connelly *et al*[110], 1984; Gonzalez-Pinto *et al*[132], 2006; Sajatovic *et al*[137], 2007a; Vega *et al*[139], 2009; Perlis *et al*[82],2010; Sajatovic *et al*[162], 2011a; Hajda *et al*[104], 2015	Lenzi *et al*[116], 1989; Licht *et al*[125], 2001; Gonzalez-Pinto *et al*[132], 2006; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[63], 2007c; Zeber *et al*[68], 2008; Mazza *et al*[75], 2009; Bauer *et al*[44], 2010; Hou *et al*[79], 2010; Savaş *et al*[85], 2011; Barraco *et al*[88], 2012; Sharma *et al*[94], 2012; Belzeaux *et al*[95], 2013; Hibdye *et al*[98], 2013; Murru *et al*[100], 2013; Azadforouz *et al*[108], 2016; Mousavi *et al*[32], 2016	
Poorly educated	Frank *et al*[158], 1985; Connelly *et al*[110], 1984; Danion *et al*[111], 1987; Johnson *et al*[61], 2007; Sajatovic et al[63], 2007c; Bates et al[76], 2010; Savaş et al[85], 2011; Hajda *et al*[104], 2015; Mousavi *et al*[32], 2016	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Gonzalez-Pinto *et al*[132], 2006; Zeber *et al*[68], 2008; Bauer *et al*[44], 2010; Hou *et al*[79], 2010; Perlis *et al*[82], 2010; Sharma *et al*[94], 2012; Belzeaux *et al*[95], 2013; Hibdye *et al*[98], 2013	
Unemployment	Aagaard *et al*[112], 1988; Perlis *et al*[82], 2010; Hibdye *et al*[98], 2013; Montes *et al*[150], 2013	Sajatovic *et al*[63], 2007c; Bauer *et al*[44], 2010; Hou *et al*[79], 2010; Perlis *et al*[82], 2010; Savaş *et al*[85], 2011; Barraco *et al*[88], 2012; Sharma *et al*[94], 2012; Murru *et al*[100], 2013; Hajda *et al*[104], 2015	
Low socioeconomic status or income	DelBello *et al*[60], 2007; Perlis *et al*[82], 2010	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Lenzi *et al*[116], 1989; Aagaard and Vestergaard[118], 1990; Johnson *et al*[61], 2007; Zeber *et al*[68], 2008; Savaş *et al*[85], 2011; Sharma *et al*[94], 2012	
Ethnic minority status	Keck *et al*[121], 1997; Strakowski *et al*[49], 1998; Kleindienst and Greil[156], 2004; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[63], 2007c; Johnson *et al*[61], 2007; Copeland *et al*[67], 2008; Zeber *et al*[68], 2008; Perlis *et al*[82], 2010; Rascati *et al*[148], 2011; Sajatovic *et al*[162] 2011a; Sajatovic *et al*[92], 2012	Fleck *et al*[58], 2005; Patel *et al*[131], 2005; Drotar *et al*[133], 2007; Baldessarini *et al*[66], 2008a; Baldessarini *et al*[138], 2008b; Bates *et al*[76], 2010; Hibdye *et al*[98], 2013; Kutzelnigg *et al*[151], 2014	
Living alone/homeless	Lenzi *et al*[116], 1989; Kleindienst and Greil [156], 2004; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b	Zeber *et al*[68], 2008; Montes *et al*[150], 2013; Murru *et al*[100], 2013; Hajda *et al*[104], 2015	

Family factors: Dysfunction, poor social support, negative attitudes	Aagaard *et al*[112], 1988; Drotar *et al*[133], 2007; Cely *et al*[83], 2011; Sajatovic *et al*[162], 2011a; Scott *et al*[140], 2012; Sharma *et al*[94], 2012; Col *et al*[141], 2014	Sajatovic *et al*[72], 2009a; Sajatovic *et al*[86], 2011b

BD: Bipolar disorder.

Table 6 Studies of clinical correlates of medication non-adherence in bipolar disorder

Clinical correlates	Studies with positive associations	Studies without positive associations	Others
Early age of onset	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Drotar *et al*[133], 2007 Perlis *et al*[82], 2010; Barraco *et al*[88], 2012	Colom *et al*[51], 2000; Scott and Pope[127], 2002a; Sajatovic *et al*[59], 2006a; Gonzalez-Pinto *et al*[132], 2006; González-Pinto *et al*[78], 2010; Murru *et al*[90], 2012; Levin *et al*[106], 2015; Azadforouz *et al*[108], 2016	Later onset - Col *et al*[141], 2014 Hajda *et al*[104], 2015
Short durations of illness	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; González-Pinto *et al*[78], 2010; Belzeaux *et al*[95], 2013; Azadforouz *et al*[108], 2016	Danion *et al*[111], 1987; Aagaard and Vestergaard[118], 1990; Schumann *et al*[123], 1999; Colom *et al*[51], 2000; Licht *et al*[125], 2001; Scott and Pope[127], 2002a; Jose *et al*[161], 2003; Gonzalez-Pinto *et al*[132], 2006; Taj *et al*[69], 2008; Sajatovic *et al*[72], 2009a; Hou *et al*[79], 2010; Savaş *et al*[85], 2011; Murru *et al*[90], 2012; Sharma *et al*[94], 2012; Montes *et al*[150], 2013; Col *et al*[141], 2014	Longer durations - Coletti *et al*[57], 2005; Belzeaux *et al*[95], 2013
Greater number of hospitalizations	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Aagaard and Vestergaard[118], 1990; Colom *et al*[51], 2000; Svarstad *et al*[52], 2001; Scott[126], 2002; Scott and Pope[128], 2002b; Gonzalez-Pinto *et al*[132], 2006; Baldessarini *et al*[138], 2008b; Gianfrancesco *et al*[168], 2008; Hassan and Lage[145], 2009; Lage and Hassan[146], 2009; Martinez-Aran *et al*[74],2009; Vega *et al*[139], 2009; Bates *et al*[76], 2010; González-Pinto *et al*[78], 2010; Hong *et al*[84], 2011; Lang *et al*[147], 2011; Savaş *et al*[85], 2011; Scott *et al*[140], 2012; Kutzelnigg *et al*[151], 2014	Johnson and McFarland[169], 1996; Keck *et al*[47], 1996a; Schumann *et al*[123], 1999; Jose *et al*[161], 2003; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[40], 2008; Clatworthy *et al*[71], 2009; Sharifi *et al*[73], 2009; Bauer *et al*[44], 2010; González-Pinto *et al*[78], 2010; Hou *et al*[79], 2010; Murru *et al*[90], 2012; Sharma *et al*[94], 2012; Montes *et al*[150], 2013; Hajda *et al*[104], 2015; Azadforouz *et al*[108], 2016	Fewer hospitalizations - Sajatovic *et al*[137], 2007a; Col *et al*[141], 2014
Higher total number of episodes	Danion *et al*[111], 1987; Gonzalez-Pinto *et al*[132], 2006; Vega *et al*[139], 2009; Gutiérrez-Rojas *et al*[81], 2010; Murru *et al*[100], 2013	Lenzi *et al*[116], 1989; Keck *et al*[47], 1996a; Jose *et al*[161], 2003; Martinez-Aran *et al*[74], 2009; Murru *et al*[90], 2012; Belzeaux *et al*[95], 2013; Col *et al*[141], 2014	Fewer episodes - Colom *et al*[51], 2000
Higher number of manic episodes	Gonzalez-Pinto *et al*[132], 2006; Vega *et al*[139], 2009; Murru *et al*[100], 2013	Johnson *et al*[61], 2007; Zeber *et al*[68], 2008; Martinez-Aran *et al*[74], 2009; Bates *et al*[76], 2010; Gutiérrez-Rojas *et al*[81], 2010; Murru *et al*[90], 2012; Col *et al*[141], 2014	Fewer hypomanic episodes - Colom *et al*[51], 2000
Higher number of depressive episodes	Danion *et al*[111], 1987; Gutiérrez-Rojas *et al*[81], 2010; Col *et al*[141], 2014	Gonzalez-Pinto *et al*[132], 2006; Johnson *et al*[61], 2007; Martinez-Aran *et al*[74], 2009; Vega *et al*[139], 2009; Bates *et al*[76], 2010; Murru *et al*[90], 2012	Fewer depressive episodes - Colom *et al*[51], 2000
Higher number of mixed episodes/ rapid cycling	Calabrese *et al*[56], 2005; Perlis *et al*[82], 2010	Maarbjerg *et al*[113], 1988; Colom *et al*[51], 2000; Sajatovic *et al*[59], 2006a; Gonzalez-Pinto *et al*[132], 2006; Sajatovic *et al*[40], 2008; Martinez-Aran *et al*[74], 2009; Murru *et al*[90], 2012; Murru *et al*[100], 2013	
BD *vs* UP disorders	Arvilommi *et al*[101], 2014; Mert *et al*[107], 2015	Connelly *et al*[109], 1982; Maarbjerg *et al*[113], 1988; Lenzi *et al*[116], 1989; Aagaard and Vestergaard[118], 1990; Schumann *et al*[123], 1999; McCleod and Sharp[37], 2001; Scott and Pope[127], 2002a; Taj *et al*[69], 2008; Ghaffari-Nejad *et al*[103], 2015	
BP Ⅰ *vs* BP Ⅱ	Martinez-Aran *et al*[74], 2009; Mazza *et al*[75], 2009	Jamison *et al*[9], 1979; Colom *et al*[51], 2000; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[40], 2008; Baldessarini *et al*[66], 2008a; Baldessarini *et al*[138], 2008b; Bauer *et al*[44], 2010; Perlis *et al*[82], 2010; Montes *et al*[150], 2013; Sylvia *et al*[42], 2014	Higher in BP Ⅱ - Murru *et al*[100], 2013
Polarity of episodes	Gutiérrez-Rojas *et al*[81], 2010; Montes *et al*[150], 2013	Danion *et al*[111], 1987; Maarbjerg *et al*[113], 1988; Sajatovic *et al*[59], 2006a; Col *et al*[141], 2014	
Overall severity of illness	Baldessarini *et al*[66], 2008a; Sajatovic *et al*[72], 2009a; Sajatovic *et al*[40], 2008; Bates *et al*[76], 2010; González-Pinto *et al*[78], 2010; Cely *et al*[83], 2011; Barraco *et al*[88], 2012; Sharma *et al*[94], 2012; Kutzelnigg *et al*[151], 2014; Hajda *et al*[104], 2015	Danion *et al*[111], 1987; Nilsson and Axelsson[117], 1989; Sajatovic *et al*[63], 2007 c; Sajatovic *et al*[72], 2009a; Mazza *et al*[75], 2009; Hong *et al*[84], 2011; Sajatovic *et al*[86], 2011b; Montes *et al*[150], 2013; Sylvia *et al*[42], 2014; Azadforouz *et al*[108], 2016; Sajatovic *et al*[152], 2016	
Manic symptoms	Van Putten[20], 1975; Connelly *et al*[109], 1982; Keck *et al*[47], 1996a; Keck *et al*[142], 1996b; Lenzi *et al*[116], 1989; Miklowitz *et al*[171], 2000; Miklowitz *et al*[172], 2003; Bowden *et al*[130], 2005; Gonzalez-Pinto *et al*[132], 2006; Gaudiano and Miller[173], 2006; Baldessarini *et al*[66], 2008a; Copeland *et al*[67], 2008; Bauer *et al*[44], 2010; González-Pinto *et al*[78], 2010; Perlis *et al*[82], 2010; Hong *et al*[84], 2011; Barraco *et al*[88], 2012; Montes *et al*[150], 2013; Sylvia *et al*[42], 2014; Levin *et al*[106], 2015	Colom *et al*[51], 2000; Rosa *et al*[136], 2007; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[63], 2007 c; Sajatovic *et al*[40], 2008; Clatworthy *et al*[71], 2009; Mazza *et al*[75],2009; Martinez-Aran *et al*[74], 2009; Sajatovic *et al*[86], 2011b; Murru *et al*[90], 2012; Belzeaux *et al*[95], 2013; Hibdye *et al*[98], 2013; Jónsdóttir *et al*[99], 2013; Ghaffari-Nejad *et al*[103], 2015; Azadforouz *et al*[108], 2016; Sajatovic *et al*[152], 2016	

Depressive symptoms	Bowden *et al*[130], 2005; Gaudiano and Miller[173], 2006; Johnson *et al*[61], 2007; Martinez-Aran *et al*[74], 2009; Bates *et al*[76], 2010; Bauer *et al*[44], 2010; Perlis *et al*[82], 2010; Hong *et al*[84], 2011; Barraco *et al*[88], 2012; Montes *et al*[150], 2013; Arvilommi *et al*[101], 2014; Bauer *et al*[45], 2013a; Bauer *et al*[153], 2013b; Murru *et al*[100], 2013; Gibson *et al*[97], 2013; Levin *et al*[106], 2015; Azadforouz *et al*[108], 2016; Sajatovic *et al*[152], 2016	Colom *et al*[51], 2000; Miklowitz *et al*[171], 2000; Miklowitz *et al*[172], 2003; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[63], 2007c; Rosa *et al*[136], 2007; Sajatovic *et al*[40], 2008; Sajatovic *et al*[72], 2009a; Clatworthy *et al*[71], 2009; González-Pinto *et al*[78], 2010; Sajatovic *et al*[86], 2011b; Murru *et al*[90], 2012; Hibdye *et al*[98], 2013; Sylvia *et al*[42], 2014; Ghaffari-Nejad *et al*[103], 2015	Better adherence with depression - Lenzi *et al*[116], 1989
Mixed symptoms	Bowden *et al*[130], 2005; González-Pinto *et al*[78], 2010; Perlis *et al*[82], 2010	Licht *et al*[125], 2001; Azorin *et al*[70], 2009; Hibdye *et al*[98], 2013; Ghaffari-Nejad *et al*[103], 2015	
Psychotic symptoms	Miklowitz *et al*[174], 1992; Maj *et al*[122], 1998; Yen *et al*[157], 2005; Martinez-Aran *et al*[74], 2009; González-Pinto *et al*[78], 2010; Murru *et al*[90], 2012; Murru *et al*[100], 2013; Levin *et al*[106], 2015; Sajatovic *et al*[152], 2016	Danion *et al*[111], 1987; Aagaard and Vestergaard[118], 1990; Colom *et al*[51], 2000; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[40], 2008; Sajatovic *et al*[72], 2009a; Perlis *et al*[82], 2010; Belzeaux *et al*[95], 2013; Azadforouz *et al*[108], 2016	
Cognitive impairment	Danion *et al*[111], 1987; Jose *et al*[161], 2003; Baldessarini *et al*[66], 2008a; Depp *et al*[175], 2008; Martinez-Aran *et al*[74], 2009; Eker and Harkin[89], 2012	Maarbjerg *et al*[113], 1988; Jónsdóttir *et al*[99], 2013	
Familial psychiatric disorder	Drotar *et al*[133], 2007	Colom *et al*[51], 2000; Gonzalez-Pinto *et al*[132], 2006; Martinez-Aran *et al*[74], 2009; Savas *et al*[85], 2011; Murru *et al*[90], 2012; Col *et al*[141], 2014; Hajda *et al*[104], 2015	
Poor insight	Schumann *et al*[123], 1999; Greenhouse *et al*[54], 2000; Jose *et al*[161], 2003; Fleck *et al*[58], 2005; Yen *et al*[157], 2005; Rosa *et al*[160], 2006; Rosa *et al*[136], 2007; Copeland *et al*[67], 2008; Sajatovic *et al*[72], 2009a; González-Pinto *et al*[78], 2010; Cely *et al*[83], 2011; Sajatovic *et al*[86], 2011b; Savaş *et al*[85], 2011; Vieta *et al*[93], 2012; Kutzelnigg *et al*[151], 2014; Mert *et al*[107], 2015; Novick *et al*[176], 2015	Wong *et al*[124], 1999; Jonsdottir *et al*[99], 2013	
Comorbid SUD	Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Weiss *et al*[50], 1998; Aagaard and Vestergaard[118], 1990; Keck *et al*[121], 1997; Keck *et al*[48], 1998; Strakowski *et al*[49], 1998; Licht *et al*[125], 2001; Fleck *et al*[58], 2005; Gonzalez-Pinto *et al*[132], 2006; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b; DelBello *et al*[60], 2007; Manwani *et al*[135], 2007; Baldessarini *et al*[138], 2008b; Copeland *et al*[67], 2008; Darling *et al*[177], 2008; Zeber *et al*[68], 2008; Sajatovic *et al*[72], 2009a; van Rossum *et al*[178], 2009; Vega *et al*[139], 2009; Bates *et al*[76], 2010; González-Pinto *et al*[78], 2010; Perlis *et al*[82], 2010; Cely *et al*[83], 2011; Hong *et al*[84], 2011; Lang *et al*[147], 2011; Sajatovic *et al*[162], 2011a; Teter *et al*[179], 2011; Barraco *et al*[88], 2012; Vieta *et al*[93], 2012; Hibdye *et al*[98], 2013; Jónsdóttir *et al*[99], 2013; Montes *et al*[150], 2013; Arvilommi *et al*[101], 2014	Nilsson and Axelsson[117],1989; Schumann *et al*[123], 1999; Colom *et al*[51], 2000; Sajatovic *et al*[63], 2007c; Sajatovic *et al*[40], 2008; Mazza *et al*[75], 2009; Sharifi *et al*[73],2009; Rascati *et al*[148], 2011; Sajatovic *et al*[86], 2011b; Murru *et al*[90], 2012; Sharma *et al*[94], 2012 Murru *et al*[100], 2013; Col *et al*[141], 2014; Kutzelnigg *et al*[151], 2014; Sylvia *et al*[42], 2014; Mert *et al*[107], 2015; Ghaffari-Nejad *et al*[103], 2015	
Comorbid personality disorders	Danion *et al*[111], 1987; Aagaard *et al*[112], 1988; Maarbjerg *et al*[113], 1988; Colom *et al*[51], 2000; Murru *et al*[100], 2013; Arvilommi *et al*[101], 2014	Aagaard and Vestergaard[118], 1990; Schumann *et al*[123],1999; Kliendienst and Griel[156], 2004; Mazza *et al*[75], 2009; Murru *et al*[90], 2012; Kutzelnigg *et al*[151], 2014	
Comorbid anxiety disorders or ADHD	DelBello *et al*[60], 2007; Baldessarini *et al*[66], 2008a; Taj *et al*[69], 2008; Perlis *et al*[82], 2010; Arvilommi *et al*[101], 2014	Sajatovic *et al*[59], 2006a; Sajatovic *et al*[144], 2007b; Drotar *et al*[133], 2007; Sajatovic *et al*[40], 2008; Cely *et al*[83], 2011; Rascati *et al*[148], 2011; Murru *et al*[90], 2012; Belzeaux *et al*[95], 2013; Kutzelnigg *et al*[151], 2014; Sylvia *et al*[42], 2014	Better adherence with comorbid anxiety disorder - Baldessarini *et al*[138], 2008b

ADHD: Attention deficit hyperactivity disorder; BD: Bipolar disorder; SUD: Substance use disorders; UP: Unipolar disorder.

(6 studies with positive associations and 2 without) with non-adherence in BD. Finally, a clear association with medication non-adherence was evident only in the case of two clinical parameters, that is comorbid SUD and lack of insight, where the number of studies with positive associations far outnumbered the studies without such associations.

Treatment-related correlates of medication non-adherence in BD

Reviews: Several studies have examined the effects of different classes of medications, the duration of treatment with medications, intensity of treatment, *i.e.*, the number of medications and their doses, and the complexity of medication regimens on medication non-adherence in BD. Reviews of literature have found occasional differences in adherence between some of the second-generation antipsychotics (SGAs), but rates of non-adherence with mood stabilizers and antipsychotics have been largely similar[2]. No differences have been found between older and newer medications; indeed rates of non-adherence in BD

appear to have remained unchanged over the years despite the availability of newer medications[4,6,15,17,19]. The influence of duration of treatment has been uncertain with non-adherence occurring both in the early as well as late phases of treatment[4,15,17,22]. The number of medications, higher doses and more complicated medication regimes are all expected to increase the risk of non-adherence, but even this has not been reported consistently[4,10,15,17,18]. The bulk of studies, however, have been about side effects of treatment. Reviews of non-adherence in BD have found a link with side effects among certain studies[3,12,21,23], both for side effects associated with mood stabilizers and antipsychotics[16,181-184]. However, many others have concluded that side effects are often not among the major reasons for non-adherence[2,4,6,14,17]. The latter reviews also agree in finding that it is the fear or concern about side effects that frequently leads to non-adherence, rather than the actual presence of side effects. Inadequate efficacy of medication-treatment has also been proposed as a risk factor for non-adherence in BD, with efficacy in reducing depressive symptoms being particularly important from the patient's perspective[3,12,23].

Studies: Similar to the results of studies examining demographic and illness related correlates of non-adherence in BD, studies examining medication-related variables have also yielded few unequivocal associations. Thus, drug classes, the duration of treatment, greater number or higher doses of medications and more complex medication regimens were associated with non-adherence only in a few studies, while the number of studies without such associations were either equal in number or far greater. A positive association with the presence of side effects was reported in 35 studies; more than a-third of these involved lithium. However, 26 studies did not find a positive association and 17 studies found that fear of side effects than their actual presence had a greater impact on non-adherence. Efficacy of treatment had a positive association with non-adherence, but only among 12 studies. These results are depicted in Table 7.

DISCUSSION

Given its chronic, relapsing and remitting nature as well as attendant disability, comorbidity and frequent negative therapeutic outcomes, BD is expected to be characterized by high rates of treatment non-adherence. The existing reviews on medication non-adherence in BD (included in Table 1) support this notion by finding that about 40% to 50% of the patients with BD do not take their medications properly. However most of these reviews are several years old and have included about 25 studies or less in most instances. The current review spanned four decades from 1976 to 2016 and was based on a more comprehensive search of the existing literature on medication non-adherence in BD. It also used somewhat broader selection criteria in an effort to include data from as many studies as possible. This resulted in a much larger list of close to 200 reviews and studies on the subject; 132 of these studies were used derive rates of medication non-adherence in BD. The obvious disadvantage of casting such a broad net was the substantial difference in methodologies across the studies that formed a part of this review. Though this significant heterogeneity did not allow a meta-analysis of the data, the results probably reflected a truer and a more up to date picture of medication non-adherence in BD than some of the existing reviews, simply because of the large number of studies included and the longer period covered by this review.

The results of the review yielded some notable findings about the rate of medication non-adherence in BD. To start with there was a wide variation in rates of non-adherence ranging from 0%-96%, which was more a result of the methodological disparities across studies. Nevertheless, the entire group of studies yielded an average rate of 41.5% and a median rate of 40% for medication non-adherence. When the rates were computed excluding outliers with very high or low rates, the mean rate of non-adherence rose to 43% and the median rate to 41%. These rates were remarkably similar to those found in the majority of previously published reviews (Table 1), which have found rates of non-adherence in BD to vary from 8% to 68% with a mean rate of about 40% and a median rate of 41%-42%. Rates of non-adherence were the highest for studies of patients on treatment with antipsychotics (mean 48%-51%; median 47%-48%) followed by studies of patients on all three classes of medications (mean 45%; median 41%-43.5%). Surprisingly, the rates were significantly lower in studies of patients being treated with mood stabilizers (mean 34%-38%; median 31.5%-34%). It was not exactly clear why this was so, particularly since other studies and reviews have not found rates to differ among different classes of medications[2,5,6,21,22].

However, studies of mood stabilizers mainly included lithium; a significant proportion of them (41%) had been conducted in the 1970s to 1990s; and, the number of studies with very low rates was higher than the other two groups. In direct contrast, studies of patients on antipsychotics were conducted more recently and were based mostly on claims data, which also meant that the sample sizes were very large in many of these studies.

Thus, the overall conclusion from the group of studies included in this review is that between a third to about half of the patients with BD are medication non-adherent. However, there is reason to treat these rates with caution because of the considerable divergence in study designs. Differences in rates of non-adherence across studies usually arise principally from the definition of adherence used, the nature and size of the patient sample included, the setting in which the study is conducted, the duration of assessment and

Table 7 Studies of treatment correlates of medication non-adherence in bipolar disorder

Treatment correlates	Studies with positive associations	Studies without positive associations	Others
Differences between mood stabilizers	Weiss *et al*[50], 1998; Revicki *et al*[155], 2005; Baldessarini *et al*[138], 2008b; Sajatovic *et al*[137], 2007a	Baldessarini *et al*[66], 2008a; Darling *et al*[177], 2008; Bauer *et al*[45], 2013a; Col *et al*[141], 2014	
Differences between antipsychotics	Gianfrancesco *et al*[184], 2005; Gianfrancesco *et al*[185], 2006; Hassan *et al*[186], 2007; Sajatovic *et al*[144], 2007b; Rascati *et al*[148], 2011; Ibrahim *et al*[105], 2015	Patel *et al*[131], 2005; Sajatovic *et al*[143], 2006b; Baldessarini *et al*[66], 2008a	
Differences between mood stabilizers and antipsychotics or antidepressants	González-Pinto *et al*[78], 2010; Lang *et al*[147], 2011; Murru *et al*[100], 2013; Arvilommi *et al*[101], 2014; Ibrahim *et al*[105], 2015	Danion *et al*[111], 1987; Keck *et al*[48], 1998; Colom *et al*[51], 2000; Patel *et al*[131], 2005; Sajatovic *et al*[143], 2006b; Baldessarini *et al*[66], 2008a; Azorin *et al*[70], 2009; Clatworthy *et al*[71], 2009; Gianfrancesco *et al*[187], 2009; Martinez-Aran *et al*[74], 2009; Mazza *et al*[75], 2009; Bates *et al*[76], 2010; Cely *et al*[83], 2011; Savaş *et al*[85], 2011; Murru *et al*[90], 2012; Bauer *et al*[153], 2013b; Hibdye *et al*[98], 2013; Arvilommi *et al*[101], 2014; Hajda *et al*[104], 2015	
Shorter duration of treatment	Johnson and McFarland[169], 1996; Colom *et al*[51], 2000; Lang *et al*[147], 2011; Azadforouz *et al*[108], 2016	Gonzalez-Pinto *et al*[132], 2006; Drotar *et al*[133], 2007; Darling *et al*[177], 2008; Sharma *et al*[94], 2012; Hibdye *et al*[98], 2013; Col *et al*[141], 2014	Longer durations - Jamison *et al*[9], 1979; Scott and Pope[127], 2002a Kessing *et al*[134], 2007 Sharifi *et al*[73], 2009; Short and long durations - Kutzelnigg *et al*[151], 2014
Greater number of medications	Keck *et al*[47], 1996a; Revicki *et al*[155], 2005; Baldessarini *et al*[138], 2008b; Gianfrancesco *et al*[187], 2009; Bates *et al*[76], 2010; Hou *et al*[79], 2010; Perlis *et al*[82], 2010; Cruz *et al*[35], 2011; Rascati *et al*[148], 2011; Bauer *et al*[45], 2013a; Bauer *et al*[153], 2013b; Ibrahim *et al*[105], 2015	Colom *et al*[51], 2000; Licht *et al*[125], 2001; Rosa *et al*[136], 2007; Baldessarini *et al*[66], 2008a; Darling *et al*[177], 2008; Depp *et al*[175], 2008; Taj *et al*[69], 2008; Martinez-Aran *et al*[74], 2009; Bauer *et al*[44], 2010; Sajatovic *et al*[86], 2011b; Savaş *et al*[85],2011; Miasso *et al*[91], 2012; Sharma *et al*[94], 2012; Col *et al*[141], 2014; Ghaffari-Nejad *et al*[103], 2015	Less intensive treatment - Johnson and McFarland[169], 1996; Keck *et al*[121], 1997; Sajatovic *et al*[59], 2006a; Sajatovic *et al*[143], 2006b; Sajatovic *et al*[137], 2007a; Sajatovic *et al*[144], 2007b; Sajatovic *et al*[40], 2008
Higher doses of medications	McCleod and Sharp[37], 2001; Gianfrancesco *et al*[185], 2006	Baldessarini *et al*[66], 2008a; Col *et al*[141], 2014; Hajda *et al*[104], 2015	Lower doses of medications - Mazza *et al*[75], 2009; Bauer *et al*[44], 2010
Complex medication regimens	Baldessarini *et al*[138], 2008b; Sajatovic *et al*[72], 2009a; Hibdye *et al*[98], 2013; Ibrahim *et al*[105], 2015	Keck *et al*[48], 1998; Baldessarini *et al*[66], 2008a; Miasso *et al*[91], 2012; Col *et al*[141], 2014	
Side effects	Bech *et al*[30], 1976; Vestergaard and Amdisen[188], 1983; Maarbjerg *et al*[113], 1988; Gitlin *et al*[189], 1989; Nilsson and Axelsson[117], 1989; Aagaard and Vestergaard[118], 1990; Maj *et al*[122], 1998; Weiss *et al*[50], 1998; Licht *et al*[125], 2001; Kliendienst and Griel[156], 2004; Lewis[190], 2005; Bowden *et al*[130], 2005; Calabrese *et al*[56], 2005; Fleck *et al*[58], 2005; Revicki *et al*[155], 2005; Johnson *et al*[61], 2007; Baldessarini *et al*[66], 2008a; Baldessarini *et al*[138], 2008b; Bates *et al*[76], 2010; Mączka *et al*[191], 2010; Wang and Henning[192], 2010; Cely *et al*[83], 2011; Cruz *et al*[35], 2011; Miasso *et al*[193], 2011; Sajatovic *et al*[162], 2011a; Teter *et al*[1179], 2011; Eker and Harkin[89], 2012; Sharma *et al*[94], 2012; Belzeaux *et al*[95], 2013; Gibson *et al*[97], 2013; Arvilommi *et al*[101], 2014; Sylvia *et al*[42], 2014; Ibrahim *et al*[105], 2015; Mert *et al*[107], 2015 Ghaffari-Nejad *et al*[103], 2015	Van Putten[20], 1975; Jamison *et al*[9], 1979; Connelly *et al*[109], 1982; Danion *et al*[111], 1987; Lenzi *et al*[116], 1989; Johnson and McFarland[169], 1996; Schuman *et al*[123], 1999; Scott[196], 2000; Scott[126], 2002; Scott and Pope[127], 2002a; Morselli *et al*[194], 2003; Morselli *et al*[195], 2004; Pope and Scott[129], 2003; Roy *et al*[33], 2005; Sajatovic *et al*[143], 2006b; Drotar *et al*[133],2007; Rosa *et al*[160], 2006; Rosa *et al*[136], 2007; Perlis *et al*[82], 2010; Savaş *et al*[85], 2011; Barraco *et al*[88], 2012; Vieta *et al*[93], 2012; Hibdye *et al*[98], 2013; Jónsdóttir *et al*[99], 2013; Kutzelnigg *et al*[151], 2014; Col *et al*[141], 2014	Fear of side effects - Cochran *et al*[31], 1984; Schumann *et al*[123], 1999; Scott[196], 2000; Scott[126], 2002; Scott and Pope[127], 2002a; Scott and Tacchi[197], 2002; Morselli *et al*[194], 2003; Morselli *et al*[195], 2004; Fleck *et al*[58], 2005; Rosa *et al*[160], 2006; Rosa *et al*[136], 2007; Clatworthy *et al*[36], 2007; Clatworthy *et al*[71], 2009; Sajatovic *et al*[198], 2009c; Kriegshauser *et al*[199], 2010; Cruz *et al*[35], 2011; Sajatovic *et al*[162], 2011a
Efficacy	Bech *et al*[30], 1976; Jamison *et al*[9], 1979; Miklowitz *et al*[171], 2000; Miklowitz *et al*[172], 2003; Lewis[190], 2005; Fleck *et al*[58], 2005; Patel *et al*[131], 2005; Gaudiano and Miller[173], 2006; Drotar *et al*[133], 2007; Johnson *et al*[61], 2007; Sajatovic *et al*[198], 2009c; Cely *et al*[83], 2011		

BD: Bipolar disorder. References in Tables 2-4 and text (No. 155-199).

the way non-adherence is estimated[4,15,18,80]. Larger studies with more representative samples and longer durations may be more likely to yield more accurate rates of non-adherence. In this review, about half of

the studies had less than 100 patients (48%) while studies with 100-500 patients formed a significant proportion of the total number of studies (39%) Studies with large and more representative samples (naturalistic studies with > 500 patients) were fewer (14%) but the mean rate of 49% obtained from them was higher than the mean rate of 41.5%-43% obtained for the entire group. Studies with longer durations (> 1-10 years) formed 25% of the sample. However, the mean rate of non-adherence (36%) among studies with longer durations was lower than the average rate of 41.5%-43% of the entire group. This was possibly due to fact that the bulk of studies with long durations involved mood stabilizers, a group in which mean rates of non-adherence (34%-38%) were lower than that for other medication classes. Different types of subjective and objective methods are often used to estimate adherence. In the absence of a "gold standard" the use of more than one method is recommended as the next best alternative[2,6,12,14,27]. In this review the majority of studies (54%) had used either self-reports or clinical interviews to estimate adherence; a smaller proportion (11%) used claims data. The low proportion of studies using multiple measures of adherence (29%) could thus cast some doubts on the rates of non-adherence obtained in this review.

A major problem of research in the area of determinants of non-adherence in BD has been the exclusive focus on demographic, illness and treatment related predictors of non-adherence[3,6,13,15,127]. This has been largely driven by the traditional medical model and compliance-based approaches to the problem of non-adherence in BD. As demonstrated in this review, studies examining demographic, illness and treatment related variables (numbering close to 160) far exceeded those that focused on patient-related factors such as attitudes and beliefs about medications, relationship with the clinician, knowledge about the illness and the influence of the wider socio-cultural environment on medication taking in BD. Social and cultural factors are of potential importance and likely to play a major role in determining treatment-adherence in BD[154]. However, despite the large number of studies and the long list of variables examined, the search to identify demographic, illness and treatment related factors associated with non-adherence in BD has yielded little of note. This review found that none of the demographic attributes of patients such as age, gender, marital status, education, employment, income or social disadvantage were consistently linked to medication non-adherence in BD. Among clinical characteristics the presence of comorbid SUD and the absence of insight were the only two factors consisted associated with non-adherence with BD. The severity of manic symptoms appeared to show some association with non-adherence among studies of BD included in this review, as did cognitive impairment in a few studies. Given that about half or more of the patients with BD might have a comorbid SUD, the usefulness of this determinant has been questioned[8]. Lack of insight is expected to adversely affect adherence more so among patients in acute symptomatic phases of mania. However, the role of insight is less certain in other phases such as depression or in the inter-episodic period. Moreover, lack of insight is only one among several influences on non-adherence in BD; therefore, the presence of adequate insight by itself may not be enough to ensure adherence. In accordance with several previous reviews[2,4,6,10,15] medication-related variables such as the types of medications, duration of treatment, greater number of medications, higher doses and complexity of treatment regimens did not demonstrate consistent associations with non-adherence among studies of BD included in this review. Earlier reviews of non-adherence in BD have found a link with side effects of medications[3,12,21,23]. A positive association with the presence of side effects was reported in 35 studies of this review; more than a-third of these involved lithium. At the same time almost an equal number of studies did not find a positive association and many found that fear of side effects than their actual presence had a greater impact on non-adherence. This indicates that side effects are often not among the major reasons for non-adherence in BD and that fear or concern about side effects (an attitudinal variable) may be the more important determinant[2,4,6,17,167].

There could be several reasons for the unequivocal findings regarding clinical and socio-demographic determinants of non-adherence in BD. The simplified and dichotomous approach to examining the association between these parameters and non-adherence in BD has usually ignored the complex relationship between several such variables. For example, the link with manic symptoms could well be related to the lack of insight or cognitive impairment during episodes rather than the severity of symptoms. Moreover, the pathways through which demographic and illness or medication related variables influence could include subjective factors such as attitudes, knowledge or other socio-environmental influences. Therefore, though some of these factors such as comorbid SUD or lack of insight may identify patient groups at higher risk for non-adherence, they cannot identify which of the patients from these high risk groups will go on to develop non-adherence.

Despite being based on a comprehensive search and a much larger number of studies than earlier reviews, the findings of this review were not without their limitations. Many reviews on the management of BD, which mention the problem of non-adherence in passing have not been included. In all likelihood the number of studies on medication non-adherence in BD is larger than the current list of studies, because some studies especially those publications not in English were probably missed. The relative lack of studies from non-Western countries was also a handicap. However, the principal shortcoming was the difficulty of drawing reliable conclusions from studies with such widely disparate methodologies. Nevertheless, it was quite evident that the rate of medication non-

adherence in BD was quite high and no different from other chronic psychiatric or medical disorders. The failure of demographic, illness and treatment related factors to predict non-adherence was also not entirely unexpected. However, this emphasizes the importance of other patient orientated factors in determining non-adherence in BD. Research over the last two decades or so has consistently endorsed the significance of several such factors including patients' attitudes and beliefs about medications, their treatment alliance with the health-care provider, their knowledge and causal beliefs about the illness, the influence of the family, and the role of stigma and treatment-access in determining non-adherence in BD[200]. A patient-centred approach to non-adherence in BD is also in consonance with the current theoretical perspectives on medication-taking behaviour and the emphasis on combining pharmacological and psychosocial strategies to enhance adherence in BD[201]. Therefore, future research which combines some of more consistent clinical and demographic correlates with patient-centred determinants is likely to predict non-adherence in BD with a greater degree of accuracy. Such an approach may also lead to a better understanding of this complex phenomenon and suggest more effective ways to deal with the continuing challenge of medication non-adherence in BD.

COMMENTS

Background

Previously published reviews on medication non-adherence in bipolar disorder (BD) have estimated rates to vary from around 8% to 68%, with mean rates ranging from 25% to 40% and median rates from 40% to 42%. However, these most of these reviews are based on a relatively small number of studies, are somewhat dated and have not comprehensively searched the existing literature. Given these drawbacks, the present review aimed to conduct a more comprehensive and systematic search for all studies estimating rates of medication non-adherence in BD and/or providing information on demographic, illness and medication related determinants of non-adherence.

Research frontiers

Treatment non-adherence in BD has attracted a lot of research attention lately because not only is it common in BD, but it also has a number of negative effects on outcome, and enhancing adherence has proved to be challenging.

Innovations and breakthroughs

The current review spanned four decades from 1976 to 2016 and was based on a more comprehensive search of the existing literature on medication non-adherence in BD. This resulted in a much larger list of close to 200 reviews and studies on the subject. Nevertheless, the results endorsed the consensus in existing literature that medication non-adherence is present in a third to about half of the patients with BD. There is also little consensus among earlier reviews regarding the association of clinical, demographic and treatment-related variables with medication non-adherence in BD. The present review clearly demonstrated that demographic and medication-related factors have little influence on medication non-adherence in BD, while among clinical factors only comorbid substance use disorder and absence of insight were clearly linked to non-adherence in BD.

Applications

The failure of clinical and demographic factors to predict non-adherence emphasizes the importance of other patient orientated factors in determining non-adherence in BD. Therefore, future research should also focus on patient-centred determinants of medication non-adherence in BD and adherence interventions should emphasize the role of these factors.

Terminology

Adherence has been defined as "the extent to which a person's behaviour, taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider".

Peer-review

The manuscript is well organized and written, the used methodology is rigorous and the conclusions are coherent with the main findings.

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Contents

Bimonthly Volume 5 Number 5 October 26, 2017

META-ANALYSIS

124 Thalidomide and thalidomide analogues in treatment of patients with inflammatory bowel disease: Meta-analysis

Sami Ullah KR, Xiong YL, Miao YL, Ummair S, Dai W

Contents

World Journal of Meta-Analysis
Volume 5 Number 5 October 26, 2017

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META-ANALYSIS

Thalidomide and thalidomide analogues in treatment of patients with inflammatory bowel disease: Meta-analysis

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Abstract

AIM

To examine the efficacy and safety of thalidomide and thalidomide analogues in induction and maintenance of remission in patients with inflammatory bowel disease (IBD).

METHODS

A literature search was performed in the following databases: PubMed, EMBASE, Web of Science, Ovid and the Cochrane Library, and Chinese databases such as the China National Knowledge Infrastructure, China Science and Technology Journal Database (VIP), Wanfang Data. The randomized controlled analysis was performed to assess the effects of thalidomide therapy on inflammatory bowel disease for patients who did show good response with other therapies.

RESULTS

Three studies (n = 212) met the inclusion criteria were used in this Meta-analysis. No difference was found between thalidomide/thalidomide analogues and placebo in the induction of remission (RR = 1.36, 95%CI: 0.83-2.22, P = 0.22), the induction of clinical response (RR = 1.14, 95%CI: 0.75-1.72, P = 0.54) and the induction of adverse events (RR = 1.41, 95%CI: 0.99-2.02, P = 0.06).

CONCLUSION

Currently, there is not enough evidence to support use of thalidomide or its analogue for the treatment in patients of any age with IBD. However, it warrants a reanalysis when more data become available.

Key words: Inflammatory bowel disease; Thalidomide; Thalidomide analogues; Treatment; Efficacy; Safety; Meta-analysis

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Core tip: The aim of this meta-analysis is to examine the efficacy and safety of thalidomide and thalidomide analogues for induction and maintenance of remission in patients with inflammatory bowel disease (IBD). The literature was searched in the databases: PubMed, EMBASE, Ovid and the Cochrane Library, and Chinese databases. The Randomized Controlled Trials was performed during this analysis to assess the effects of thalidomide therapy on IBD patients that did show good response with other therapies. Weighted pooled outcomes were synthesized with a fixed-effects model to account for clinical heterogeneity. This meta-analysis showed that there is not enough evidence to support the use of thalidomide or its analogues in the treatment of IBD for patients of any age.

Sami Ullah KR, Xiong YL, Miao YL, Ummair S, Dai W. Thalidomide and thalidomide analogues in treatment of patients with inflammatory bowel disease: Meta-analysis. *World J Meta-Anal* 2017; 5(5): 124-131 Available from: URL: http://www.wjgnet.com/2308-3840/full/v5/i5/124.htm DOI: http://dx.doi.org/10.13105/wjma.v5.i5.124

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract with the long period of clinical relapse and remission[1]. Crohn's disease and ulcerative colitis are two main subtypes of inflammatory bowel diseases[1]. The quality of life of the patients who are suffering from IBD is highly affected. The causes of IBD are still unclear but many researchers believe that environmental factors and microbial triggers might induce IBD[2,3].

The prevalence of IBD varies considerably around the world with diagnostic criteria vary between geological regions. It is believed that IBD is associated with increased industrialization of countries. The highest prevalence of IBD is observed in North America and Europe[4] (2.6 million in Europe and 1.2 million in North America)[5,6].

There is no cure of IBD to date, aims of the therapy are induction and maintenance of remission[1,2]. Corticosteroids are the mostly used drugs, which shows effectiveness but only in, inducing remission but not in maintenance of remission for IBD[7,8].

There are many drugs that have been used in the treatment of IBD, however, maintaining remission remains a challenge. A safe and effective drug for the treatment of IBD remains to be found Thalidomide was initially used as a sedative and antiemetic drug. It was removed from the market during 1960s because it births related defects[9].

It was discovered later that thalidomide could inhibit the synthesis of tumor necrosis factor-α (TNF-α) by accelerating the degradation of its mRNA[10]. The immune regulatory property of thalidomide raised peoples' interests in its potential for the treatments of autoimmune diseases in recent years. The efficacy of thalidomide treatment has been demonstrated by a series of clinical trials in a serious clinical disease like human immunodeficiency virus (HIV) associated wasting syndrome, hereditary hemorrhagic telangiectasia[11], refractory cutaneous lesion of lupus erythematous[12], multiple myeloma[13], and Bachet's disease[14].

The increased production of TNF-α in IBD plays a major role in the pathophysiology of IBD[15,16] and TNF-α tends to increase with the disease progression[13,14].

The development of thalidomide analogues was spurred due to emerging clinical evidence supports that the drug has anti-angiogenic and anti-inflammatory properties[17]. So far there have been many thalidomide analogues but the most famous ones are Lenalidomide, Pomalidomide and Apremilast. They all work is similar manner and have similar mechanisms for the treatment of diseases It is believed that they work by different mechanisms in different diseases[18,19]. Apremilast works differently by reducing PDE4 activity and causing an increase in cAMP concentrations, which lead to inhibition of many pro-inflammatory cytokines and increased production of anti-inflammatory cytokines[20]. Literature review shows no evidence to support or deny the use of thalidomide analogues for the treatment of IBD, nor does it show any difference in efficacy compared with thalidomide.

In a Cocranine review of thalidomide analogues for the induction of remission and maintenance of of Crohn's disease, lenalidomide showed no statistically significant benefits over placebo[21,22].

Thalidomide has the property to suppressing the synthesis of TNF-α[23,24]. Thalidomide can reduce the production of TNF-α by lipopolysaccharide or phytohaemaglutinin-stimulated monocytes and macrophages and mitogen-induced T-cells[25,26]. Although the exact mechanisms by which TNF-α involves in diseases is not clear, thalidomide seems to be effective for the treatment of diseases[10].

The aim of this study was to systematically review the current evidence examining the efficacy and safety of thalidomide and thalidomide analogues for the induction and maintenance of remission in patients with IBD.

MATERIALS AND METHODS

Literature search strategy

Two authors (Khan Rana Sami Ullah and Yu-Lin Xiong) independently carried out a retrieval of literatures that investigated the association between thalidomide or thalidomide analogues and IBD. A literature search was performed in the following databases: PubMed, EMBASE, Web of Science, Ovid and the Cochrane Library, and chinese databases including the China National Knowledge Infrastructure, China Science and Technology

Table 1 Summary of included studies

Study/yr	Country	Patients No. (intervention/ control)	Mean age (intervention/ control)	Gender (male/ female)	Participants
Luo/2008	China	23/23	37.2/36.5	27/19	Aged 18 to 70 yr, with mild-to-moderate CD
Lazzerini/2013	Italy	28/26	14.0/15.0	32/22	Aged 2 to 18 yr with active CD
Mansfield/2007	United Kingdom	23/28	41.5/41.3	21/30	Aged 18 to 75 yr with moderately severe CD
		33/28	37.5/41.3	33/29	

CD: Crohn's disease.

Table 2 Summary of included studies

Study/yr	Intervention	Control	Remission (intervention/ control)	Response (intervention/ control)	Adverse effects (intervention/control)
Luo/2008	Thalidomide100 mg/d	SASP 4 g/d	6/5	15/13	10/9
Lazzerini/2013	Thalidomide 50, 100 and 150 mg/d	Unknown	13/3	5/5	Unknown/1
Mansfield/2007	lenalidomide 25 mg/d,	Unknown	2/7	4/4	18/10
	lenalidomide 5 mg/d		10/7	6/4	12/10

Journal Database, Wanfang Data. The Medical Subject Terms (MeSH) and Keywords used for this research were: Thalidomide OR lenalidomide AND "inflammatory bowel disease" OR "Crohn's disease" OR "Ulcerative colitis". The last search was performed on April 20, 2015. We performed a further manual search of references from original or review articles on this topic.

Selection criteria

The titles and abstracts of published studies were screened independently by two authors (Khan Rana Sami Ullah and Yu-Lin Xiong)to determine whether they met the following inclusion criteria: (1) randomized controlled trials (RCTs), assessed the efficacy and safety of thalidomide and thalidomide analogues for treating patients with IBD, including UC and CD; (2) participants: Patients with IBD of all age groups, including UC and CD; (3) intervention: Thalidomide and thalidomide analogues (any route, dose, duration); (4) provided sufficient data for estimation of a relative risk (RR) and corresponding 95%CI; and (5) published in the English or Chinese language.

Data extraction

The methodological quality of selected trials was assessed independently by two authors (Khan Rana Sami Ullah and Yu-Lin Xiong) using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions[27] and the Jadad scale[28]. The former is based on the evidence of a strong relationship between allocation concealment and direction of effect. The Jadad scale is a validated five point, scale which measures some important factors that impact on the quality of a trial. They are summarized below: (1) was the study described as randomized? (2) was the method of randomization well described and appropriate? (3) was the study described as double blind? (4) was the double blinding well described and appropriate? and (5) were the withdrawals and dropouts described?

A data extraction form was developed and used to extract information on relevant features and results of included studies. The two authors (Khan Rana Sami Ullah and Yu-Lin Xiong) independently extracted and recorded data on the predefined checklist. Differences were resolved by discussion. Extracted data included the following items (Tables 1 and 2): (1) characteristics of patients: Author, publish year, age, sex, country, participants, duration of therapy; (2) total number of patients originally assigned to each intervention group; (3) intervention: Thalidomide, Lenalidomide; (4) control: No intervention, placebo or other interventions; and (5) outcomes: Primary outcome: Clinical remission as defined by the primary studies and expressed as a percentage of patients with Secondary outcomes: Clinical response as defined by the primary studies, and adverse events.

Statistical analysis

The Cochrane Collaboration review manager software (RevMan version 5.0) was used for data analysis. Results were analyzed according to the intention-to-treat principle. We assessed the efficacy and safety of thalidomide and thalidomide analogues for treating patients with IBD by calculating the pooled RR and corresponding 95%CI using meta-analysis. The Cochrane *Q*-test was used to evaluate the heterogeneity among those studies. I^2 was used to quantify the size of heterogeneity. When there was no significant heterogeneity (I^2 < 50%), we used the fixed-effects model to analyze the data. Otherwise, we used the random-effects model. In this study, we performed a sensitivity analysis to test the stability of results. Patients with final missing outcomes were

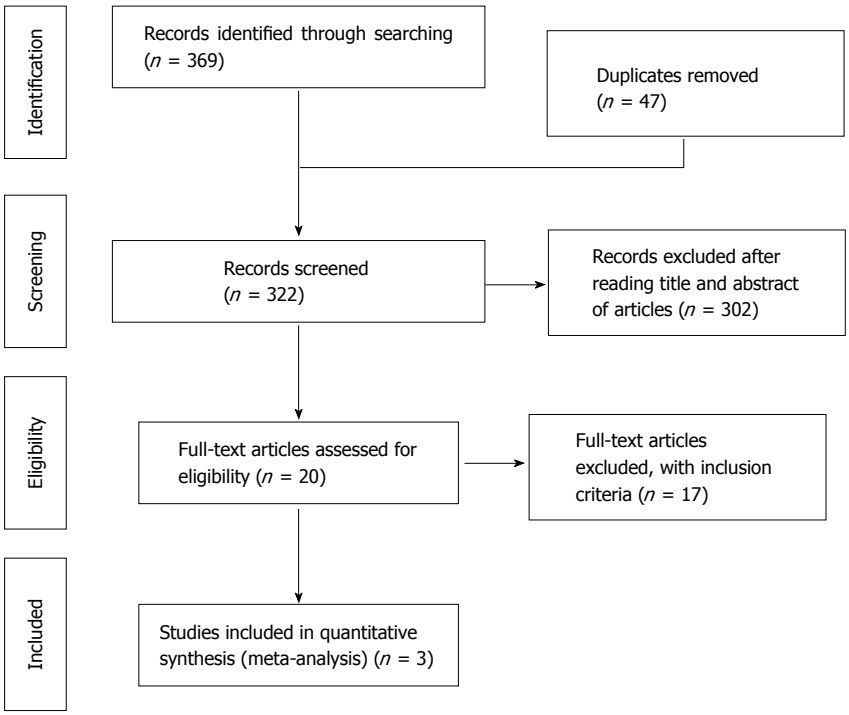


Figure 1 PRISMA selection. Study selection process according to the PRISMA statement meaningful analysis, funnel plots were not used to investigate publication bias.

assumed to be treatment failures. Funnel plots were not conducted to investigate publication bias as there were not enough studies included in each comparison to produce a meaningful analysis.

RESULTS

Literature retrieval

The above described search strategy identified 362 citation. There was also additional references added through other approach (7 articles), and the total number of articles used for literature review was 369 (362 + 7). Out of these 369 articles, 47 duplicates were removed, leaving only 322 primary articles (369 - 47 = 322). Out of these 322 primary articles, 302 were excluded after reading titles and abstract of articles. The remaining 20 articles assessed the efficacy and safety of thalidomide and thalidomide analogues for treating patients with IBD, including UC and CD. Only 3 out of the 20 articles were used for the meta-analysis as 17 failed to meet the inclusion criteria. The process of the included articles were shown Figure 1.

Methodological quality of included studies

The assessment of the risk of bias for the three studies used in the meta-analysis was summarized in Figures 2 and 3. Overall, the Lazzerini's study[29] has high quality (Jadad score = 5). The two studies[30,31] were rated as having high risk of bias (Jadad score = 3) due to not providing sufficient information on the method of randomization and lack of proper blinding controls. All data were analyzed based on the intention-to-treat principle. Due to an insufficient number of studies to produce a meaningful analysis, funnel plots were not used to investigate publication bias.

Induction of remission

The frequency of induction of remission for patients treated with thalidomide was studied in 3 trials that consisted of 212 patients. Significant heterogeneity was detected between these trials (I^2 = 57%, P = 0.07). We divided these trials into two subgroups (adults and children), and no significant heterogeneity was detected in the adult's trials (I^2 = 15%, P = 0.31). No meta-analysis was performed for Children's IBD as there was only one trial available. Meta-analysis using a fixed effects model showed no difference between thalidomide and placebo for the maintenance of clinical remission (RR = 1.36, 95%CI: 0.83 - 2.22, P = 0.22; Figure 4).

Induction of clinical response

The frequency of induction of clinical response for patients treated with thalidomide was studied in 3 trials that consisted of 212 patients. No significant heterogeneity was detected between these trials (I^2 = 0%, P = 0.98). We divided these trials into two subgroups, adults and children. Meta-analysis using a fixed effect model showed no difference between thalidomide and placebo for the maintenance of clinical remission (R.R = 1.14, 95%CI: 0.75-1.72, P = 0.54; Figure 5).

Induction of adverse events

Adverse events were reported in two out of the three trials (one trial is not clear) which consisted of 69

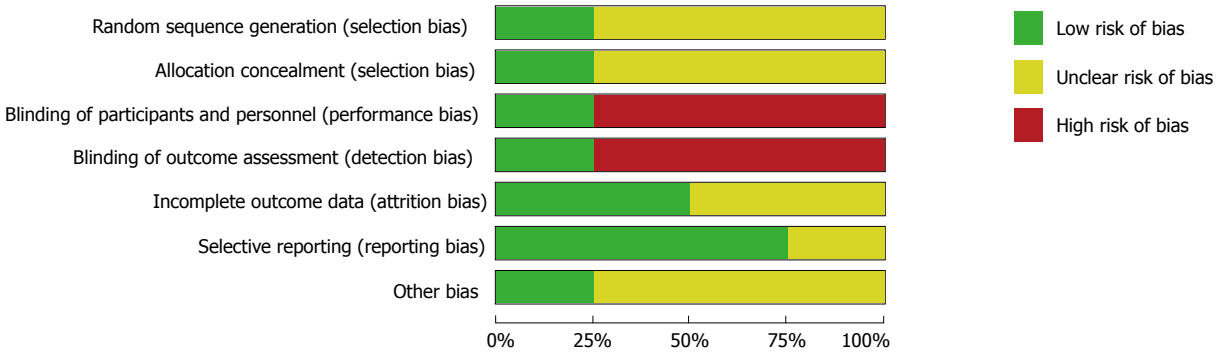


Figure 2 Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies.

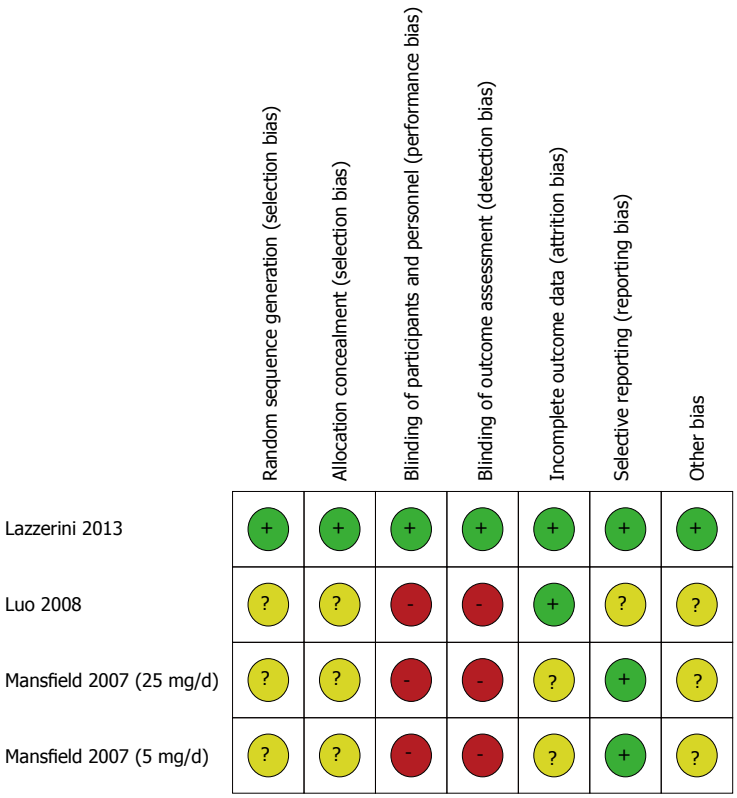


Figure 3 Risk of bias summary: Review authors' judgments about each risk of bias item for each included study.

patients, therefore the Meta analysis included only two trials. No significant heterogeneity detected between the two trials (I^2 = 49%, P = 0.14), Meta- analysis using a fixed effects model showed no difference between thalidomide and placebo for the occurrence of serious side effects (RR = 1.41, 95%CI: 0.99-2.02, P = 0.06; Figure 6).

Sensitivity analysis and publication bias

All of the outcomes were re-analyzed using a random effects model to estimate the stability of the meta-analysis. We excluded either one study at a time and analyzed the remaining studies to assess whether a particular study had an excessive influence on the results. Most of the results were consistent, as described above.

DISCUSSION

The treatment of IBD is quiet challenging in clinical practice for gastroenterologists. There is no cure for IBD; the main goals of therapy are induction and maintenance of remission. Many drugs have been used to treat IBD, but only corticosteroids are commonly used. However, corticosteroids are only effective in inducing remission, but not in maintain remission.

IBD is chronic inflammation of the gastrointestinal tract with a long period of clinical relapse and remission[1]. A wide range of drugs have been used for the treatment of IBD, such as amino salicylic acids, thiopurines, immunomodulators such as azathioprine (AZA), mercaptopurine, methotrexate, infliximab, adalimumab. And corticosteroids. However, the effective rates of these drugs are low and

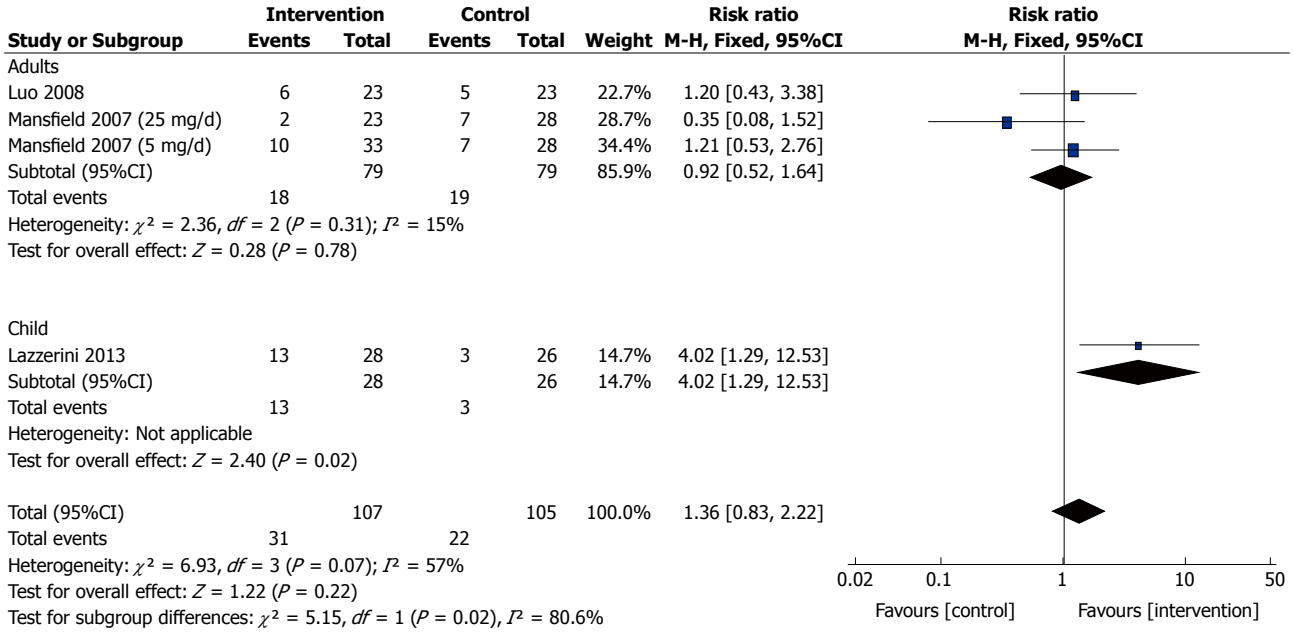


Figure 4 Remission: Fixed effects model forest plot of weighted pooled estimate.

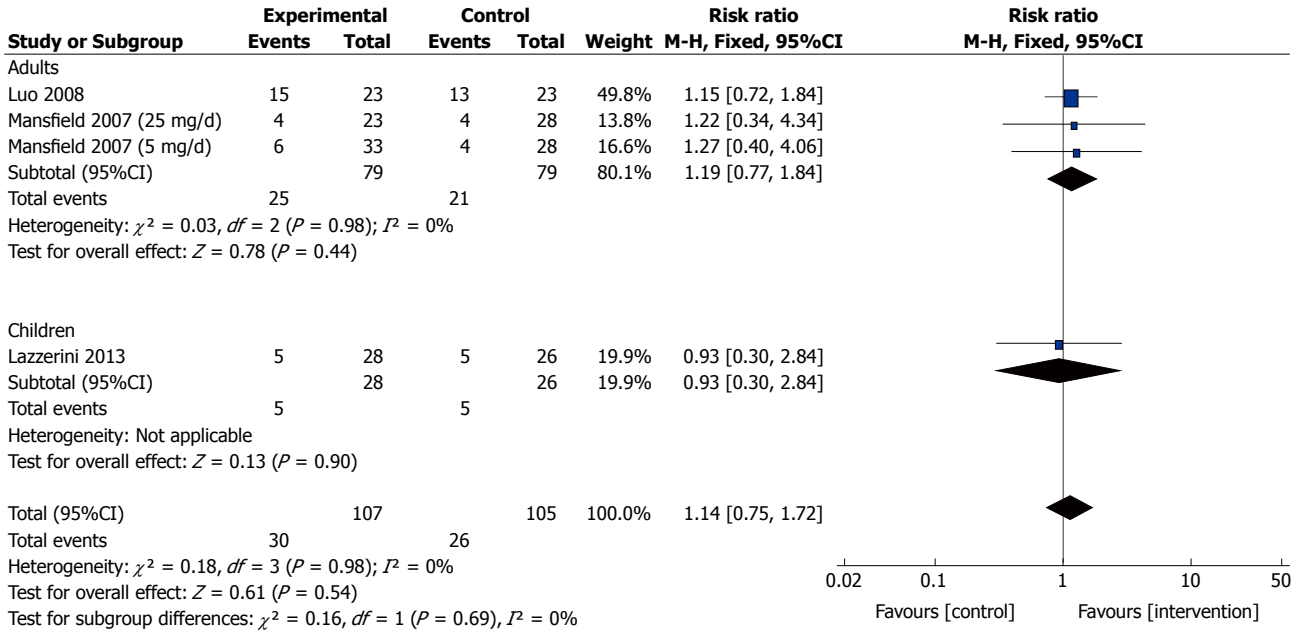


Figure 5 Clinical response: Fixed effects model forest plot of weighted pooled estimate.

they are associated with many adverse side effects[32,33]. It has now been recognized that the treatment goals should go beyond just controlling the symptoms of IBD. Rather, IBD treatments should aim to rapidly induce steroid-free remission, while minimizing serious complications and side effects[34]. The side effects that have been reported including an increased risk of infections, occurrence of autoimmune disorders[35], and risk of lymphoma or other malignancy[36].

The efficacies of thalidomide and thalidomide analogues for the treatment of IBD are of interest. Three published studies (n = 212) were included in the meta-analysis. No statistically significant difference was found between thalidomide/thalidomide analogues and placebo in terms of frequency of clinical remission and clinical response.

The main side effects that have been reported including Peripheral neuropathy, bradycardia, amenorrhea, and so on. Adverse events were reported in two out of three trials. They were not reported in one trial was not clear. We tried to contact the author by e-mail, but we were unsuccessful in retrieving the full data of these studies. Meta-analysis of the two studies did not show any statistically significant benefits from the use of thalidomide and thalidomide analogues.

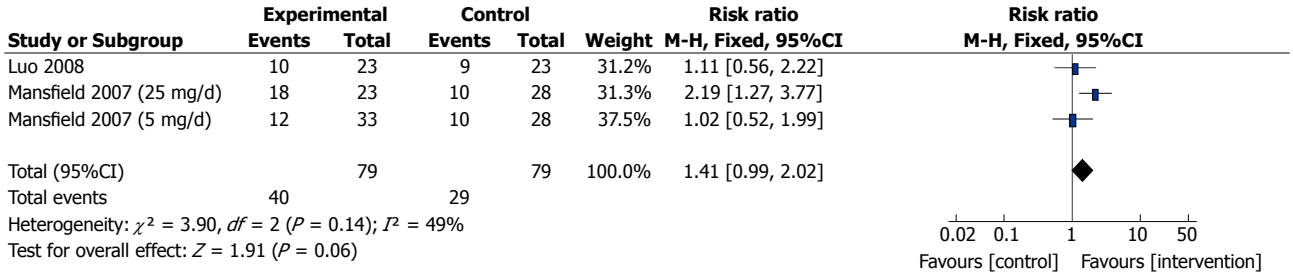


Figure 6 Adverse events: Fixed effects model forest plot of weighted pooled estimate.

Despite strict inclusion criteria have been used to reduce heterogeneity, there are still several limitations within this study. First, the degree of IBD of the patients of the trials included in this study vary considerately, ranging from mild-to-moderate to moderately severe. Second, evaluation of response was not uniform upon trial initiation, some trials enrolled patients with PCDAI $\leqslant$ 10, response: Reduction in PCDAI of $\geqslant$ 25%, while others enrolled those with CDAI < 150, reduction in CDAI by $\geqslant$ 100, and response: Reduction in CDAI by $\geqslant$ 70. Third, dosage of thalidomide and thalidomide analogues used differ between trials. All of these variability could affect the results of our analysis.

In summary, this meta-analysis has shown that there is not enough evidence to support the use of thalidomide or its analogues for the treatment of IBD for patients of any age. Many studies published so far on the use of thalidomide and thalidomide analogues for the treatment of IBD are handicapped by their small sample sizes and debatable interpretation. There were no case–control or cohort study and there were only three RCTs in publications. Therefore, it will be necessary to perform a re-analysis when more data become available.

COMMENTS

Background

Inflammatory bowel disease (IBD) is chronic inflammation of the gastrointestinal tract with a long period of clinical relapse and remission. A wide range of drugs have been used for the treatment of IBD. However, the effective rates of these drugs are low and they are associated with many adverse side effects. The increased production of tumor necrosis factor-α (TNF-α) in IBD plays a major role in the pathophysiology of IBD and TNF-α tends to increase with the disease progression.

Research frontiers

The treatment of IBD is quiet challenging in clinical practice for gastroenterologists. There is no cure for IBD, the main goals of therapy are induction and maintenance of remission. Many drugs have been used to treat IBD, but only corticosteroids are commonly used. However, corticosteroids are only effective in inducing remission, but not in maintain remission. The efficacies of thalidomide and thalidomide analogues for the treatment of IBD are of interest. Three published studies (n = 212) were included in the meta-analysis. No statistically significant difference was found between thalidomide/thalidomide analogues and placebo in terms of frequency of clinical remission and clinical response.

Innovations and breakthroughs

In this meta-analysis, the authors examined the efficacy and safety of thalidomide and thalidomide analogues for induction and maintenance of remission in 53 patients with IBD. No difference was found between thalidomide and placebo in the induction of remission (P = 0.22), clinical response (P = 0.54) and adverse events (P = 0.06). Therefore, it is concluded that there is not enough evidence to support the use of thalidomide or its analogues in the treatment of IBD patients of any age.

Applications

This meta-analysis has shown that there is not enough evidence to support the use of thalidomide or its analogues for the treatment of IBD for patients of any age. Many studies published so far on the use of thalidomide and thalidomide analogues for the treatment of IBD are handicapped by their small sample sizes and debatable interpretation.

Peer-review

This article, after making the meta-analysis, concluded that no enough evidence to support use of thalidomide or its analogue for the treatment in patients of any age with IBD. This article may be beneficial to the clinicians.

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WJMA World Journal of Meta-Analysis

Contents

Bimonthly Volume 5 Number 6 December 26, 2017

ORIGINAL ARTICLE

Retrospective Study

132 Different types of mechanical complications after surgical correction of adult spine deformity with osteotomy

Barton C, Noshchenko A, Patel VV, Cain CMJ, Kleck C, Burger EL

SYSTEMATIC REVIEWS

150 Synthetic *vs* biologic mesh for the repair and prevention of parastomal hernia

Knaapen L, Buyne O, van Goor H, Slater NJ

META-ANALYSIS

167 Complete revascularization reduces adverse outcomes in patients with multivessel coronary artery disease

Auchoybur ML, Chen X

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ORIGINAL ARTICLE

Retrospective Study

Different types of mechanical complications after surgical correction of adult spine deformity with osteotomy

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Author contributions: Barton C substantial contributions to conception and design of the study, acquisition of data, and drafting of the article; Noshchenko A provided statistical analysis and interpretation of the obtained results, drafting the article; Patel VV, Cain CMJ and Kleck C contributed equally to this work making critical revisions related to important intellectual content of the manuscript; Burger LE provided data quality control, critical revision of the manuscript and final approval of the version of the article to be published.

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Abstract

AIM

To determine the incidence and risk factors for mechanical complications (MC) after surgical correction of adult spinal deformity (ASD) with osteotomy.

METHODS

A retrospective study was performed. Inclusion criteria: Surgical correction of ASD using osteotomy; male or female; > 20 years old; follow-up ⩾ 24 mo or revision. The MC of spine and spinal instrumentation were studied separately. Risk analysis included assessment of the association between more than 50 different characteristics (demographic, clinical, radiographic, and instrumentation) with different types of MC.

RESULTS

The medical records of 94 operations in 88 subjects were analyzed: Female (68%), mean age 58.6 (SD, 12.7) years. Cumulative incidence of MC at 2 year follow-up was 43.6%. Of these, 78% required revision ($P < 0.001$). The following characteristics had significant ($P \leqslant 0.05$) association with MC: (1) Preoperative: osteoporosis, smoking, previous spinal operation, sagittal vertical axis (SVA) > 100 mm, lumbar lordosis (LL) < 34°; (2) postoperative: SVA > 75 mm; operative correction: SVA > 75 mm, LL > 30°, thoracic kyphosis > 25°, and pelvic tilt > 9°; a fall; pseudarthrosis; and (3) device and surgical technique: use of previously implanted instrumentation; use of domino and/or parallel connectors; type of osteotomy (PSO *vs* SPO) if preoperative SVA < 100 mm; lumbar osteotomy location; *in-situ* rod contouring > 60°; and fixation to sacrum/pelvis.

CONCLUSION

Risk of MC after surgical correction of ASD is substantial. To decrease this risk over- and/or insufficient correction of the sagittal imbalance should be avoided.

Key words: Adult spinal deformity; Osteotomy; Risk factors; Mechanical complications

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Core tip: The main study goal was evaluation of incidence and risk factors for different mechanical complications (MC) after surgical correction of adult spine deformity with osteotomy. Around half of patients experienced complications during two postoperative years; 78% of these cases required additional surgery. MC of spine occurred earlier and more often required revision than the MC of spinal instrumentation. The main risk factors for MC included severe preoperative sagittal imbalance, inadequate correction of the spinopelvic alignment, preoperative comorbidities (osteoporosis), postoperative events (falls), and features of the spinal instrumentation.

Barton C, Noshchenko A, Patel VV, Cain CMJ, Kleck C, Burger EL. Different types of mechanical complications after surgical correction of adult spine deformity with osteotomy. *World J Meta-Anal* 2017; 5(6): 132-149 Available from: URL: http://www.wjgnet.com/2308-3840/full/v5/i6/132.htm DOI: http://dx.doi.org/10.13105/wjma.v5.i6.132

INTRODUCTION

Surgical correction of adult spinal deformity (ASD) often requires one or more osteotomies such as a Smith-Petersen (SPO) and/or pedicle subtraction (PSO); SPO involves resection of the posterior column of the spine while PSO utilizes a resection of a triangular wedge through the pedicle and vertebral body[1,2]. In general a PSO can achieve significantly greater correction than a single SPO, and has been utilized for spinal deformities with severe sagittal imbalance, with relatively good clinical outcomes[3-10]. However, this method increases the risk of postoperative complications, which may result in revision surgeries[8-14]. The reported cumulative rate of revisions after surgical correction of ASD ranged from 28% at 24 mo follow-up[15] to 48% at 49 mo follow-up[11], with an increased cost in treatment. It was noted that the majority of these reoperations were related to mechanical complications (MC)[11,16]. Currently, there is no generally accepted definition of MC in spinal surgery. These have been described as failure of the fusion, spine or instrumentation. Therefore, the reported incidence of MC after surgical treatment in ASD is heterogeneous, and varies from 3.7% to 37%[10-12,17-24]. Published data concerning risk factors for MC in ASD corrected with an osteotomy are fragmented and suffer from several limitations. In particular, it was found that rate of postoperative symptomatic pseudarthrosis identified at 2-5 years after PSO was 10.5%. Patients with pseudarthrosis had significantly higher rates of previous fusion surgeries with pseudarthrosis, previous lumbar decompression, preoperative radiation of the spine/sacrum, and a preoperative history of inflammatory arthropathies/neurological disorders[25]. However, the level of corresponding risk was not evaluated. It was also noted that insufficient correction of spinal sagittal alignment with a PSO may be linked to pseudarthrosis and proximal junctional failure (PJF)[26]. However, the level of correction was defined by an integral index, making interpretation of the results difficult, and risk analysis was not performed. The reported incidence of symptomatic rod fracture (RF) after surgical correction of ASD with any osteotomy is cosistent: 5.3%[27], and 6.8%[14]; after a PSO it was higher: 15.8%[14] and 16.2%[27]. The following risk factors of RF were revealed ($P \leqslant 0.05$): Fusion construct crossing the thoracolumbar and lumbosacral junctions (OR = 9.1); maximum sagittal rod contour $\geqslant$ 60° (OR = 10.0); application of dominos and/or parallel connectors in the instrumentation constract (OR = 10.0); pseudarthrosis diagnosed at $\geqslant$ 1 year follow-up (OR = 28.9); and fixation to pelvis[27]. However, only a limited number of RF cases were included, which could cause an underestimation of the risks associated with other factors.

While the literature lacks clear evidence about the risk factors for MC after osteotomies, we expanded our literature search to MC after surgery for ASD (non-specific to osteotomy). This yielded several factors significantly ($P \leqslant 0.05$) associated with MC. In particular: The number of instrumented segments; fusion to the sacrum; and high preoperative pelvic tilt (PT), > 26°[11]. This was limited as MC were not specified, and were combined with neurological complications. In another study, MC after spinal fusion in ASD were classified as: (1) Proximal junctional complications including fracture of upper instrumented vertebra (UIV) and/or one level above (UIV + 1); and postoperative pseudarthrosis[16]. In this study the following

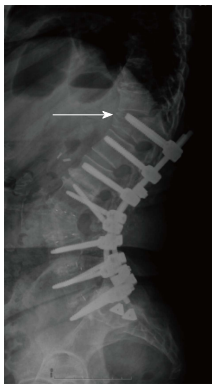


Figure 1 Example of radiographic findings of proximal junctional failure. Compression fracture of T11 proximal junctional failure (PJF) with screw pullout is shown by a black arrow. It was diagnosed at 1 mo follow-up after the surgical adult spine deformity correction using lumbar osteotomy and long thoracolumbar fusion surgery with fixation to sacrum. Before diagnosis of PJF, the patient experienced increased back pain limiting walking distance and increasing sagittal imbalance. The patient was revised with removal of the pedicle screws at T11 with extension of instrumentation to T9 two months after the index surgery.

risk factors were revealed: ⩾ 3 comorbidities, hazard ratio (HR) = 3.2; smoking, HR = 3.3; and preoperative sagittal imbalance with sagittal vertical axis (SVA) > 95 mm, HR = 2.7[16]. When compiling the data from multiple studies, the following preoperative spinopelvic measurements were identified as risk factors for PJF: SVA > 50 mm, OR = 2.5[28]; thoracic kyphosis (TK) > 30°, HR = 3.2[29-31]; and pelvic incidence (PI) > 55°[29,31]. Risk factors for PJF were also associated with postoperative overcorrection of the spinopelvic alignment, including: Postoperative SVA change[32], in particular, postoperative SVA < 50 mm[33]; change of TK > 10°[34], or > 30°, OR = 2.5[28]; and change of lumbar lordosis (LL) > 30°, OR = 4.8[28], HR = 2.4[31]. Risk factors for PJF associated with instrumentation and surgical technique included: Posterior spinal fusion[32], and fixation to the sacrum or pelvis, OR = 2.2[28,32,33]. Finally, risk of PJF was linked to the following demographic data: Male[8]; age > 55[35-37]; osteoporosis[32]; and increased body mass index (BMI)[35,36]. However, in some of the studies referenced above, the level of risk was not assessed properly. It is unclear how the revealed risk factors can be modified by the implementation of an osteotomy; whether there is a synergistic effect of different risk factors? If normal postoperative SVA < 50 mm is associated with risk of MC[28], what postoperative SVA or combination of factors is associated with less risk? The predictive value of the revealed risk factors was not defined.

The purpose of this study was to evaluate the most clinically relevant MC seen after surgical correction of ASD with corrective osteotomies, taking into account the incidence, period of occurrence, association with additional surgeries, and assessment of risk factors associated with the MC and their predictive value.

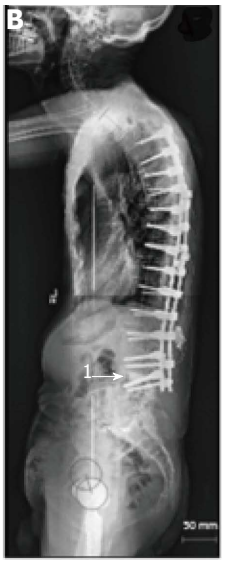
MATERIALS AND METHODS

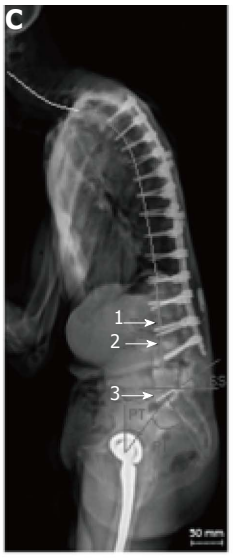
After institutional review board approval (COMIRB #14-1258), medical records and radiographic images were retrospectively identified in patients with ASD undergoing surgical correction with an instrumented spinal fusion including one or more osteotomies of the thoracic and/or lumbar spine. These operations were performed between 2007 and 2014 by 4 surgeons at a single institution. Inclusion criteria were used: (1) Demographics: Age > 20 years; gender, male and female; (2) diagnosis of ASD from any of the following etiologies: fixed sagittal imbalance, idiopathic or degenerative scoliosis, kyphosis or kyphoscoliosis, posttraumatic kyphosis, idiopathic or postoperative flat back syndrome, and ankylosing spondyloarthropathies; and (3) operation consisting of ⩾ 2 spinal posterior instrumented fusion levels (with or without interbody fusion) of the lumbar, or thoracic spine and having an osteotomy (PSO and/or SPO). All patients had to have follow-up not less than 2 years or undergone revision/reoperation prior to 2 year follow-up. Exclusion criteria consisted of: Malignancy, infection, congenital diseases, acute trauma, or latest follow-up < 2 year (unless revision surgery was performed at any postoperative time-point). If a patient had multiple SPOs during one operation, it was analyzed as one SPO procedure. If an operation included both SPOs and PSO, it was analyzed as one PSO procedure. The final decisions regarding inclusion/exclusion for each case was made by the project principal investigator (EB).

The following MC were taken into consideration: (1) MC of the spine: Vertebral fracture (VF): Single or multiple fractures of the vertebral body, vertebral endplate, and/or pedicle at any level(s) of the spine; PJF: Fracture and/or severe spondylolisthesis of the UIV and/or adjacent vertebra (UIV+1) (Figure 1); Distal segment degeneration/failure (DSF): Vertebral fracture and/or significant spondylolisthesis, collapse of the intervertebral disc(s) with or without herniation, stenosis with neurologic claudication at the lowest instrumented fused level (LIV) or caudally (Figure 2); and (2) MC of instrumentation: Screw loosening (SL): Failure of the bone-screw interface, including screw pull-out from the pedicle, sacrum, or ilium (Figure 3); RF: Fracture of one or both rods (Figure 4); iliac bolt connector failure (IBCF): loosening or fracture; disassociation of instrumentation (DI): Disconnection/loosening between any element(s) of the posterior fusion construct (Figure 5).

All types of MC were diagnosed radiographically and/or during revision surgery. The specific postoperative period when each MC was diagnosed was collected. The following characteristics were collected and assessed as potential risk factors: (1) Demographic: Age, gender, ethnicity, BMI, and smoking status at the time of the index operation; (2) Clinical: Primary diagnosis, indication for the index operation, osteoporosis, history of pseudarthrosis after previous operation (in cases of revision surgery); (3) Characteristics of the studied (index) operation: primary or revision, type of osteotomy (SPO/PSO), osteotomy location, number of posterior levels fused, transition segments of the spine crossed by posterior instrumentation, connection of new instrumentation to indwelling







PT 15°		PT 29°		PT 38°	
PI 27°		PI 50°		PI 68°	
LL -25°		LL -31°		LL -12°	
SS 12°		SS 21°		SS 30°	
PI-LL 5°		PI-LL 19°		PI-LL 56°	
SVA (C7) 92 mm		SVA (C7) 50 mm		SVA (C7) 156 mm	
TK 62°		TK 48°		TK 39°	
L4/L5 disc height		L4/L5 disc height		L4/L5 disc height	
Anterior	Posterior	Anterior	Posterior	Anterior	Posterior
9.2 mm	11.3 mm	9.6 mm	5.8 mm	3.2 mm	3.4 mm
L5/S1 disc height		L5/S1 disc height		L5/S1 disc height	
Anterior	Posterior	Anterior	Posterior	Anterior	Posterior
8.7 mm	5.7 mm	5.0 mm	1.7 mm	3.9 mm	1.3 mm
L5/S1 spondylolisthesis		L5/S1 spondylolisthesis		L5/S1 spondylolisthesis	
1 mm		2.5 mm		4.0 mm	

Figure 2 Example of distal segment degeneration/ failure. This event was observed after surgical correction of adult spine deformity in a patient (67 years old male) with idiopathic kyphoscoliosis complicated by degenerative disc disease and lumbar stenosis. A: Severe preoperative spinal kyphosis; B: Postoperative correction by T3-L4 posterior instrumented fusion with L3/L4 decompression, transforaminal interbody fusion by cage placement (1), and multilevel (T5-T11) Smith-Petersen osteotomy; C: Distal segment degeneration/ failure at 35 mo follow-up with deformation and/or fracture of L3 (1) subsidence of the interbody cage (2), collapse of L4/L5 and L5/S1 intervertebral discs with L5/S1 spondylolisthesis (3), loss of sagittal balance, and progression of proximal junctional kyphosis. Interestingly, these changes were accompanied by significant increase of pelvic incidence (PI) from 27o to 68o due to simultaneous increase of pelvic tilt (PT) and sacral slope which suggested that position of sacrum relatively to pelvis changed after surgery. Likely, this is the result of displacement in the sacroiliac joints. This finding contravenes the concept concerning postoperative stability of PI.

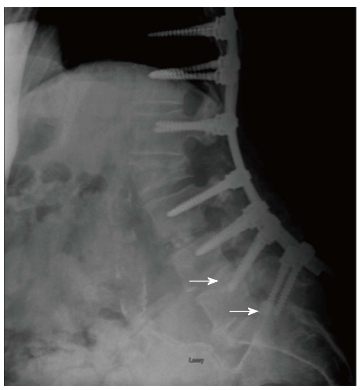


Figure 3 An example of radiographic findings of screw pullout/loosening. Screw pullout is shown by black arrows at L5 and S1 bilaterally identified at the 6 mo follow-up visit after surgical correction of adult spine deformity with osteotomy. Pseudarthrosis was diagnosed later at 12 mo post-operative. The patient experienced increasing low back pain and "popping" with movement. A revision operation was performed at 12 mo follow-up to revise the fusion and re-instrument, including placement of iliac bolts.

hardware, cement use, use of anterior supplemental fixation, fixation to the sacrum, fixation to the pelvis; (4) Characteristics of the instrumentation: Type of screws (polyaxial/monoaxial), screw manufacturer, type of rods (precontoured by manufacturer/no), rod material, thickness and shape of rods, greatest angle of rod contouring, manufacturer of rods, method of the rod contouring, number of crosslinks, number of domino and/or parallel connectors, use of bone morphogenetic protein (BMP); (5) Radiographic characteristics of spinopelvic alignment in standard preoperative and postoperative (1^{st}-4^{th} week after operation) images: SVA, LL, TK, PT, pelvic incidence (PI), PI-LL mismatch with discrete and absolute differences between postoperative and preoperative values of each spinopelvic parameter; and (6) Postoperative events: Fall after operation, but before diagnosis of MC, and postoperative pseudarthrosis (nonunion at the fused site(s) confirmed radiographically (plane radiography or computed tomography) or during revision at more than 1 year follow-

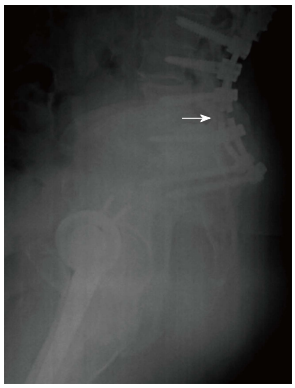


Figure 4 An example of radiographic findings of rod fracture. Bilateral L5-S1 rod fractures are shown by black arrow; they were diagnosed consequently at 12 and 20 mo follow-up after surgical correction of adult spine deformity, and accompanied with L5-S1 pseudo-arthrosis. The pseudo-arthrosis at L5-S1 was diagnosed simultaneously with the second rod fracture at 20 mo follow-up. The patient experienced increasing low back pain and sagittal imbalance. A revision operation was performed at 21 mo follow-up with revision of the fusion and an osteotomy to correct residual sagittal imbalance.

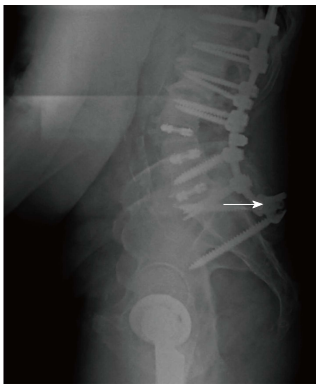


Figure 5 An example of radiographic findings of disassociation of instrumentation. Uncoupling of the rod from the iliac bolts disassociation of instrumentation is shown by black arrow; it was diagnosed at 4 mo follow-up after surgical correction of adult spine deformity. The patient experienced ongoing low back pain. A revision operation was performed with replacement of iliac screws and connectors. Intraoperatively, it was noted that the right pelvic screw cap had disengaged.

ups) Osteoporosis/osteopenia information was obtained from the patients' medical records by analyzing the results of dual energy X-ray absorptiometry or ultrasound evaluation.

Clinical and demographic data were extracted from the medical records by an experienced researcher (CB) under control of the project PI (EB). Spinopelvic parameters were defined by retrospective analysis of radiographic images using Surgimap surgical planning software (Nemaris Inc, New York, NY, United States) by a trained researcher (CB). Ten percent of the performed measurements were additionally evaluated by the PI (EB) to assess correspondence. Correspondence between these two measurements was assessed by the Kappa test[38]. Measurements were regarded identical, if deviation between them did not exceed 10% of the smaller value. The studied spinopelvic parameters were defined using currently accepted standards of measurement as outlined in previous studies[39,40]. If the quality of a radiographic image did not allow accurate assessment of a studied index, this index was excluded from analysis. Decisions concerning the exclusion were made by the project PI (EB) after discussion with Musculoskeletal Radiologists. All these exclusions were then taken into consideration as a potential source of bias.

The collected data were entered in to the electronic data base for further analysis. Data quality control was performed by 2 experts (EB and AN), and disagreements were resolved by discussion.

Statistical analysis

Following indices were applied to characterize the studied population: Quantitative characteristics were analyzed using number of observations, mean, standard deviation, median, minimum and maximum values[38]. Percentiles were applied for better description of distribution of spinopelvic characteristics before and after operation, and also difference between postoperative *vs* preoperative values (level of correction)[38,41]. Categorical characteristics were analyzed using percentage[38].

Cumulative number and incidence rate for each of MC for the studied postoperative period was calculated as a rate (0-1) or percentage with 95% confidence limits (95%CI)[41]. To define the postoperative period with maximum likelihood of occurrence, distribution of latent periods (time between the index operation and diagnosis of MC) were analyzed using percentiles[41]. Risk of postoperative revision/reoperation associated with each type of MC was defined by OR with 95%CI[41]. The *P*-value was defined by the χ^2-test[41]; if the number of studied events in any of the analyzed subgroups was small ($\leqslant$ 5), the Fisher-exact test (F) was applied[41]. Analysis of risk factors associated with MC was performed in a few stages. Initially, there were revealed factors that have statistically significant ($P \leqslant 0.05$) association with any type of MC. This analysis was performed using the logistic regression[38]. Then, quantitative characteristics that showed such association were categorized to define an exact range with the most significant risk of MC. The level of risk was assessed by OR (95%CI), and *P*-value was defined by the χ^2 or the Fisher exact tests[41]. Categorical indices were analyzed to identify a category having the most significant association with the MC. The level of risk was also assessed by OR (95%CI), and *P*-value by the χ^2 or the Fisher exact tests[41]. Grouping analysis was applied to reveal risk factors that are general for all or a few types of MC; in particular, those that are mainly associated with MC of the spine, and those that are mainly linked with MC of spinal instrumentation. Impact of confounders and combinations of different risk factors was defined by stratification, if it was applicable due to the number of cases[38]. Multiple regression analysis was applied to define prognostic capability of an integrative approach when a few risk factors having significant association with MC are taken into consideration. The JMP®7.0.1 (SAS

Table 1 Main demographic and clinical characteristics of the studied case series (patients who underwent surgical correction of adult spine deformity with osteotomy, *n* = 94)

Demographic characteristic	Subgroup (if applicable)	Measure units	Statistical characteristics	Value
Age	NA	Years	*n*	94
			Median	59.5
			Mean	58.6
			SD	12.7
			Min	23
			Max	82
Gender	Male	Subjects	Number (%)	30 (32)
	Female		Number (%)	64 (68)
Body mass index	NA	Conventional units	Number	79
			Median	26.6
			Mean	27.2
			SD	5.6
			Min	16.2
			Max	43.5
Primary diagnosis	Degenerative scoliosis	Subjects	Number (%)	9 (9.6)
	Idiopathic scoliosis		Number (%)	29 (31.1)
	Degenerative kyphosis		Number (%)	13 (13.9)
	Mixed and other adult spine deformities		Number (%)	43 (45.4)
Smoking status	Never	Subjects	Number (%)	38 (40.4)
	Former		Number (%)	37 (39.4)
	Current		Number (%)	14 (14.9)
	Not specified		Number (%)	5 (5.3)
Ethnicity	Caucasians	Subjects	Number (%)	82 (87.2)
	Hispanic		Number (%)	7 (7.4)
	Not specified		Number (%)	5 (5.3)
Osteoporotic status	Osteoporosis or osteopenia	Subjects	Number (%)	29 (30.3)

NA: Not applicable; SD: Standard deviation; Min: Minimum value; Max: Maximum value.

Institute Inc., United States; www.jmp.com) statistical program was used for analysis. The next stage of analysis included assessment of predictive values for each revealed risk factor. The predictive values included sensitivity (Sn), specificity (Sp), positive (+PV) and negative (-PV) predictive values[38]. There was applied following definition for each predictive value taking into consideration context of this study: Sn is the probability of risk factor presence if the MC has been diagnosed during the studied follow-up period; Sp is the probability of risk factor absence if the MC has been not diagnosed during the studied follow-up period; +PV is the probability of diagnosed MC during the studied follow-up period if the risk factor is present; -PV is the probability of absence of diagnosed MC during the studied follow-up period if the risk factor is absent. The Bayesian method was used to generalize the obtained results with previous findings, if it was applicable due to the quality of the previously published data. The previously published data were used as prior odds combining of which with the result of current study provided posterior odds (PO) which combined effects of the previous and the current data[42,43]. If the PO was $\geqslant 5$ or $\leqslant 0.2$, it was considered as a sufficient level of evidence of the generalized effect[42,43]. The statistical analysis was performed by statistician experienced in analysis of biomedical data who is a coauthor this publication (AN).

RESULTS

Initially, 118 patients who underwent 130 osteotomies were identified. Thirty patients and 36 corresponding operations were excluded due to < 2 year postoperative follow-up. Eighty-eight patients who had 94 operations were included; 6 of 88 patients had 2 operations, each was analyzed as a separate case. In total, 94 cases were analyzed. Mean follow-up was 30 mo.

The demographic characteristics of the included cases were: Female 68%, male 32%; mean age, 58.6 (SD, 12.7); mean BMI, 26.6 (SD, 5.6); smoking at the time of operation, 14.9%; ethnicity: Caucasians 87.2%, Hispanic 7.4, other 5.3% (Table 1).

The primary diagnosis included: Degenerative scoliosis and/or kyphosis, 23.5%; idiopathic scoliosis, 31.1%; combination of different etiologies of adult spine deformity, 45.4%. Concomitant osteoporosis or osteopenia: 30.3% (Table 1).

The characteristic of the studied (index) operations included: Primary, 21%; revision, 79%; number of levels fused: median 8, minimum 2 and maximum 17; type of osteotomy: SPO, 46%; PSO, 54%; osteotomy location: Lumbar, 62%; thoracic, 21%, thoracolumbar junction, 14%, and sacrum, 3%; transitional segments crossed by instrumentation: cervicothoracic, 2%; thoracolumbar, 26%; lumbosacral, 14%; thoracolumbar and lumbosacral, 51%; fixation to sacrum, 40%; fixation to pelvis, 23%; use of anterior fusion, 38%; number of anterior levels fused: Median, 2; minimum 2 and maximum 6; supplemental anterior fixation, 66%; cement use, 25%; BMP use, 52%; use of individually precontoured posterior rods, 34%; connecting of new

Table 2 Main characteristics of the index operation (surgical correction of adult spinal deformity with posterior instrumentation and osteotomy, *n* = 94)

Characteristics of operation	Subgroup (if applicable)	Measure units	Statistical characteristic	Value
Index operation	Primary	Subjects	Number (%)	20 (21)
	Reoperation		Number (%)	74 (79)
Number of fused levels	NA	Number	Median	8
			Min; max	2; 17
Type of osteotomy	PSO	Subjects	Number (%)	51 (54)
	SPO		Number (%)	43 (46)
Osteotomy location	Lumbar	Subjects	Number (%)	58 (62)
	Thoracic		Number (%)	20 (21)
	Thoracolumbar junction		Number (%)	13 (14)
	Sacrum		Number (%)	3 (3)
Inter-level junctions crossing by instrumentation	Cervicothoracic	Subjects	Number (%)	2 (2)
	Thoracolumbar		Number (%)	24 (26)
	Lumbosacral		Number (%)	13 (14)
	Thoracolumbar and lumbosacral		Number (%)	48 (51)
	No		Number (%)	7 (7)
Fixation to sacrum (not pelvis)	NA	Subjects	Number (%)	38 (40)
Fixation to sacrum and/or pelvis	NA	Subjects	Number (%)	59 (63)
Use of anterior fusion	NA	Subjects	Number (%)	36 (38)
Number of anterior levels fused	NA	Subjects	Median	2
			Min; max	1; 6
Supplemental anterior support/fixation by implant or instrumentation	NA	Subjects	Number (%)	62 (66)
Use of cement	NA	Subjects	Number (%)	23 (25)
Use of bone morphogenetic protein	NA	Subjects	Number (%)	49 (52)
Use of individually precontoured posterior rods	Precontoured	Subjects	Number (%)	32 (34)
	In situ contouring	Subjects	Number (%)	62 (66)
Connecting to previously implanted instrumentation	NA	Subjects	Number (%)	16 (17)
Use of Domino and/or parallel connectors	2	Subjects	Number (%)	2 (2)
	1		Number (%)	11 (12)
	0		Number (%)	81 (86)

NA: Not applicable; SD: Standard deviation; PSO: Pedicle subtraction osteotomy; SPO: Smith-Peterson.

instrumentation to previously implanted, 17%; use of domino and/or parallel connectors, 14% (Table 2).

The number of high quality images adequate for obtaining spinopelvic parameters was limited, but was enough to reach statistically significant results. Two independent evaluations of the studied radiographic indices showed good agreement by the Kappa test, 0.85 (SE, 0.09), $P = 0.08$.

Preoperative and postoperative characteristics of sagittal spinopelvic alignment were highly heterogeneous having distribution close to the normal (bell shaped curve) (Table 3). In particular, preoperative SVA ranged from 0 to 203 mm; 70% of patients had anterior sagittal imbalance (SVA > 50 mm, Table 3). After operative treatment the mean SVA decreased from 73.9 mm to 41.7 mm ($P < 0.001$) with the percentage of patients with the sagittal imbalance decreasing to 35%. However, variability remained high with values ranging from -66 mm to 167 mm. The absolute difference between postoperative and preoperative values ranged from 0 to 182 mm (Table 3).

Preoperative LL ranged from 4° to 99° with mean value 34.4°. After surgical treatment the mean value increased to 51.3° ($P < 0.001$), but variability remained high (Table 3). Absolute difference between postoperative and preoperative LL values varied from 1° to 50° (Table 3).

The mean preoperative TK was 39.4°, and extreme values ranged from -3° to 109°. While the mean value did not change significantly after operative treatment (41.9°), the absolute difference between postoperative and preoperative values varied from 0° to 41° with the mean value 12° suggesting significant ($P < 0.001$) reciprocal postoperative change (Table 3).

Preoperative PT ranged from 8° to 40° with a mean value of 27.8°. After surgery the mean decreased to 20.2 ($P < 0.001$), but variability remained high with extreme values from -4° to 51°. The absolute difference between postoperative and preoperative values ranged from 0° to 29° with a mean of 9.9° (Table 3).

Preoperative PI-LL ranged from -43° to 66° with the mean 20.9°. The mean decreased postoperatively to 3.8° ($P < 0.001$), but the range remained approximately the same. The absolute difference between postoperative and preoperative values ranged from 0° to 48° with the mean, 19.2° (Table 3).

A fall after surgery was observed in 15% (95%CI: 11.3; 18.7) of cases. Postoperative pseudoarthrosis was revealed in 10.6% (95%CI: 7.4; 13.6) of cases. One MC had 27.6% (95%CI: 23.0; 32.2), and multiple MC (from 2 to 4) had 16% (95%CI: 12.2; 19.8) of the patients.

Table 3 Characteristics of sagittal spinopelvic alignment before and after index operation, and level of perioperative change

Spinopelvic characteristic, units	Subgroup	*n*	Characteristics of distribution								
			Percentiles							Mean	SD
			Min	10	25	50	75	90	Max		
Sagittal vertical axis, mm	Preop	94	0	15	33	74	105	128	203	73.9	42.4
	Postop	61	-66	0.2	14	40	60	94	167	41.7	38.4
	Postop-Preop	61	73	34	-5	-30	-59	-96	-182	-33.1	47.8
	Postop-Preop (abs)	61	0	10	20	38	60	96	182	46	35.7
Lumbar lordosis, L1-S1, degree	Preop	77	4	8	19	36	45	56	99	34.4	19.4
	Postop	90	3	32	43	52	61	71	97	51.3	16.6
	Postop-Preop	74	-37	-6	4	16	30	38	50	16.1	17.4
	Postop-Preop (abs)	74	1	3	9	17	31	37	50	19.7	13.2
Thoracic kyphosis, T1-T12, degree	Preop	64	-3	11	23	39	54	64	109	39.4	21.9
	Postop	81	9	18	32	44	51	58	75	41.9	14.7
	Postop-Preop	62	-41	-19	-10	1	13	25	34	1.6	15.9
	Postop-Preop (abs)	62	0	1	2	12	18	29	41	12	10.3
Pelvic tilt, degree	Preop	68	8	13	19	27	35	43	48	27.8	10.4
	Postop	78	-4	9	13	20	27	33	51	20.2	9.7
	Postop-Preop	61	10	5	-2	-8	-15	-19	-29	-7.9	9.1
	Postop-Preop (abs)	61	0	2	5	8	15	19	29	9.9	6.7
Pelvic incidence – lumbar lordosis mismatch, degree	Preop	68	-43	-10	9	23	37	47	66	20.9	21.6
	Postop	78	-41	-17	-7	2	13	28	41	3.8	15.6
	Postop-Preop	61	25	4	-2	-18	-31	-37	-48	-16.2	16.6
	Postop-Preop (abs)	62	0	3	9	18	31	37	48	19.2	13.2

n: Number of measured cases; SD: Standard deviation; SEM: Standard error of the mean; Postop-preop: Difference between postoperative and preoperative values; Postop-preop(abs): Difference between postoperative and preoperative characteristics in absolute value.

Table 4 Undesirable postoperative events and additional treatment after surgical correction of adult spinal deformity with osteotomy (*n* = 94)

Index	Number of cases	Rate, % (95%CI: min; max)
Fall after operation before mechanical complication(s)	14	15% (11.3; 18.7)
Postoperative pseudarthrosis	10	10.6% (7.4; 13.6)
Cases with 1 mechanical complication	26	27.6% (23.0; 32.2)
Cases with a few (2-4) mechanical complications	15	16.0% (12.2; 19.8)
Additional surgical treatment (revision/reoperation)	40	42.5% (37.4; 47.6)
Additional conservative treatment	14	15.0% (11.3; 18.7)

Additional postoperative treatment was required in 57.5% of cases, including 42.5% (95%CI: 37.4; 47.6) requiring revision surgery, and 15% (95%CI: 11.3; 18.7) conservative treatment in only (Table 4).

The total incidence of cases with MC was 43.6% (95%CI: 33.4; 53.8%). MC of the spine occurred in 25.5% (95%CI: 16.5; 34.5); and MC of the instrumentation in 25.5% (95%CI: 16.5; 34.5, Table 5). Cases with MC of the spine included: VF in 20.2% (95%CI: 12.0; 28.4), PJF in 11.7% (95%CI: 5.2; 18.2), and DSF in 6.4% (95.5CI: 1.4; 11.4%, Table 5). Cases with MC of the instrumentation included: SL in 18.1% (95%CI: 14.1; 22.1), fracture of the screw in 2.1% (95%CI: 0; 4.9), RF in 7.4% (95%CI: 4.7; 10.1), IBCF in 4.3% (95%CI: 2.2; 6.5), and DI in 7.4% (95%CI: 4.7; 10.1) (Figure 6 and Table 5).

An association between MC and secondary surgical treatment was strong, OR = 20 (95%CI: 6.9; 57.4, $P < 0.001$) with 78% of cases of MC (32 of 41) leading to revision surgery. This association was the most significant ($P < 0.04$) in cases with MC of the spine, in particular: VF, PJF and DSF. It was also significant in MC of the instrumentation such as: SL and DI (Table 5).

Majority of MC (70%) were diagnosed during the 1st postoperative year (Figure 7). The shortest latent period had PJF, VF, SL (specifically screw fracture), and DI ($\geqslant$ 70% of these cases was revealed during 1st year). Longer latent periods (> 1 year in majority of cases) were seen in MC such as DSF, SL, RF, IBCF (Figure 7).

The following factors had significant association with MC (all types): Preoperative SVA > 110 mm, OR = 4.5 (95%CI: 1.3; 15.4), $P = 0.011$; postoperative SVA > 74 mm, OR = 5.4 (95%CI: 1.4; 21.1), $P = 0.014$; preoperative LL < 20°, OR = 5.5 (95%CI: 1.8; 16.9), $P = 0.002$; postoperative change of LL > 34°, OR = 4.7 (95%CI: 1.2; 18.0), $P = 0.028$; postoperative change of PI-LL > 34°, OR = 6.4 (95%CI: 1.2; 33.2), $P = 0.033$; type of osteotomy, SPO *vs* PSO, OR = 0.42 (95%CI: 0.18; 1.0), $P = 0.045$; fixation to sacrum with or without fixation to pelvic after PSO if number of fused

Table 5 Association of different types of mechanical complications with postoperative revision/reoperation after surgical correction of adult spinal deformity with osteotomy (n^1 = 94)

Mechanical complication	n^1	Association with revision/reoperation after index operation		
		n^2	OR (95%CI)	*P* value
Total (failure of spine and/or instrumentation)	41	32	20.0 (6.9; 57.4)	< 0.0001
Failure of spine (total)	24	21	18.8 (5.0; 70.3)	< 0.0001
Vertebral fracture (total)	19	17	19.2 (4.1; 90.1)	< 0.0001
PJF	11	11	> 19.0	< 0.0001
DSF	6	5	7.6 (0.8; 67.6)	0.033
Instrumentation failure (total)	24	18	6.6 (2.3; 18.8)	0.001
Screw loose	17	12	4.2 (1.3;13.2)	0.014
Screw fracture	2	2	NA	0.161
Rod fracture	7	4	1.9 (0.4; 8.9)	0.453
Iliac bolt connector (loose and/or fracture)	4	3	5.7 (0.6; 53.4)	0.308
Disconnection of instrumentation	7	6	9.4 (1.1; 81.1)	0.022

n^1: Number of cases with exact type(s) of mechanical complication; n^2: Number of cases required revision and/or reoperation after index operation; OR: Odds ratio; 95%CI: 95% Confidence limits; PJF: Proximal junctional failure; DSF: Distal segment degeneration/failure; NA: Not applicable.

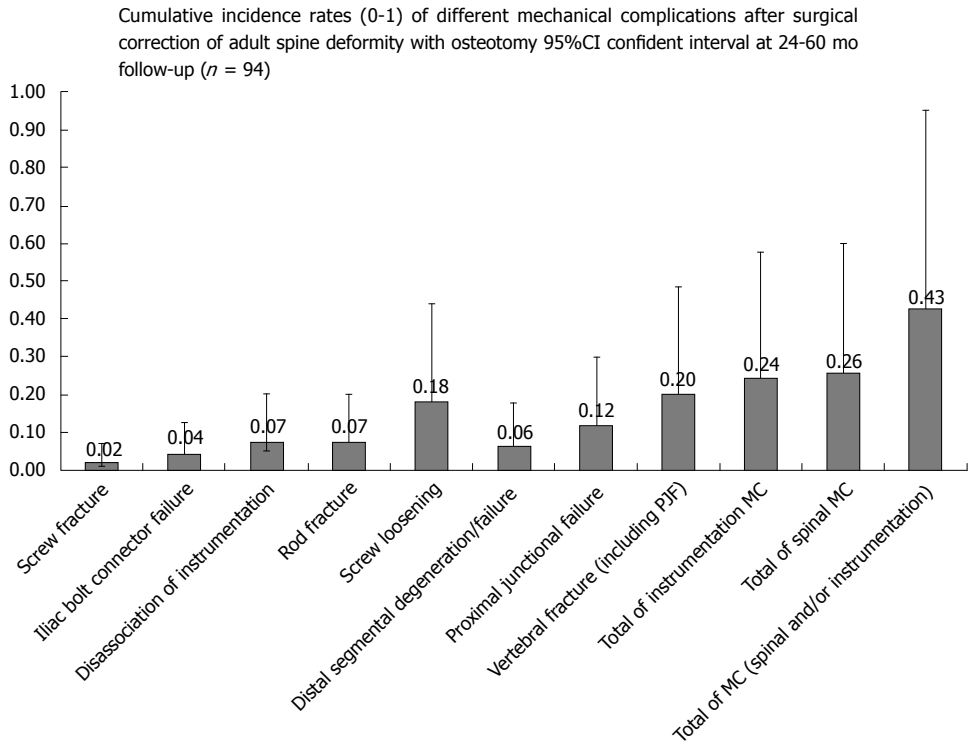


Figure 6 Cumulative incidence rates of different mechanical complications after surgical correction of adult spine deformity with osteotomy at long term postoperative follow-up; the error bars show 95%CI. PJF: Proximal junctional failure; MC: Mechanical complications.

levels > 4, OR = 3.6 (95%CI: 0.92; 13.9), *P* = 0.056; postoperative pseudarthrosis, OR = 14.6 (95%CI: 1.8; 120.9), *P* = 0.002 (Table 6). However, in spite of statistical significance, prediction capacity of these factors was limited, in particular, majority of them had low Sn (< 40%) (Table 6). To take into consideration all factors listed above, an integral index was obtained by multiple regression analysis using equation (1) described below. With this equation risk of MC ranged from 0 to 1. Analysis showed that the index values ⩾ 0.46 have the highest association with MC (OR = 31.7, 95%CI: 6.7; 149.3, *P* < 0.0001, Table 6). Predictive capacity of this integral index was in general higher than that of single characteristics, but did not exceed moderate level: Sn, 79%; Sp, 89%; +PV, 86%, and -PV, 83%.

$$y = 0.84 + X_1 + X_2 + X_3 + X_4 + X_5 + X_6 + X_7 + X_8 + X_9 \quad (1)$$

Where: y is risk of MC ranged from 0 to 1; X_1 is preoperative LL: < 20° match to 0.22, and ⩾ 20° match to (-0.22); X_2 is fall after surgery, but before MC: "yes", match to 0.15, and "no", match to (-0.15); X_3 is fixation to sacrum or pelvic: "yes", match to 0.07, and "no", match to (-0.07); X_4 is preoperative SVA: ⩾ 110 mm match to 0.04, and < 110 mm match to (-0.04); X_5 is

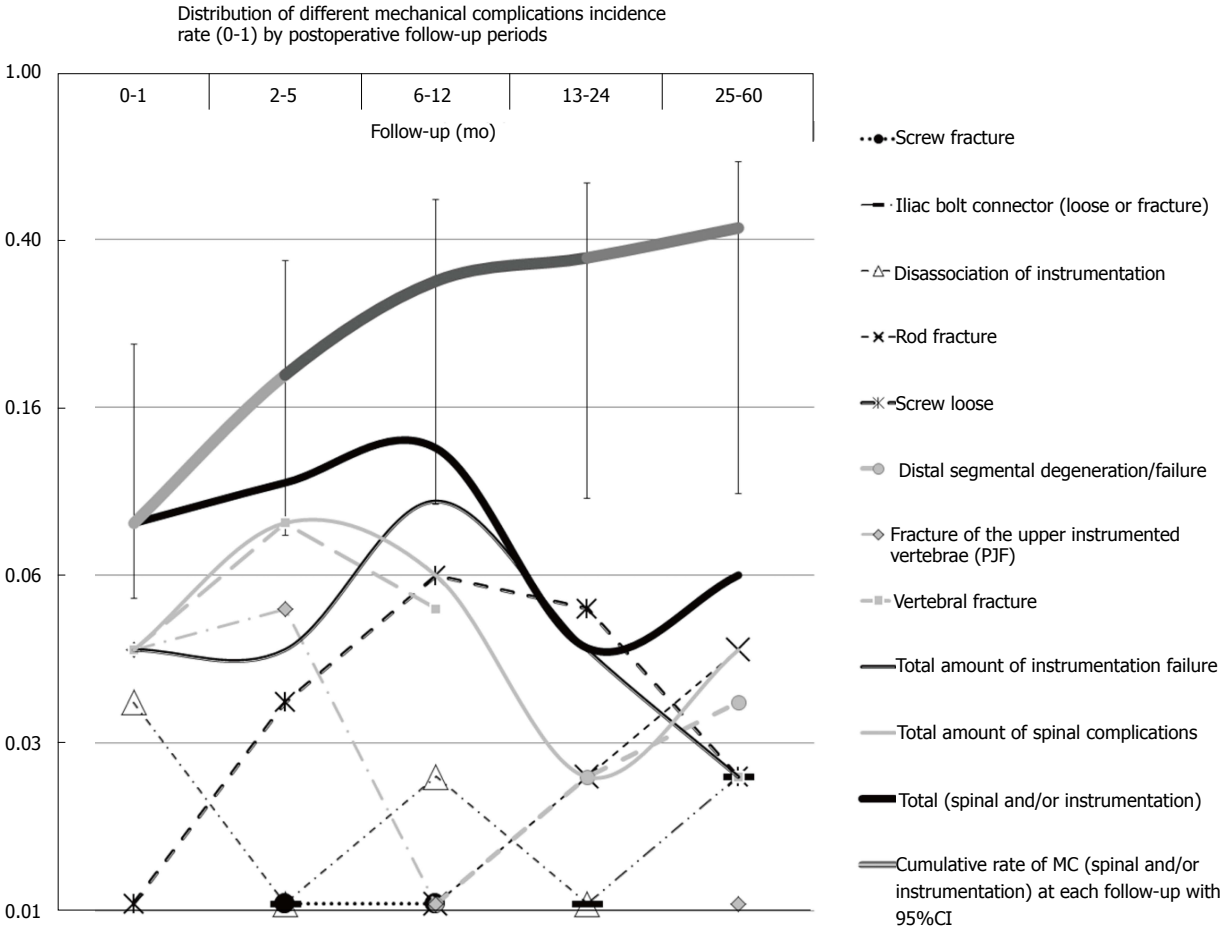


Figure 7 Distribution of different types of mechanical complications after surgical correction of adult spine deformity with osteotomy by different periods of long-term postoperative follow-up; the error bars show 95%CI. MC: Mechanical complications.

Table 6 Risk factors for mechanical complications (all types: Failure of spine and/or instrumentation) after surgical correction of adult spine deformity with osteotomy

Risk factor(s)	OR (95%CI: min; max)	*P* value	Predictive values			
			Sn	Sp	+PV	-PV
Preoperative SVA > 110 mm	4.5 (1.3; 15.4)	0.011	0.27	0.92	0.73	0.62
Postoperative SVA > 75 mm	5.4 (1.4; 21.1)	0.014	0.24	0.94	0.77	0.62
Preoperative LL< 20°	5.5 (1.8; 16.9)	0.002	0.37	0.91	0.75	0.65
Postoperative change of LL > 34° (absolute values)	4.7 (1.2; 18.0)	0.028	0.22	0.94	0.75	0.61
Postoperative change of PI-LL > 34° (absolute values)	6.4 (1.2; 33.2)	0.033	0.29	0.94	0.80	0.62
Type of osteotomy SPO *vs* PSO	0.42 (0.18; 1.0)	0.045	0.34	0.45	0.33	0.47
Fall after operation before mechanical complication	6.1 (1.6; 23.7)	0.007	0.27	0.94	0.79	0.63
Fixation to sacrum or pelvic if number of fused levels > 4	2.4 (0.9; 6.4)	0.068	0.74	0.46	0.53	0.68
Fixation to sacrum or pelvic if number of fused levels > 4 with PSO	3.6 (0.92; 13.9)	0.053	0.78	0.50	0.67	0.64
Postoperative pseudarthrosis	14.6 (1.8; 120.9)	0.002	0.22	0.98	0.90	0.62
Integral index based on parameters presented above by results of multiple regression modeling (1) ⩾ 0.46	31.7 (6.7; 149.3)	< 0.001	0.79	0.89	0.86	0.83

SVA: Sagittal vertical axis; LL: Lumbar lordosis; PI-LL: Pelvic incidence (PI) - lumbar lordosis (LL) mismatch; PSO: Pedicle subtraction osteotomy; SPO: Smith-Peterson osteotomy; OR: Odds ratio; 95%CI: min; max: 95% confidence limits, maximum and minimum values; Sn: Sensitivity; Sp: Specificity; +PV: Positive predictive value; -PV: Negative predictive value.

postoperative SVA: ⩾ 75 mm match to 0.14, and < 75 mm match to (-0.14); X_6 is postoperative change of LL: ⩾ 35° match to 0.07, and < 35° match to (-0.07); X_7 is postoperative change of PI-LL: ⩾ 35° match to 0.001, and < 35° match to (-0.001); X_8 is type of osteotomy: PSO match to 0.05, and SPO match to (-0.05); and X_9 is presence of postoperative pseudarthrosis: "yes", match to 0.17, and "no" match to (-0.17).

Table 7 Risk factors for mechanical complications of spine (all types: Vertebral fracture, proximal junctional failure, and distal segment degeneration/failure) after surgical correction of adult spinal deformity with osteotomy

Risk factor(s)	OR (95%CI: min; max)	*P* value	Predictive values			
			Sn	Sp	+PV	-PV
Postoperative SVA > 106 mm	11.3 (1.1; 118.1)	0.043	0.20	0.98	0.75	0.79
Type of osteotomy: SPO *vs* PSO	0.39 (0.1;1.1)	0.046	0.29	0.49	0.16	0.67
Fall after operation before mechanical complication	5.3 (1.6; 17.5)	0.006	0.33	0.91	0.57	0.80
Postoperative change of TK > 25° (absolute values)	4.8 (1.1; 20.8)	0.041	0.31	0.91	0.56	0.79
Postoperative change of PT > 8° (absolute values)	3.3 (0.9; 11.1)	0.045	0.69	0.60	0.38	0.84
Postoperative change of PI-LL > 34° (absolute values)	3.8 (0.9; 15.6)	0.065	0.31	0.89	0.50	0.79
Integral index by multiple regression modeling (1) ≥ 0.46	14 (2.7; 73.6)	< 0.001	0.85	0.72	0.50	0.93

SVA: Sagittal vertical axis; TK: Thoracic kyphosis; PT: Pelvic tilt; PI-LL: Pelvic incidence (PI)-lumbar lordosis (LL) mismatch; PSO: Pedicle subtraction osteotomy; SPO: Smith-Peterson osteotomy; OR: Odds ratio; 95%CI: min; max: 95% confidence limits, maximum and minimum values; Sn: Sensitivity; Sp: Specificity; +PV: Positive predictive value; -PV: Negative predictive value.

Factors that have significant association with MC of the spine include: Postoperative SVA > 107 mm, OR = 11.3 (95%CI: 1.1; 118.1), *P* = 0.043; type of osteotomy (SPO *vs* PSO), OR = 0.39 (95%CI: 0.1; 1.1), *P* = 0.046; fall after surgery, OR = 5.3 (95%CI: 1.6; 17.5), *P* = 0.006; postoperative change of TK > 25° in absolute values, OR = 4.8 (95%CI: 1.1; 20.8), *P* = 0.041; postoperative change of PT ⩾ 9° in absolute values, OR = 3.3 (95%CI: 0.9; 11.1), *P* = 0.049; postoperative change of PI-LL ⩾ 35° in absolute values, OR = 3.8 (95%CI: 0.9; 15.6), *P* = 0.059. The integral characteristic ⩾ 0.46 showed higher association, OR = 14.0 (95%CI: 27; 73.6), *P* < 0.001 (Table 7). Nevertheless, all these indices had limited predictive values, in particular, low Sn and +PV (Table 7). Prognostic capability of the integrative characteristic was somewhat better, but +PV was only 50% (Table 7).

Factors having significant association with VF were: smoking, OR = 5.7 (95%CI: 1.7; 19.1), *P* = 0.008; SPO *vs* PSO if osteotomy, OR = 0.25 (95%CI: 0.1; 0.8), *P* = 0.02; and fall after operation, OR = 4.3 (95%CI: 1.3; 14.5), *P* = 0.024 (Table 8). However, Sn and +PV of these variables was < 50% (Table 8). The integrative index had twice higher association, OR = 11.7 (96%CI: 2.2; 61.5), *P* < 0.001, as well as general prognostic capacity, but +PV was approximately the same (Table 8). Those factors having significant association with PJF included: Smoking, OR = 4.2 (95%CI: 1.0; 16.8), *P* = 0.05; SPO *vs* PSO of osteotomy, OR = 0.23 (95%CI: 0.05; 1.1), *P* = 0.041; a fall after the operation, OR = 4.2 (95%CI: 1.0; 16.8), *P* = 0.05; osteoporosis or osteopenia in cases treated with a PSO having > 5 fused levels, OR = 10.4 (95%CI: 0.8; 137.8), *P* = 0.039; reoperation *vs* primary operation, OR = 20.1 (95%CI: 2.5; 163.6), *P* < 0.001 (Table 8). However, all these characteristics had low +PV (< 30%) (Table 8). The integrative index did not show significant association with PJF, *P* = 0.167 (Table 8).

Factors having significant association with DSF included: preoperative LL ⩽ 20°, OR = 20.9 (95%CI: 2.3; 190.6), *P* = 0.002; crossing the thoracolumbar junction, OR = 18.6 (95%CI: 2.0; 164.9), *P* = 0.004; fixation to the sacrum or pelvis, OR = 0.08 (95%CI: 0.01; 0.73), *P* = 0.001 (Table 8). However, +PV of these characteristics was low (< 25%) (Table 8). The integrative index did not show significant association with DSF, *P* = 0.167 (Table 8).

Factors having significant association with MC of instrumentation were: Preoperative SVA ⩾ 100 mm, OR = 4.1 (95%CI: 1.5; 11.3), *P* = 0.007; postoperative change of SVA > 76 mm in absolute value, OR = 4.4 (95%CI: 1.1; 18.0), *P* = 0.041; postoperative SVA < 50 mm in cases with preoperative SVA > 110 mm, OR = 9.3 (95%CI: 1.4; 63.2), *P* = 0.025; crossing the thoracolumbar and/or lumbosacral junction(s), OR = 6.5 (95%CI:1.4; 30.2), *P* = 0.0.6; fixation to the sacrum and/or pelvis, OR = 4.0 (95%CI: 1.2; 12.1), *P* = 0.025; maximum rod contouring angle ⩾ 60°, OR = 4.4 (95%CI: 1.2; 16.1), *P* = 0.025; the use of rods individually precontoured by the manufacturer, OR = 0.35 (95%CI: 0.1;1.3), *P* = 0.05; use of more than 1 domino and/or parallel connectors, OR = 6.3 (95%CI: 0.5; 72.6), *P* = 0.06; preoperative LL ranging from 48° to 60°, OR = 0.15 (95%CI: 0.01; 1.3), *P* = 0.05; postoperative pseudarthrosis, OR = 9.2 (95%CI: 2.1; 39.3), *P* = 0.002, and the integrative index ⩾ 0.46, OR = 7.8 (95%CI: 2.0; 29.9), *P* = 0.002 (Table 9). In spite of the revealed statistically significant association the predictive capacity of all these characteristics was limited, in particular, +PV did not exceed 70% (Table 9).

The factors having significant association with SL included: Preoperative SVA > 100 mm, OR = 5.1 (95%CI: 1.6; 15.4), *P* = 0.005; postoperative change of SVA in absolute value > 76 mm, OR = 5.4 (95%CI: 1.3; 22.9), *P* = 0.026; postoperative SVA < 50 mm in cases with preoperative SVA > 110 mm, OR = 20.6 (95%CI: 2.6; 163.8), *P* = 0.004; fixation to sacrum and/or pelvis, OR = 2.5 (95%CI: 0.8; 8.3), *P* = 0.103; preoperative LL < 34°, OR = 3.4 (95%CI: 1.0; 10.9), *P* = 0.034; postoperative pseudoarthrosis, OR = 9.9 (95%CI: 2.4; 40.0), *P* = 0.001; rod fracture, OR = 15.6 (95%CI: 2.7; 89.8), *P* = 0.001; and the integrative index ⩾ 0.46, OR = 29.0 (95%CI: 3.3; 251.9), *P* < 0.001 (Table 10). The predictive capability of all these characteristics was limited, +PV ⩽ 71% (Table 10).

The factors having significant association with RF were: preoperative SVA > 100 mm, OR = 9.6 (95%CI: 1.7; 53.5), *P* = 0.008; postoperative change of SVA

Table 8 Risk factors for different mechanical complications of spine after surgical correction of adult spinal deformity with osteotomy

Mechanical complication of spine	Risk factors	OR (95%CI: min; max)	*P* value	Predictive values			
				Sn	Sp	+PV	-PV
Vertebral fracture	Current smoking	5.7 (1.7; 19.1)	0.008	0.37	0.91	0.50	0.85
	Type of osteotomy: SPO *vs* PSO	0.25 (0.1; 0.8)	0.020	0.21	0.48	0.09	0.71
	Fall after operation before mechanical complication	4.3 (1.3; 14.5)	0.024	0.32	0.89	0.43	0.84
	Integral index by multiple regression modeling (1) ⩾ 0.46	11.7 (2.2;61.5)	< 0.001	0.83	0.70	0.45	0.93
Proximal junctional failure	Current smoking	4.2 (1.0; 016.8)	0.055	0.36	0.88	0.29	0.91
	Osteoporosis/osteopenia	3.19 (0.9; 11.3)	0.075	0.55	0.72	0.21	0.92
	PSO and > 5 levels fused in osteoporosis/osteopenia	10.4 (0.8; 137.8)	0.039	1.00	0.84	0.29	1.00
	Fall after operation before mechanical complication	4.2 (1.0; 16.8)	0.055	0.36	0.88	0.29	0.91
	Reoperation *vs* primary operation	20.1 (2.5; 163.6)	< 0.001	0.92	0.65	0.28	0.98
	Type of osteotomy: SPO *vs* PSO	0.23 (0.05; 1.1)	0.048	0.18	0.51	0.05	0.82
	Integral index by multiple regression modeling (1) ⩾ 0.46	4.6 (0.4; 47.3)	0.167	0.75	0.60	0.14	0.97
Distal segmental degeneration/ failure	Preoperative LL ⩽ 20°	20.9 (2.3; 190.6)	0.002	0.83	0.81	0.23	0.99
	Thoracolumbar crossing junction	18.6 (2.0; 164.9)	0.004	0.83	0.78	0.21	0.99
	Fixation to sacrum or pelvic	0.08 (0.01; 0.73)	0.001	0.14	0.33	0.02	0.83
	Integral index by multiple regression modeling (1) ⩾ 0.46	2.9 (0.1; 89.1)	0.186	0.67	0.59	0.05	0.98

PSO: Pedicle subtraction osteotomy; SPO: Smith-Peterson osteotomy; OR: Odds ratio; 95%CI: min; max: 95% confidence limits with minimum and maximum values; Sn: Sensitivity; Sp: Specificity; +PV: Positive predictive value; -PV: Negative predictive value; LL: Lumbar lordosis.

Table 9 Risk factors for instrumentation failure (all types) after surgical correction of adult spinal deformity with osteotomy

Factors	OR (95%CI: min; max)	*P* value	Predictive values			
			Sn	Sp	+PV	-PV
Preoperative SVA ≥ 100 mm	4.1 (1.5; 11.3)	0.007	0.46	0.83	0.48	0.82
Postoperative change of SVA > 76 mm (absolute values)	4.4 (1.1; 18.0)	0.041	0.32	0.90	0.60	0.75
Postoperative SVA < 50 mm, if preoperative SVA⩾ 110 mm	9.3 (1.4; 63.2)	0.025	0.67	0.82	0.40	0.93
Preoperative LL 48°-60°	0.15 (0.01; 1.3)	0.043	0.05	0.76	0.07	0.67
Thoracolumbar and/or lumbosacral crossing junction(s)	6.5 (1.4; 30.2)	0.006	0.92	0.37	0.36	0.92
Fixation to sacrum and/or pelvic	4.0 (1.2; 12.8)	0.026	0.83	0.44	0.34	0.89
Maximum rod contouring angle > 60°	4.4 (1.2; 16.1)	0.025	0.62	0.73	0.40	0.87
Precontoured posterior rods *vs* in situ contouring	0.35 (0.1; 1.3)	0.050	0.38	0.36	0.16	0.65
Domino and/or parallel connectors number > 1	6.3 (0.5; 72.6)	0.063	0.08	0.99	0.67	0.76
Postoperative pseudarthrosis	9.2 (2.1; 39.3)	0.002	0.29	0.96	0.70	0.80
Integral index by multiple regression modeling (1) ⩾ 0.46	7.8 (2.0; 29.9)	0.002	0.75	0.72	0.55	0.87

SVA: Sagittal vertical axis; LL: Lumbar lordosis; Sn: Sensitivity; Sp: Specificity; +PV: Positive predictive value; -PV: Negative predictive value.

absolute value > 76 mm, OR = 11.3 (95%CI: 2.0; 63.3), *P* = 0.007; postoperative SVA < 50 mm in cases with preoperative SVA > 110 mm, OR = 33.0 (95%CI: 2.6; 424.1), *P* = 0.002; preoperative LL < 20°, OR = 4.9 (95%CI: 1.0; 24.3), *P* = 0.05; postoperative change of absolute values in LL ⩾ 30°, OR = 7.4 (95%CI: 1.3; 41.5), *P* = 0.022; postoperative pseudoarthrosis, OR = 8.6 (95%CI: 1.6; 46.2), *P* = 0.019; use of domino and/or parallel connectors, OR = 5.8 (95%CI: 1.1; 29.6), *P* = 0.052; sagittal rod contouring angle > 56°, OR = 9.8 (95%CI: 1.1; 85.2), *P* = 0.019; connecting to previously placed instrumentation, OR = 8.3 (95%CI: 1.7; 41.9), *P* = 0.014; iliac bolt connector loose and/or fracture, OR = 17.0 (95%CI: 1.9; 147.0), *P* = 0.026; the integrative index ⩾ 0.46, OR = 6.9 (95%CI: 0.7; 66.5), *P* = 0.027 (Table 10). The predictive value of these characteristics was limited, in particular, +PV ranged from 12% to 75% (Table 10).

The factors having significant association with IBCF included: Preoperative SVA > 100 mm, OR = 24.0 (95%CI: 1.6; 356), *P* = 0.02; and postoperative change in absolute value of SVA > 76 mm, OR = 7.4 (95%CI: 0.7; 81.4) > 8, *P* = 0.029. The integrative index did not show significant association with this type of MC (Table 11). The predictive capability was limited, +PV of these characteristics did not exceed 60% (Table 11).

Finally, factors having significant association with DI were: SPO *vs* PSO, if osteotomy applied, OR = 0.15 (95%CI: 0.02; 1.3), *P* = 0.050; osteotomy of the lumbar spine, OR = 7.4 (95%CI: 0.7; 81.4), *P* = 0.029; and fixation to sacrum and/or pelvis, OR = 4.80.2, *P* = 0.04, the integrative index did not show significant association with this type of MC, Table 11. The predictive capability was limited; +PV of these characteristics was ⩽ 40% (Table 11).

DISCUSSION

To evaluate the postoperative MC and associated risk factors after surgical correction of ASD with an

Table 10 Risk factors for screw loosening and rod fracture after surgical correction of adult spinal deformity with osteotomy

Instrumentation failure	Risk factors	OR (95%CI: min; max)	*P* value	Predictive values			
				Sn	Sp	+PV	-PV
Screw loosening	Preoperative SVA ⩾ 100 mm	5.1 (1.6; 15.4)	0.005	0.53	0.82	0.39	0.89
	Postoperative change of SVA > 76 mm (absolute values)	5.4 (1.3; 22.9)	0.026	0.38	0.90	0.50	0.84
	Postoperative SVA < 50 mm, if preoperative SVA ⩾ 110 mm	20.6 (2.6; 163.8)	0.004	0.67	0.91	0.57	0.94
	Preoperative LL < 34°	3.4 (1.0; 10.9)	0.034	0.69	0.61	0.31	0.88
	Fixation to sacrum and/or pelvic	2.5 (0.8; 8.3)	0.103	0.78	0.42	0.24	0.89
	Postoperative pseudarthrosis	9.9 (2.4; 40.0)	0.001	0.35	0.95	0.60	0.87
	Rod fracture	15.6 (2.7; 89.8)	0.001	0.29	0.97	0.71	0.86
	Integral index by multiple regression modeling (1) ⩾ 0.46	29.0 (3.3;251.9)	< 0.001	0.92	0.73	0.50	0.97
Rod fracture	Preoperative SVA ⩾ 100 mm	9.6 (1.7; 53.5)	0.008	0.71	0.79	0.22	0.97
	Postoperative change of SVA > 76 mm (absolute values)	11.3 (2.0; 63.3)	0.007	0.57	0.89	0.40	0.94
	Postoperative SVA < 50 mm, if preoperative SVA ⩾ 110 mm	33.0 (2.6; 424.1)	0.002	0.50	0.97	0.75	0.92
	Preoperative LL < 20°	4.9 (1.0; 24.3)	0.050	0.57	0.79	0.21	0.95
	Postoperative change of LL ⩾ 30°	7.4 (1.3; 41.5)	0.022	0.71	0.75	0.23	0.96
	Postoperative pseudarthrosis	8.6 (1.6; 46.2)	0.019	0.43	0.92	0.30	0.95
	Domino and/or parallel connectors	5.8 (1.1; 29.6)	0.052	0.43	0.89	0.23	0.95
	Sagittal rod contouring angle > 56°	9.8 (1.1; 85.2)	0.019	0.86	0.62	0.15	0.98
	Number of crossing junctions > 1	5.6 (0.7; 48.5)	0.087	0.86	0.48	0.12	0.98
	Connecting to previously implanted instrumentation	8.3 (1.7; 41.9)	0.014	0.57	0.86	0.25	0.96
	Iliac bolt connector loose and/or fracture	17 (1.9;147.0)	0.026	0.67	0.89	0.50	0.94
	Integral index by multiple regression modeling (1) ⩾ 0.46	6.9 (0.7; 66.5)	0.027	0.80	0.63	0.18	0.97

SVA: Sagittal vertical axis; LL: Lumbar lordosis; Sn: Sensitivity; Sp: Specificity; +PV: Positive predictive value; -PV: Negative predictive value.

Table 11 Risk factors for iliac bolt connector loosening/fracture and disassociation of instrumentation after surgical correction of adult spinal deformity with osteotomy

Instrumentation failure	Risk factors	OR (95%CI: min; max)	*P* value	Predictive values			
				Sn	Sp	+PV	-PV
Iliac bolt connector loosening/fracture	Preoperative SVA ⩾ 100 mm	24.0 (1.6; 356.0)	0.021	0.75	0.89	0.60	0.94
	Postoperative change of SVA > 76 mm (absolute values)	7.4 (0.7;81.4)	0.029	0.80	0.65	0.40	0.92
	Integral index by multiple regression modeling (1) ⩾ 0.46	4.69 (0.4; 47.3)	0.069	0.75	0.60	0.14	0.97
Disassociation of instrumentation	Type of osteotomy, SPO *vs* PSO	0.15 (0.02; 1.3)	0.050	0.13	0.51	0.02	0.86
	Lumbar osteotomy	7.4 (0.7; 81.4)	0.029	0.80	0.65	0.40	0.92
	Fixation to sacrum or pelvic	4.8 (0.6; 40.8)	0.039	0.88	0.41	0.12	0.97
	Integral index by multiple regression modeling (1) ⩾ 0.46	4.5 (0.4; 47.4)	0.069	0.75	0.60	0.14	0.97

SVA: Sagittal vertical axis; LL: Lumbar lordosis; SPO: Smith-Petersen osteotomy; PSO: Pedicle subtraction osteotomy; Sn: Sensitivity; Sp: Specificity; +PV: Positive predictive value; -PV: Negative predictive value.

osteotomy, a case-series of 94 consecutive operations performed in 88 patients were studied. The incidence of postoperative return to the operating room after the index surgery was 42.5%. The cumulative incidence of MC was 43.6%. The incidence of MC of the spine and MC of instrumentation were approximately similar, 25%. Of those, 16% of cases had multiple MC. The most typical MC of the spine were VF (20.2%), PJF (11.7%), and less common DSF (6.4%) (Figure 6 and Table 5). The most typical MC of instrumentation was SL (18.1%), other MC of instrumentation had incidence ranging from 2% to 7.4% (Figure 6 and Table 5).

Around 70% of all MC were diagnosed during the 1st postoperative year. The majority of MC with the shortest latent period were linked with failure of the spine (VF and PJF, where 70% of cases were revealed during 8 mo of follow-up) (Figure 7). Approximately the same latent period also showed higher rates of SL (specifically screw fracture) and DI (Figure 7). It is necessary to note that 2 cases of screw fracture observed in the current study were accompanied with fractures of the pedicle. The MC with a longer latent period (70% of cases were revealed at ⩾ 19 mo of follow-up) tended to be linked with instrumentation failure. This included RF, and IBCF (Figure 7). As expected, DSF had a longer latent period closer to that of IBCF (Figure 7).

The MC had significant association with postoperative return to the operating room (OR = 20.0). The strongest association showed MC of the spine, in particular: VF, PJF (OR ⩾ 19.0), and DSF (OR = 7.6). Among MC of instrumentation, significant association with secondary surgical treatment showed cases of SL (OR = 4.2) and DI (OR = 9.4). It may be explained by the fact that MC of the spine occurred early, preceding solid fusion, and provoked the corresponding severe clinical symptoms. Some of the MC of instrumentation,

in particular RF and IBCF occurred later. There were seen even after the development of solid intervertebral fusion. They were less likely to lead to spinal instability and clinical symptoms requiring surgical treatment.

The revealed characteristics that have significant association with increased risk of MC may be classified into subgroups. First, indices linked with severity of the preoperative sagittal imbalance including: SVA > 100°; and LL< 34°. Second, preoperative comorbidities such as: smoking, and osteoporosis/osteopenia (specifically, in cases after PSO with more than 5 levels fused). Third, postoperative events such as: a fall and pseudoarthrosis. The fourth subgroup reflects insufficient correction of the sagittal imbalance (postoperative SVA > 75 mm). The fifth group includes indices linked with over-correction of the sagittal imbalance and spinopelvic alignment or reciprocal changes including: Postoperative SVA < 50 mm, if preoperative SVA ⩾ 110 mm; postoperative changes in absolute values for SVA > 76 mm, TK > 25°, LL > 29°, PI-LL > 35°, and PT > 9°. Also, characteristics of the index operation and the surgical technique were associated with MC: Revision surgery, type of osteotomy (PSO), lumbar location of the osteotomy, crossing transitional spinal segments (thoracolumbar, lumbosacral, and > 1 junction crossed). The seventh group included characteristics of the instrumentation and the fusion construct including: Sagittal rod contouring > 60°, fixation to the sacrum or pelvis (specifically after PSO with > 5 level fused), use of dominos and/or parallel connectors, and connecting to the previously implanted instrumentation. Finally, the other device failures, in particular, RF associated with SL.

Off note, some factors had significant association with low risk of MC or had multiple effects. This was seen in particular with cases having preoperative LL ranging between 47° and 61° (showed lower risk of MC of instrumentation), fixation to the sacrum with or without fixation to pelvis increased risk of SL, but expected decreased risk of DSF, and use of rods individually precontoured by manufacturer decreased risk of MC of instrumentation.

Unlike previous investigators we regarded postoperative pseudarthrosis as a risk factor rather than a MC. This showed that pseudarthrosis was significantly association with MC of instrumentation, in particular SL and RF. This association may reflect progression of postoperative instability, which increases strain at the fused spinal segments preventing ossification of the callus and contributing to the risk of instrumentation failure.

The main results of the current study correspond with previous findings. The results revealed the incidence of pseudarthrosis, revision/reoperation, and severe PJF values very close to those previously reported[11,16,25]. The postoperative period of occurrence for PJF and RF also corresponded with the previously published time-frames[27,44]. It was demonstrated by Charosky *et al*[11] (2012) that the use of a PSO is associated with higher risk of MC. This corresponds with the results of the current study. However, an additional analysis has shown that a PSO (as expected) is more often applied in cases with severe preoperative sagittal imbalance (SVA ⩾ 100 mm). This high starting SVA is also a risk factor of MC, making the argument somewhat circular. Stratification demonstrated that in cases with a preoperative SVA < 100 mm, a PSO showed higher risk of MC than SPO (OR = 2.3; *P* = 0.1), while in the cases with the SVA ⩾ 100 mm this difference was absent (OR = 0.95; *P* = 0.96). It suggests that SPO has benefit only in cases with small or moderate sagittal imbalance. While this seems intuitive, this finding requires further confirmation due to the relatively small number of cases in the studied subgroups after the stratification. The same authors, previously cited, suggested that fixation to sacrum is associated with a higher risk of MC (OR = 3.7)[11]. The results of current study confirm this finding with important details: Fixation to sacrum with or without fixation to pelvis was associated with instrumentation failure (OR = 4.0, Table 9), in particular SL (OR = 2.5, Table 10). However, it simultaneously minimized risk of DSF as would be expected (OR = 0.08, Table 8). Inoue *et al*[16] (2015) showed that preoperative SVA > 95 mm is a risk factor of MC (HR = 2.6). Our results confirmed this finding with somewhat higher SVA threshold (SVA > 110 mm, OR = 4.5, Table 6). Combining of these findings by the Bayesian method suggested strong evidence (PO = 11.7) that severe preoperative anterior sagittal imbalance contributes to the risk of postoperative MC. Smoking was shown as a risk factor of MC (HR = 3.3)[16]. It was also confirmed by the present study, particularly for VF (OR = 5.7) and PJF (OR = 4.2), with a strong level of evidence by the Bayesian method (PO > 13.8). Smith *et al*[33] (2015) reported that postoperative SVA < 50 mm is a risk factor of PJF; however, adequate risk analysis and acceptable interpretation of this finding were not shown. The results of the current study have added details necessary for adequate interpretation of this finding. It was shown that the postoperative SVA < 50 mm can be associated with MC (SL), but specifically in patients with a preoperative SVA > 110 mm. This suggests significant correction, not SVA < 50 mm, is the more important factor to consider. Yagi *et al*[32] (2012) showed that progress of proximal junctional kyphosis is more significant in patients with osteoporosis. The results of present study confirmed the role of osteoporosis as a risk factor of PJF, specifically in cases after PSO and more than 5 levels fused. The obtained results regarding risk factors of RF are close to those previously published[27]. However, a few additional factors were revealed which are linked with severity of the preoperative sagittal imbalance and level of correction (Table 10). A relatively high incidence of SL appears contradictory to the experimental data, which showed that force around 1300N is necessary to cause pedicle screw failure. Supplemental hooks have not been shown to change this force[45]. Forces in the fusion construct are considerably less, but they act constantly during a long period of time which can cause permanent strain (micromotion).

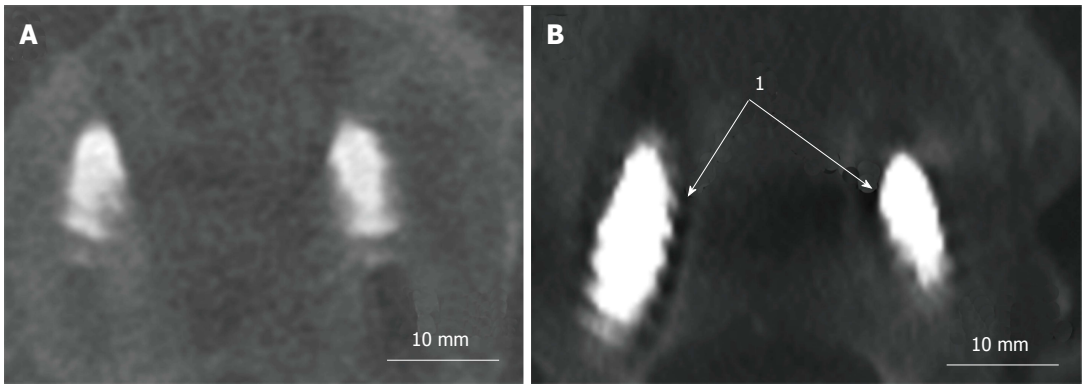


Figure 8 Failure of the bone-screw interface. This effect was observed in a 75-year-old male after surgical correction of adult spine deformity with T12-L2 instrumented fusion, L1/L2 Smith-Petersen osteotomy, and transforaminal interbody fusion. A: Postoperative pedicle screws placed at T12 with good contact between the screws and the bone (absence of noticeable radiolucency around the screws); B: Loosening of the screws with loss of boney fixation that was revealed at 6 mo follow-up. This effect is viewed as radiolucency around the screw (1). This may be due to bone resorption, starting the process of screw pullout at 6-mo follow-up.

This strain may stimulate bone remodeling, decreasing contact surface between screws and the bone[46,47]. Finally, it may result in screw pullout (Figure 8). This process may take anywhere from one to several months.

In the current study we did not reveal a significant association between MC and such demographic characteristics as age, gender and BMI unlike some previous studies[8,35-37]. It may be explained by more severe preoperative sagittal imbalance in the cases that were included in the present study. This suggests the impact of factors other than demographic data prevailed in the studied case series. Devices and techniques for preoperative planning of correction were recently introduced at our institution[48]. These utilize patient specific rods precontoured by the manufacturer according to a preoperative surgical plan. The present study has shown that the use of this approach decreases the risk of the instrumentation failure (Table 9).

Analysis of the risk factors as presented above allows assumption that permanent mechanical stress in the spine and in the implanted devices, as a result of spinal correction, is the main risk of MC. The mechanical strength of bone and ligaments is less than that of the instrumentation; therefore MC of the spine occurred earlier than MC of instrumentation. Other factors such as surgical technique, type of instrumentation, and preoperative health status of patient may significantly modify the effect of this constant stress. This statement corresponds well with the previous experimental data suggesting that stiff instrumentation, which provides stability, simultaneously increases strain in the construct through a physiologic range of motion[49]. There are therefore two main sources of the postoperative mechanical stress. First is proportional to the preoperative spinal deformity, sagittal imbalance, abnormality of the spinopelvic alignment, and the level of correction; second is caused by the patient's postoperative posture and motion. The first maybe increased by over-correction and the second may be worsened by insufficient correction. The combination of these 2 main effects causes somewhat contradictory results. An optimal balance between these two mechanical stresses is important to minimize the risk of the postoperative MC.

The results of the current and previous studies provide guidelines that may decrease the risk of postoperative MC. First, the absolute difference between postoperative and preoperative spinopelvic parameters should not exceed SVA > 75 mm, LL > 30°, TK > 25°, PI-LL > 30°, and PT > 9°. Second, postoperative anterior sagittal imbalance should not exceed 75 mm, and in patients with preoperative SVA > 110 mm, a postoperative SVA from 50 mm to 75 mm may be regarded as an acceptable. Third, in situ contouring of rods > 60° and repetitive contouring should be avoided. Fourth, the use of dominos and/or parallel connectors should be avoided or minimized. Fifth, the combination of pedicle screws with hooks may be appropriate in cases with preoperative SVA > 100 mm, having concomitant osteoporosis, and requiring significant correction with long posterior instrumented fusion (> 5 levels) and an osteotomy. Sixth, in cases with preoperative SVA < 100 mm, SPO is preferred to a PSO, if there is no specific indication for a PSO (such as ankylosing spondylitis) and adequate correction may be obtained. Finally, the use of preoperative planning with precontoured rods decreases the risk of instrumentation failure. The protective effect of this method may be enhanced by the application of optimal spinopelvic parameters, which provide criteria correction[50].

This study had several limitations, including the retrospective design with an inherent risk of selection bias and the incomplete/limited quality of the radiographic data, which may cause underestimation of significance for several of the studied risk factors. In particular, the role of sacral slope and pelvic incidence was not evaluated in the current study. The causes of the postoperative falls were not studied, and it is still unclear whether it was consequences of vestibular, vascular, mental or other diseases. The revealed risk factors, in spite of high statistical significance, had limited predictive capability, in particular, low positive predictive value. There may other risk factors that were not taken into consideration in the current study.

However, in spite of these limitations, the combination of obtained results with the previously published findings confirms the consistency of the revealed effects. Therefore, the presented results should be viewed as a grounded, preliminary basis for further research with higher levels of evidence.

Incidence of MC after surgical correction of ADS is relatively high, and often requires additional surgical treatment. To diminish the risk of MC, the correction of sagittal imbalance and spinopelvic alignment should be appropriate, over- and insufficient correction should be avoided. Treatment strategy, surgical technique, and instrumentation should be improved for cases with severe anterior sagittal imbalance, spine compromised by previous surgical interventions, and, specifically, with concomitant osteoporosis.

ARTICLE HIGHLIGHTS

Research background

It has been pointed out during last decades that mechanical complications (MC) after surgical correction of adult spine deformity (ASD) are most typical, and often require additional surgical treatment. However, these complications were not clearly defined. Their specific appearances, incidence, distribution by postoperative follow-ups, and risk factors were not studied well.

Research motivations

New knowledge concerning nature and causes of the MC would enable diminish their occurrence and improve postoperative clinical outcomes after surgical correction of ASD.

Research objectives

The main objectives of the study were identification of the most clinically relevant MC seen after surgical correction of ASD with corrective osteotomies, defining of their incidence, the most likelihood period of occurrence, association with additional surgeries; revealing of risk factors and assessment their predictive value. Achievement of these purposes would have enabled formulation of grounded recommendation to diminish risk of such complications and contribute to defining directions for further research in this field.

Research methods

The retrospective clinical study was performed. Medical records, operation protocols, and radiographic images were studied in patients who underwent surgical correction of adult spine deformity with osteotomy. Preoperative, perioperative, and postoperative data were collected for 2 and more years of follow-up. Postoperative mechanical failures of spine and implanted instrumentation were studied in detail including: their features, latent periods, incidence, required additional treatment, and different risk factors such as: Demographic, preoperative and postoperative spinopelvic alignment, level of correction, spinal instrumentation, features of surgical intervention, *etc*.

Research results

It was shown that around half of patients experienced MC during two postoperative years; majority of these cases required additional surgery. MC of spine occurred earlier and more often required revision than breakage of the instrumentation. The main risk factors included severe preoperative sagittal imbalance, inadequate correction of the spinopelvic alignment, preoperative comorbidities (osteoporosis, smoking), postoperative events (falls), and features of the spinal instrumentation. There was developed method that enables recognition of patients with high risk of postoperative MC.

Research conclusions

The performed study is first that performed a clear classification of the clinically relevant MC after surgical correction of ASD with osteotomy. In particular, there were specified those complications that are linked with failure of spine, breakage of the instrumentation; and disassociation between different elements of the spinal fusion construct. First time, impact of more than 50 potential risk factors of the MC and their combinations was assessed. There were revealed risk factors and their combinations that had statistically significant association with one or a few MC. The predictive value of each of these risk factors for each type of MC was evaluated. The obtained results allowed development of a new method to recognize patients with high risk of postoperative MC; and provide newel grounded recommendations to diminish risk of such complications. Implication for clinical practice: implementation of these methods can contribute to improvement of treatment outcomes after surgical correction of ASD with osteotomy, and diminish treatment expenses.

Research perspectives

The obtained results and recommendations require further confirmation by studies with higher level of evidence such as prospective cohort and randomized clinical trials. The predictive capability of the risk factors revealed in the current study showed underestimation of risk of MC after surgical correction of ASD. It suggests that other currently unknown risk factors likely also exist. Therefore, further researches are needed in this field to reveal these factors.

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SYSTEMATIC REVIEWS

Synthetic *vs* biologic mesh for the repair and prevention of parastomal hernia

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Abstract

AIM

To outline current evidence regarding prevention and treatment of parastomal hernia and to compare use of synthetic and biologic mesh.

METHODS

Relevant databases were searched for studies reporting hernia recurrence, wound and mesh infection, other complications, surgical techniques and mortality. Weighted pooled proportions (95%CI) were calculated using StatsDirect. Heterogeneity concerning outcome measures was determined using Cochran's Q test and was quantified using I^2. Random and fixed effects models were used. Meta-analysis was performed with Review Manager software with the statistical significance set at $P \leqslant 0.05$.

RESULTS

Forty-four studies were included: 5 reporting biologic mesh repairs; 21, synthetic mesh repairs; and 18, prophylactic mesh repairs. Most of the studies were retrospective cohorts of low to moderate quality. The hernia recurrence rate was higher after undergoing biologic compared to synthetic mesh repair (24.0% *vs* 15.1%, $P = 0.01$). No significant difference was found concerning wound and mesh infection (5.6% *vs* 2.8%; 0% *vs* 3.1%). Open and laparoscopic techniques were comparable regarding recurrences and infections. Prophylactic mesh placement reduced the occurrence of a parastomal hernia (OR = 0.20, $P < 0.0006$) without increasing wound infection [7.8% *vs* 8.2% (OR = 1.04, $P = 0.91$)] and without differences between the mesh types.

CONCLUSION

There is no superiority of biologic over synthetic mesh for parastomal hernia repair. Prophylactic mesh placement

during the initial surgery significantly reduces parastomal hernia occurrence regardless of the mesh type.

Key words: Parastomal hernia; Synthetic mesh repair; Biologic mesh repair; Prophylactic mesh repair

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Core tip: This review and meta-analysis outlines all current evidence regarding prevention and treatment of parastomal hernia and compares the use of synthetic and biologic mesh. There is no superiority of biologic over synthetic mesh for parastomal hernia repair concerning parastomal hernia recurrence, wound infection and mesh infection. Prophylactic mesh placement during the initial surgery significantly reduces parastomal hernia occurrence regardless of the mesh type.

Knaapen L, Buyne O, van Goor H, Slater NJ. Synthetic *vs* biologic mesh for the repair and prevention of parastomal hernia. *World J Meta-Anal* 2017; 5(6): 150-166 Available from: URL: http://www.wjgnet.com/2308-3840/full/v5/i6/150.htm DOI: http://dx.doi.org/10.13105/wjma.v5.i6.150

INTRODUCTION

Parastomal hernia is a common complication of stoma formation during colorectal surgery, with incidences up to 50%. The risk of parastomal hernia is highest within the first few years after formation of the stoma but may develop as much as 20 years later[1]. Hernias are often asymptomatic and managed with conservative treatment. However, 11% to 70% of patients undergo surgery due to discomfort, pain, obstructive symptoms and cosmetic dissatisfaction[2]. These treatment percentages vary because surgeons are often reluctant to repair a parastomal hernia due to the high recurrence rate, complicated operation and co-morbidity of patients. Indeed, a parastomal hernia is regarded as a complex incisional hernia by hernia experts[3]. Hence, many patients suffer but never undergo surgery.

The recurrence rate of parastomal hernia is the lowest after mesh repair (0%-33%), whereas primary fascial closure (46%-100%) and relocation of the stoma (0%-76%) result in much higher rates. Although low recurrence rates are reported after synthetic mesh repair, concerns have been raised regarding the safety of synthetic meshes in (potentially) contaminated fields due to the risk of mesh infection and subsequent removal. Other mesh-related complications include chronic infection, bowel stenosis, erosion of the mesh through the bowel and skin and enteroatmospheric fistulisation. These complications led to the development of biologic mesh, which due to its bio-degradable nature, has the potential to ameliorate these problems in infected and contaminated fields.

The high prevalence of parastomal hernias and the difficulty of repair have led to a shift of focus from repair towards prevention using prophylactic mesh reinforcement at the time of stoma formation. However, prophylactic mesh placement coincides with risk of the same mesh-related morbidities of hernia repair.

There are no trials comparing biologic and synthetic mesh repair for parastomal hernias. Available studies show a large range in reported parastomal hernia recurrence rates and no difference in mesh type concerning hernia recurrence or infection resistance[4-7].

No clear answer can be given as to whether there is a difference between the outcomes of synthetic and biologic mesh repair. However, given the financial costs of biologic mesh, the evidence for superiority and more beneficial outcomes compared to synthetic mesh is mandatory to support its use.

There are various approaches regarding the anatomic position of the mesh during parastomal hernia repair. Meshes are implanted in an inlay, onlay, sublay or underlay (intraperitoneal) position. Laparoscopic repair involves the intraperitoneal technique, and open repair may involve any of the anatomical planes of the mesh. The inlay technique places the mesh within the fascial defect and is sutured to the fascial edges. With onlay repair, the mesh is placed subcutaneously and fixed onto the fascia of the anterior rectus sheath and the aponeurosis of the external oblique abdominal muscle. When using a retromuscular or sublay technique, the prosthesis is placed dorsally to the rectus muscle and anteriorly to the posterior rectus sheath after mobilization of the latter. When performing intraperitoneal repair, the choice can be made between the Sugarbaker and keyhole repair techniques. Regarding the Sugarbaker technique, the hernia defect is closed with intraabdominal placement of the prosthetic mesh securely sutured or tacked to the abdominal wall. Between the abdominal wall and the prosthesis, the bowel is lateralized passing from the hernia sac into the peritoneal cavity[8]. During keyhole mesh repair, a 2-3 cm hole is fashioned in the mesh for passage of the stoma, and the rest of the mesh covers the entirety of the hernia orifice, including sufficient overlap (5 cm beyond the edge of the hernia defect is recommended). Both the keyhole and Sugarbaker techniques can be performed open or laparoscopically[9,10].

The primary aim of the current study was to compare biologic and synthetic mesh use for the treatment and prevention of parastomal hernia by systematic review and meta-analysis of available data in the literature. The secondary aim was to evaluate the different anatomical positions and surgical techniques used for parastomal hernia repair. With the absence of rigorous data focused on hernia recurrence in the literature, this review contributes to the increased understanding of parastomal hernias.

MATERIALS AND METHODS

Search strategy

Articles for this review were identified by searching the electronic databases PubMed and Medline (January 1946 to present) and by manual cross-reference searches. The last search was performed on 19-4-2016. The search included the following terms: "Parastomal hernia", "Parastomal", "Paracolostomy", "Paraileostomy", "Stoma" and "Colostomy" to represent the population. These terms were combined with terms relevant to the outcomes, such as "Ventral hernia", "Defect", "Mesh", "Synthetic mesh", "Biologic mesh", "Closure", "Reconstruction", "Prosthesis", "Scaffold", "Prevention" and "Prophylactic". The full search strategy is provided in Appendix 1. No limitation to date or language was considered. Randomized and non-randomized studies were included. When multiple studies describing the same population were published, the most complete report was used. The systematic review was performed in accordance with PRISMA[11].

Critical appraisal

All selected papers were evaluated for methodological quality using the Cochrane risk-of-bias tool for randomized controlled trials and the Newcastle-Ottawa Scale (NOS) for all non-randomized and single group studies[12,13]. Assessment using the Cochrane risk-of-bias tool is based on sequence generation, allocation concealment, blinding of participants, personnel, outcomes assessors, incomplete outcomes data, selective outcomes reporting, and other sources of bias, such as baseline imbalance, early stopping bias, academic bias, and source of funding bias. The NOS is an instrument for assessing methodological quality and potential bias in non-randomized studies. A maximum of nine points were assigned to each study. Studies that scored four for selection, two for comparability, and three for assessment of outcomes were regarded as having a low risk of bias. Studies with two or three stars for selection, one for comparability, and two for outcome were considered as having a medium risk of bias. Any study with a score of one for selection or outcome, or zero for any of the three domains, was deemed as having a high risk of bias. A modification in the NOS was made for single group studies, which consisted of excluding the points for comparability with a maximum of six points: three for selection and three for outcome. After screening titles and abstracts, two reviewers (Knaapen L and Slater NJ) independently reviewed full-text articles for eligibility using the critical appraisal approach. Any disagreement was resolved by consensus with a third reviewer (van Goor).

Outcome measures

Studies were identified according to the following inclusion criteria: Participants (human adults, minimum of 18 years of age), intervention (parastomal hernia repair with a synthetic or biologic mesh and prophylactic placement of mesh), and sufficient data available (10 or more patients).

The following criteria were used for exclusion: Stoma relocation, primary suture repair, and unspecified surgical technique. Studies published only as abstracts were excluded because quality assessment could not be performed.

The primary outcome measure was the recurrence rates of parastomal hernia as defined by the respective authors. Secondary outcomes were wound infection, mesh infection, mortality, other complications (medical and surgical), anatomic position of the prosthesis and surgical approach (open or laparoscopic).

Data extraction and statistical analysis

All full-text articles that met the inclusion criteria were thoroughly reviewed, and the data for primary and secondary outcomes were extracted and recorded in a data form. Year of publication, study period, level of evidence, mean age, gender, number of patients included and evaluated, type of stoma, surgical technique (open or laparoscopic, anatomical mesh position, keyhole or Sugarbaker), type of mesh (biologic or synthetic) and duration of follow-up were also noted. Weighted pooled proportions with a 95%CI were determined for recurrence, wound infection, mesh infection, other complications and mortality using StatsDirect statistical software[14]. The heterogeneity concerning the outcome measures was determined with Cochran's Q test and quantified using I^2. A random-effects model was used unless heterogeneity was 0%, in which case, a fixed-effects model was used. Meta-analysis was performed using Review Manager[15] with the statistical significance set at $P < 0.05$.

RESULTS

A flowchart overview of the search including reasons for exclusion of studies is shown in Figure 1. A total of 44 studies were included. Five studies provided information on 84 biologic mesh repairs; 21 studies, on 669 synthetic mesh repairs; and 18 studies, on 500 prophylactic mesh placements.

The following were included in the current study: Seven randomized controlled studies (level 1 evidence; all prophylactic mesh repair), 5 non-randomized comparative studies (level 2 evidence) and 32 single-group studies (level 3 evidence). Concerning the risk of bias assessment of seven randomized controlled trials (Figure 2): Sequence generation was unclear in 4 (57%) and low in 3 (43%) studies; allocation concealment was unclear in 1 (14%) and low in 6 (86%) studies; performance bias was high in all 7 (100%) studies; detection bias was low in 3 (43%) and high in 4 (57%) studies; attrition bias was low in all 7 (100%) studies; reporting bias was low in 6 (86%) and high in 1 (14%) study; and other bias was unclear in 2 (29%), low in 3 (43%) and high in 2 (29%) studies.

The Newcastle-Ottawa Scale for quality assessment

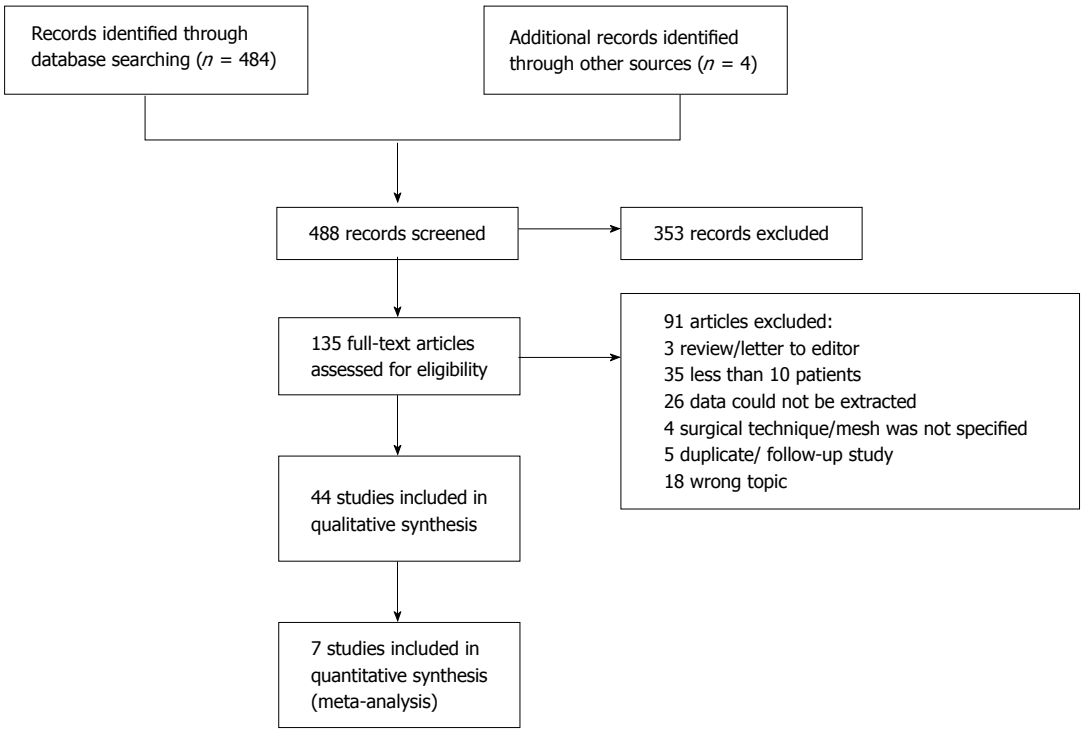


Figure 1 Search flow-chart following PRISMA.

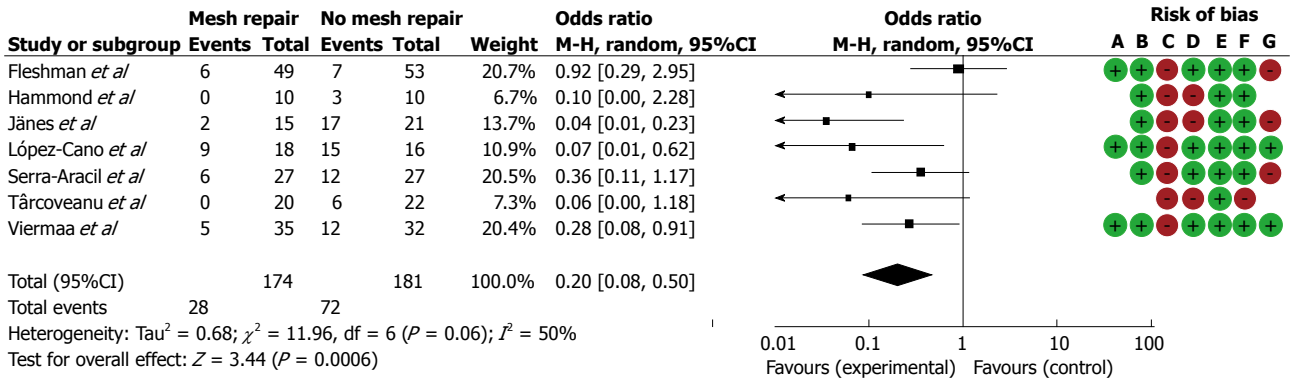


Figure 2 Incidence of parastomal hernia after prophylactic mesh placement *vs* no mesh placement. A: Random sequence generation (selection bias); B: Allocation concealment (selection bias); C: Blinding of participants and personnel (performance bias); D: Blinding of outcome assessment (detection bias); E: Incomplete outcome data (attrition bias); F: Selective reporting (reporting bias); G: Other bias.

showed that all 37 non-randomized studies had a low risk of bias for study selection. The five non-randomized two-group studies showed a low risk of bias regarding comparability in 1 study (20%), medium risk in 2 studies (40%), and high risk in 2 studies (40%). The risk of bias for outcome assessment was low in 20 (54%) studies, medium in 15 (41%) studies, and high in two (5%) studies (Figure 3).

Use of funding was not reported in 32 studies (73%). Five studies (11%) reported no funding[2,5,8,16,17]. Industry sponsored 4 biologic mesh studies (9%)[4,18-20]. The manufacturer supplied the mesh material in one biologic and one synthetic mesh study (5%)[21,22]. The state funded one study without financial disclosures reported[23]. Fifty-three percent of patients were female, and the mean age was 64.6 years. The indication for stoma placement was reported in 32 studies: benign disease in 9%, malignant disease in 68%, inflammatory bowel disease or diverticulitis in 19% and other causes in 4%. Patient demographics, study characteristics and critical appraisals are described in Table 1.

Biologic mesh repair of parastomal hernias

Biological grafts used in the included studies were Surgisis, AlloDerm, Permacol and Peri-Guard (Table 2). Five retrospective studies reported parastomal hernias that were repaired with a biologic mesh and included a combined enrolment of 84 patients. Patient follow-up ranged from 9-50 mo. One case of mortality was reported due to renal failure unrelated to the mesh[4]. Study characteristics and outcomes, including weighted-pooled rates of recurrence and wound-re-

Table 1 Patient demographics, study characteristics and critical appraisal of included studies

Ref.	Year	Inclusion period	Level of evidence	Mean age, years	Male (%)	Newcastle-Ottawa Scale			Cochrane risk of bias						
Târcoveanu *et al*[44]	2014	2010-2011	1	NS	NS				?	?	-	-	+	-	?
Ventham *et al*[63]	2012	2003-2010	2	I: 69, C: 68	I: 42%, C: 35%	****	**	***							
Hansson *et al*[8]	2013	2005-2010	3	63	35%	***		***							
López-Cano *et al*[40]	2012	2007-2010	1	I: 72, C: 66	I: 58%, C: 42%				+	+	-	+	+	+	+
Hauters *et al*[16]	2012	2008-2010	3	69 (median)	40%	***		***							
Fei *et al*[34]	2012	2008-2010	3	63	45%	***		***							
Mizrahi *et al*[2]	2012	2005-2010	3	64	34%	***		***							
Wara *et al*[5]	2011	1997-2008	3	62 (median)	50%	***		***							
Janson *et al*[64]	2010	2003-2007	3	65	40%	***		**							
Jänes *et al*[42]	2010	2003-2006	2	63	66%	****		**							
Pastor *et al*[26]	2009	1999-2006	2	I: 60, C: 54	I: 42%, C: 54%	****	*	***							
Lüning *et al*[65]	2009	1997-2006	3	65	27%	***		**							
Serra-Aracil *et al*[6]	2009	2004-2006	1	I: 68, C: 67	I: 70%, C: 59%				?	+	-	+	+	+	-
Hansson *et al*[31]	2009	2002-2006	3	63	49%	***		***							
Vijayasekar *et al*[45]	2008	2002-2007	3	61	52%	***		***							
Jänes *et al*[43]	2009	2001-2003	1	I: 70, C: 71	I: 56%, C: 59%				?	+	-	-	+	+	-
Berger *et al*[35]	2009	2004-2008	3	69 (median)	NS	***		***							
Muysoms *et al*[27]	2008	2001-2007	2	70	54%	****	*	***							
Guzmán-Valdivia *et al*[32]	2008	NS	3	67	64%	***		**							
Berger[39]	2008	2006-2007	3	72 (median)	64%	***		**							
Craft *et al*[66]	2008	2004-2006	3	66	NS	***		***							
Berger *et al*[7]	2007	1999-2006	3	70 (median)	39%	***		***							
Mancini *et al*[29]	2007	2001-2005	3	60	44%	***		**							
Marimuthu *et al*[46]	2006	2002-2005	3	67	44%	***		**							
Gögenur *et al*[22]	2006	2003-2005	3	71 (median)	60%	***		**							
van Sprundel *et al*[37]	2005	2000-2003	3	57	31%	***		***							
de Ruiter *et al*[33]	2005	1988-2002	3	NS	NS	***		***							
Longman *et al*[67]	2005	2000-2004	3	NS	NS	***		**							
LeBlanc *et al*[28]	2005	NS	3	42-89	NS	***		***							
Stelzner *et al*[36]	2004	1994-2002	3	70 (median)	60%	***		**							
Steele *et al*[30]	2003	1988-2002	3	64	50%	***		***							
Hofstetter *et al*[38]	1998	NS	3	NS	NS	***		***							
Viermaa *et al*[23]	2015	2010-2013	1	I: 67 C: 65	I: 51% C: 54%				+	+	-	+	+	+	+
Asif *et al*[17]	2012	2004-2011	3	62	60%	***		**							
Figel *et al*[62]	2012	2005-2008	3	63	67%	***		**							
Smart *et al*[4]	2011	2007-2009	3	72 (median)	44%	***		*							
Taner *et al*[25]	2009	2006-2007	3	NS	39%	***		**							
Hammond *et al*[68]	2008	NS	1	I: 43, C: 50	I: 30%, C: 40%				?	+	-	-	+	+	?
Hammond *et al*[21]	2008	NS	3	NS	NS			*							
Aycock *et al*[18]	2007	2004-2006	3	56	36%	***		**							
Araujo et al[24]	2005		3	57	27%	***		***							
Ellis *et al*[19]	2010	2004-2007	3	64	65%	***		***							
Fleshman *et al*[20]	2014	2010-2012	1	I: 60, C: 59	I: 55%, C: 50%				+	+	-	+	+	+	-
Williams *et al*[41]	2015	2011-?	2	I: 49, C: 59	I: 27%, C: 45%	***		**							

Level of evidence: 1: (Systematic reviews, meta-analyses) randomized controlled trials; 2: Two groups, non-randomized studies (*e.g.*, cohort, case-control); 3: One group, non-randomized; 4: Descriptive studies that include analysis of outcomes; and 5: Case reports and expert opinion that include narrative reviews and consensus statements. NS: Not significant.

lated complications, are shown in Table 3. Five studies reported 23 hernia recurrences with a weighted-pooled proportion of 24% (95%CI: 8.6-44.1) (Figure 4). Only three of these studies reported treatment after recurrence. Araujo *et al*[24] relocated the stoma and, Ellis *et al*[19] reported a reoperation using a bioprosthetic not further specified. Taner *et al*[25] reported two asymptomatic recurrences that were both treated conservatively. There were 4 wound infections that were reported with a weighted-pooled proportion of 5.6% (95%CI: 1.4-12.1)[4,18,25]. One was conservatively treated, one was treated with systemic antibiotics, and two were treated with local wound care[4,18,25]. No mesh infections were reported [0% (95%CI: 0-5.4)]. Other complications [13.4% (95%CI: 1.9-32.7)] were minor complications, including six seroma formations (four treated by drainage and two conservatively treated).

Synthetic mesh repair of parastomal hernias

Characteristics of the synthetic mesh used in the included studies are given in Table 2. One of the 21 studies was a prospective trial that recruited 12 patients with synthetic mesh repair and 13 control patients without mesh repair. The other 20 studies had a combined enrolment of 669 patients with synthetic mesh repairs[26]. Patient follow-up ranged from 7 to 51 mo.

Table 2 Characteristics of synthetic and biologic prostheses used for parastomal hernia repair

Name	Material	Coating	Absorbable	Pore size	Weight
StomaMesh Surgipro Prolene Central ring enforced polypropylene	Polypropylene	None	No	Small to medium 0.8 mm or large 1.0-3.6 mm	Heavy weight or light weight
DUALMESH	Composite multifilament expanded polytetrafluoroethylene	None	No	Very small 3/22 μm	Heavy weight
Proceed	Polypropylene Encapsulated in polydioxanone	Oxidized regenerated cellulose	Partially 180 d and 28 d	Large	Light weight
Parietex	Composite multifilament Polyester/collagen	Type I collagen, polyethylene glycol, and glycerol layer	Partially 20 d	Large > 3 mm	Medium weight
ULTRAPRO	Composite monofilament Polypropylene	Poliglecaprone-25 (monocryl)	Partially 140 d	Large > 3 mm	Light weight
VICRYL	Multifilament polyglactin	None	Yes, 60-90 d	Small 0.4 mm	Medium weight
Vypro	Polypropylene	PG910	Partially 42 d	Large > 3 mm	Light weight
Composix Parastomal hernia patch	Polypropylene/expanded polytetrafluoroethylene	None	No	Medium 0.8 mm	Light weight
DynaMesh	Polypropylene	PVDF	Partially	Large 1-2 mm	Medium weight
Surgisis	Porcine small intestine submucosa	None			
AlloDerm	Human acellular dermis	None			
Permacol	Cross-linked acellular porcine collagen	Yes, hexamethylene diisocyanate			
Peri-Guard	Bovine pericardium	Yes; glutaraldehyde			
STRATTICE	Non-crosslinked porcine-derived acellular dermal matrix	None			

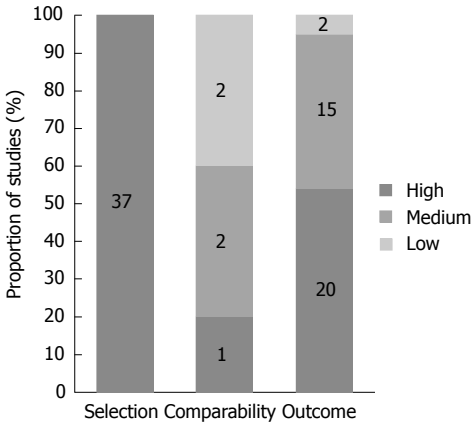


Figure 3 Quality assessment using the Newcastle-Ottawa Scale for risk of bias included in the systematic review. The absolute numbers of the studies are shown in boxes.

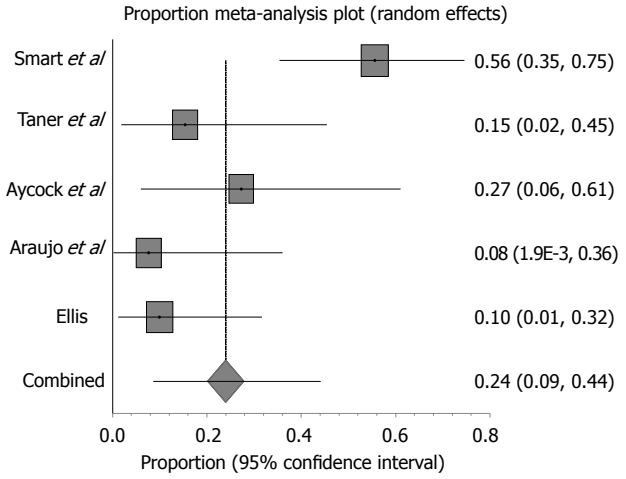


Figure 4 Proportion of hernia recurrences after biologic mesh repair of parastomal hernia. The square shape represents the weight of the study, and the horizontal line through the square represents the confidence interval of the effect estimate (random effects model; Cochran's *Q* test = 15.8; I^2 = 74.7%; *P* = 0.0033).

One study did not specify mean or median follow-up. The overall mortality was 1.9% (11 patients, weighted-pooled proportion, 95%CI: 0.9-3.2). None of the deaths were related to the mesh. Four post-operative deaths were due to progressive metastatic disease, two deaths were due to aspiration and subsequent cardiopulmonary arrest, and two deaths were due to secondary cardiopulmonary complications[8,27-29]. Wara *et al*[5] reported one death due to a neglected bowel injury that resulted in multiorgan failure and another death due to uncontrollable bleeding that resulted from portal hypertension that was unknown prior to surgery. One post-operative death was reported by Mizrahi *et al*[2] following sepsis that was not further specified and caused by an infected retroperitoneal haematoma, which necessitated a second operation.

Study characteristics and outcomes, including weighted pooled rates of recurrence and wound-related complications, are shown in Table 3. Nineteen studies

Table 3 Study characteristics and outcomes of synthetic mesh and biologic mesh repair of parastomal hernia *n* (%)

Ref.	No. patients (completed follow-up)		Type of stoma	Material; technique	Recurrence of parastomal hernia[1]		Wound infection		Mesh infection	Other[3]		Mortality	Follow-up (mo)
	Mesh	No mesh			Mesh	No mesh	Mesh	No mesh	Mesh	Mesh	No mesh		
Hansson *et al*[8]	61	-	C: 55 I: 4 U: 2	L: 55; IPOM: SB; ePTFE	4 (7)	-	1 (2)	-	1 (2)	21 (34)	-	1[2] (2)	26
Fei *et al*[34]	11	-	C: 6 I: 5	O: 11 Sublay: K; PP	1 (9)	-	0	-	NS	3 (27)	-	0	24
Mizrahi *et al*[2]	29 (28)	-	C: 18 I: 10 U: 1	L: 29 IPOM: K; ePTFE	13 (46)	-	NS	-	1 (4)	3 (11)	-	1[2] (4)	28
Wara *et al*[5]	72	-	C: 48 I: 24	L: 72 IPOM: K; PP+ePTFE	2 (3)	-	1 (1)	-	3 (4)	20 (28)	-	2[2] (3)	36
Pastor *et al*[26]	12	13	C: 10 I: 15	L: 12 O: 13 IPOM: K 3 SB: 7, lateral slit: 1 e-PTFE	4 (33)	7 (54)	2 (17)	2 (15)	0	1 (8)	0	0	14
Lüning *et al*[65]	15	-	C: 12 I: 3	O: 16 Onlay PP 7; PE 6; VICRYL 1; CRE-PPM 2	3 (20)	-	0	-	1 (7)	1 (7)	-	NS	33
Hansson *et al*[31]	55	-	C: 47 I: 5 U: 3	L 55 IPOM; K ePTFE	20 (36)	-	0	-	2 (4)	29 (53)	-	0	36 (median)
Berger *et al*[35]	47	-	NS	L: 46 O: 1 Sandwich PVDF-PP	1 (2)	-	1 (2)	-	NS	3 (6)	-	0	20 (median)
Muysoms *et al*[27]	24	-	C:20 I: 4	L: 24 IPOM K:11 non-slit SB 13 Parietex 11; DUALMESH 10; Composix 3	10 (42)	-	NS	-	NS	2 (8)	-	5[2] (21)	K: 31 SB: 14
Guzmán-Valdivia *et al*[32]	25	-	C:25	O: 25; Sublay PP	2 (8)	-	2 (8)	-	0	2 (8)	-	0	12
Craft *et al*[66]	21	-	C: 5 I: 7 U: 9	L: 21; IPOM K: 5 SB: 16 DUALMESH	1 (5)	-	1 (5)	-	2 (10)	8 (38)	-	0	14
Berger *et al*[7]	66	-	C:58 I:7 U:1	L: 66; IPOM SB: 41 Sandwich: 25 DUALMESH (until 4-2004) and Polyvinylidene	8 (12)	-	1 (2)	-	2 (3)	5 (8)	-	0	24 (median)
Mancini *et al*[29]	25	-	C: 15 I: 5 U: 6	L: 25; IPOM SB DUALMESH	1 (4)	-	1 (4)	-	1 (4)	3 (12)	-	1[2] (4)	19 (median)
van Sprundel *et al*[37]	16	-	C: 8 I: 5 U: 4	O: 16; IPOM K DUALMESH	1 (6)	-	0	-	0	5 (31)	-	0	29 (median)
de Ruiter *et al*[33]	46	-	C: 46	O: 46 Onlay CRE-PPM	7 (15)	-	0	-	3 (7)	2 (4)	-	0	51
Longman *et al*[67]	10	-	C: 7 I: 3	O: 10 Sublay K PP	0	-	0	-	0	1 (10)	-	0	30 (median)
LeBlanc *et al*[28]	12	-	C: 8 I: 2 U: 2	L: 12 IPOM SB 7, K 5 e-PTFE	1 (8)	-	0	-	0	2 (17)	-	1[2] (8)	20
Stelzner *et al*[36]	20 (19)	-	C: 20	O: 20 IPOM SB e-PTFE	3 (16)	-	1 (5)	-	0	3 (16)	-	0	42
Steele *et al*[30]	58	-	C: 31 I: 27	O: 58 Onlay "Stove pipe hat" PP	15 (26)	-	2 (3)	-	0	9 (16)	-	0	51
Hofstetter *et al*[38]	13	-	C: 13	O: 13 IPOM K e-PTFE	0	-	0	-	0	0	-	0	NS

Asif *et al*[17]	33		C: 12 I: 21	L: 33 SB:14 K:19 DUALMESH	11 (33)[4]	-	4 (12)		0	9 (27)		0	SB: 7 K: 36
Weighted pooled % (95%CI)					15.1% (9.7-21.6)		2.8% (1.6-4.4)		3,1% (1.8-4.6) FE	17,8% (12.0-24.4)		1.9 (0.9-3.2)	
Smart *et al*[4]	27	-	C: 20 I:7	O: 20 Onlay: K; Permacol	15 (55)	-	1 (4)	-	0	0	-	1[2] (4)	17
Taner *et al*[25]	13	-	NS	O: 13 Overlay + Underlay (sandwich) AlloDerm	2 (15)	-	1 (8)	-	0	4 (31%)	-	0	10
Aycock *et al*[18]	11	-	C:2 I:9	O: 11 Inlay 8; Onlay 3; AlloDerm	3 (27)	-	2 (18)	-	NS	1 (9)	-	0	9
Araujo *et al*[24]	13	-	C: 13	O: 13 Onlay; Peri-Guard	1 (8)	-	0	-	NS	NS	-	0	50
Ellis[19]	20	-	C: 17 I: 3	O: 20 IPOM; SB; Surgisis	2 (10)	-	0	-	0	4 (20)	-	0	18
Weighted pooled % (95%CI)					24% (8.6-44.1)		5.6% (1.4-12.1)		0% (0-5.4) FE	13.4% (1.9-32.7)		2.6% (0.3-6.9) FE	

Synthetic mesh repair: [1]With regard to lost after follow-up; [2]Unrelated to mesh; [3]Seroma 41 (48, 74, 121, 149, 171, 178, 201, 257); Cardiopulmonary 11 (48, 121, 171, 203, 487); Urinary tract infection 1 (243); Cutaneous/ fascial dehiscence 1 (252); Stoma complication 8 (121, 243, 245, 285); Ileus 13 (48, 87, 171, 212, 272); Post-operative bleeding 5 (48, 121, 171); Haematoma 6 (74, 171); Bowel stenosis 19 (121, 161, 178, 203, 207, 243, 272, 285, 487); Fistula formation 2 (285); Renal failure 4 (179, 203); Peritonitis 3 (121, 171); Other 18 (87, 171, 203, 207, 212, 243, 257, 272, 487); [4]All keyhole. Biologic mesh repair: [1]With regard to lost after follow-up; [2]Unrelated to mesh; [3]Complications other: Seroma 6 (165, 429), Incisional separation 2 (165), Epidural infection 1 (242). FE: Fixed-effect model. L: Laparoscopic; O: Open; C: Colostomy; I: Ileostomy; SB: Sugarbaker; K: Keyhole PP: Polypropylene mesh; IPOM: Intraperitoneal mesh; PCM: Parietex composite mesh; ePTFE: Expanded polytetrafluoroethylene; CRE-PPM: Central ring enforced polypropylene mesh; PP + ePTFE: Polypropylene-based mesh covered with ePTFE.

reported 108 hernia recurrences after mesh repair with a weighted-pooled proportion of 15.1% (95%CI: 9.7-21.6) (Figure 5). From the 19 studies that described hernia recurrence, 10 studies reported treatment. Three studies described 34 reoperations because of symptomatic hernia not further specified[30-32]. Two studies reported 2 patients who required reoperation that involved relocation of their stoma and mesh repairs[27,28]. Van Sprundel *et al*[33] noted one hernia recurrence due to a wide circle cut in the mesh, and in a second operation, the hernia content was removed, and the circle was narrowed with sutures. Ruiter and co-workers reported 5 patients who had the prosthesis definitively removed (not specified), 1 patient who had a smaller-sized prosthesis implanted and 1 patient who had only the hernia sac closed after midline laparotomy. Muysoms *et al*[27] noted one patient with a recurrence in whom a second laparoscopy was performed because of obstructive symptoms and was treated with a modified Sugarbaker technique. Another patient needed a laparotomy for a colonic abscess due to Crohn's disease. After colonic resection and mesh removal, a translocation of the colostomy was performed. Two reoperations for parastomal hernia recurrences were described by Fei *et al*[34] and Berger *et al*[35] due to the breakdown of the sutures used for closing and keeping the mesh in place. Berger *et al*[35] reported three other patients who were treated with the sandwich technique and one with the Sugarbaker technique. All other described hernia recurrences were asymptomatic and treated conservatively.

Surgical wound infection was mentioned in eleven studies reporting 17 patients with a weighted-pooled proportion of 2.8% (95%CI: 1.6-4.4). Four studies reported treatment of wound infection[5,26,29,32]. Two patients were treated by surgical drainage, and five were treated with systemic antibiotics. Pastor *et al*[26] reported 1 patient with a parastomal abscess and subsequent fistula development repaired by laparotomy, transection of the fistula tract, and re-siting of the ileostomy[26]. Sixteen mesh infections were observed with a weighted-pooled proportion of 3.1% (95%CI: 1.8-4.6), resulting in mesh removal from 14 patients. Other complications [17.8% (95%CI: 12.0-24.4%)] were seroma (31.1%), cardiopulmonary event (8.3%), urinary tract infection (0.8%), cutaneous/fascial dehiscence (0.8%), stoma complications (6.1%), ileus (9.9%), peritonitis (2.3%), post-operative bleeding (3.8%), haematoma (4.5%), bowel stenosis (14.4%), fistula formation (1.5%), renal failure (3%) and other (13.6%). Five of the 41 seromas were treated by surgical drainage, 12 were conservatively treated, and 24 did not have any reported treatment[8,32,34,35].

Comparison of biologic mesh repair and synthetic mesh repair: When comparing the prevalence of

Table 4 Summary of pooled proportions of outcome measures of biologic mesh repair *vs* synthetic mesh repair

Hernia repair	No of studies	No of mesh repairs	Recurrence	Complications		
				Wound infection	Mesh infection	Other
Biologic mesh	5	84	24% (8.6-44.1)	5.6% (1.4-12.1)	0% (0-5.4) FE	13.4% (1.9-32.7)
Synthetic mesh	21	669	15.1% (9.7-21.6)	2.8% (1.6-4.4)	3.1% (1.8-4.6) FE	17.8% (12.0-24.4)
P value			0.01	0.32	0.39	0.15

Two-tailed Fisher's exact test was used because of too small frequencies. FE: Fixed-effect model.

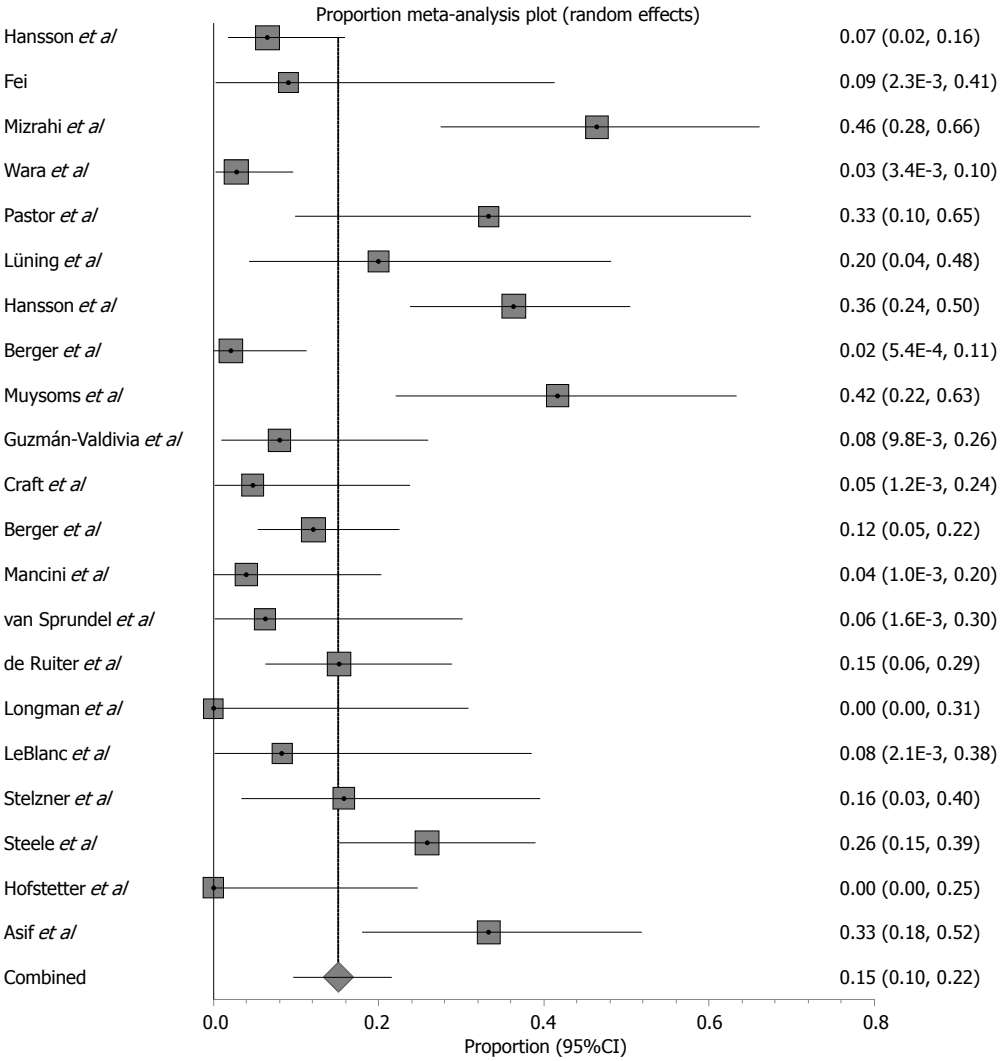


Figure 5 Proportion of hernia recurrences after synthetic mesh repair of parastomal hernia. The square shape represents the weight of the study, and the horizontal line through the square represents the confidence interval of the effect estimate (random-effects model; Cochran's *Q* test = 90.8; I^2 = 78%; $P \leqslant 0.0001$).

hernia recurrence, synthetic mesh repair resulted in a significantly lower rate compared to biologic mesh repair (OR = 1.96; 95%CI: 1.16-3.30; *P* = 0.01). No significant difference was found concerning wound infection (OR = 1.76; 95%CI: 0.58-5.38; *P* = 0.32), mesh infection (OR = 0.29; 95%CI: 0.02-4.83; *P* = 0.39) or other complications (OR = 0.59; 95%CI: 0.29-1.22; *P* = 0.15) (Table 4).

Anatomic position of the prosthesis

Various mesh positions were applied concerning biologic mesh repair, including inlay, onlay, sublay and underlay (intraperitoneal) placement of the mesh. Two retrospective series reported on 40 cases that involved onlay mesh repairs. Hernias recurred in 31.3% (weighted pooled proportion, 95%CI: 0.9-78.8) of patients. Smart *et al*[4] placed 16 stomas lateral to the rectus sheath, which showed a high recurrence rate (75%) compared to 11 stomas within the rectus sheath (27%)[4,24]. Ellis *et al*[19] placed the mesh intraperitoneally using the Sugarbaker technique. Two of 20 (10%) patients had a recurrent hernia after a

Table 5 Summary of pooled proportions of outcome measures of open synthetic mesh repair *vs* laparoscopic synthetic mesh repair

Hernia repair	No. of studies	No. of mesh repairs	Recurrence	Complications		
				Wound infection	Mesh infection	Other
Open repair	9	213	13.5% (8.1-20.2)	3% (1.2-5.7) FE	2.3% (0.7-4.8) FE	12.8% (7.4-19.4)
Laparoscopic repair	10	397	18% (8.9-29.5)	2.4% (0.804.8) FE	3.6% (1.9-5.7) FE	23.8% (14.5-34.6)
P value			0.37	0.79	0.5	⩽ 0.0001

FE: Fixed-effect model.

follow-up of 18 mo. The sandwich technique, which combines the onlay and sublay technique, was reported by Taner *et al*[25]. After a mean follow-up of 10 mo, two of 13 (15%) patients had a recurrent hernia. One other study reported multiple surgical techniques (including inlay and onlay) and did not allow for stratified outcome extraction[18]. Considering the anatomical position for open synthetic mesh repair, 3 retrospective studies using a series of onlay synthetic mesh repairs, reporting a total of 119 repairs, were included in this study. Hernias recurred in 21.5% (weighted pooled proportion, 95%CI: 14.7-29.3) of patients. In three studies, the mesh was placed in the sublay position, and 3 hernia recurrences with a weighted-pooled proportion of 8.1% (95%CI: 2.1-17.4) were reported.

The mesh was placed intraperitoneally by the open approach in three studies reporting 48 repairs (19 Sugarbaker and 29 keyhole technique repairs)[36-38]. The weighted-pooled proportion of recurrence was 8.8% (95%CI: 1.8-20.2). Seven studies described laparoscopic synthetic mesh repair using the Sugarbaker technique, and the weighted-pooled proportion of hernia recurrence was 10.9% (95%CI: 3.7-21.4). The keyhole technique was used in 8 studies, and hernia recurrence was reported in 35.6% (weighted pooled proportion; 95%CI: 14.6-60.1).

Surgical approach

All biologic mesh repairs were *via* the open approach. Considering the surgical approach used for synthetic mesh repair, 9 studies reported open repairs, 10 studies reported laparoscopic repairs, and 2 studies reported combined open and laparoscopic repairs. Unfortunately, separate data of the different approaches in these last two studies could not be extracted. Within the nine studies that reported 213 open synthetic mesh repairs, hernias recurred in 13.5% (weighted pooled proportion; 95%CI: 8.1-20.2) of patients. Wound infection, mesh infection and other complications were reported in 3% (95%CI: 1.2-5.7), 2.3% (0.7-4.8) and 12.8% (95%CI: 7.4-19.4) of the cases, respectively. Ten studies reported 397 laparoscopic synthetic mesh repairs. The weighted-pooled proportion of hernia recurrence was 18% (95%CI: 8.9-29.5). Wound infection, mesh infection and other complications were reported in 2.4% (95%CI: 0.8-4.8), 3.6% (95%CI: 1.9-5.7) and 23.8% (95%CI: 14.5-34.6) of the cases, respectively.

Comparison of surgical approach: Comparing open *vs* laparoscopic mesh repair did not result in a significant difference in hernia recurrence (OR = 0.81; 95%CI: 0.51-1.28; *P* = 0.37), wound infection (OR = 1.17; 95%CI: 0.38-3.62; *P* = 0.79) or mesh infection (OR = 0.67; 95%CI: 0.21-2.14; *P* = 0.50). A significantly (OR = 0.39; 95%CI: 0.25-0.63; *P* ⩽ 0.0001) lower occurrence rate of other complications was observed with open repair (Table 5). Regarding laparoscopic synthetic mesh repair, the Sugarbaker technique resulted in a significantly lower recurrence rate of parastomal hernia compared to the keyhole technique (OR = 0.35; 95%CI: 0.21-0.59; *P* ⩽ 0.0001).

Prophylactic mesh placement

Eighteen studies reported a total of 500 prophylactic mesh placements, which included 13 studies consisting of 382 patients with synthetic mesh repair and 5 studies consisting of 118 patients with biologic mesh repair. The follow-up ranged from 7-65 mo.

The overall mortality was 2.5% (21 deaths, weighted pooled proportion, 95%CI: 1.3-4.2) None of the deaths were related to the mesh. Two postoperative deaths were due to progressive metastatic disease, one was due to a pulmonary thromboembolism, and two were due to cardiopulmonary complications[22,23,39-41]. Jänes *et al*[42] reported five deaths due to septic or cardiovascular complications not further specified. Fleshman *et al*[20] described eleven deaths, none of which were related to the device or treatment not further specified.

Study characteristics and outcomes, including weighted-pooled rates of hernia occurrence and wound-related complications, are shown in Table 6. When comparing prophylactic placement of biologic mesh with synthetic mesh, there was no significant difference in hernia occurrence (OR = 0.79, 95%CI: 0.40-1.55; *P* = 0.49) or wound infection (OR = 0.30, 95%CI: 0.07-1.28; *P* = 0.10). In the mesh group, 58 hernia occurrences were observed with a weighted-pooled proportion of 11.5% (95%CI: 7.1-16.8) (Figure 6) and 31 wound infections with a weighted-pooled proportion of 6.9% (95%CI: 3.6-11.1), and no infections of the prosthesis were reported [0% (95%CI: 0-2.0)].

From the 15 studies reporting hernia occurrence, 9 elaborated on treatment received. Five studies reported 21 reoperations because of a symptomatic hernia not further specified[6,20,23,40,43]. Two studies reported 5

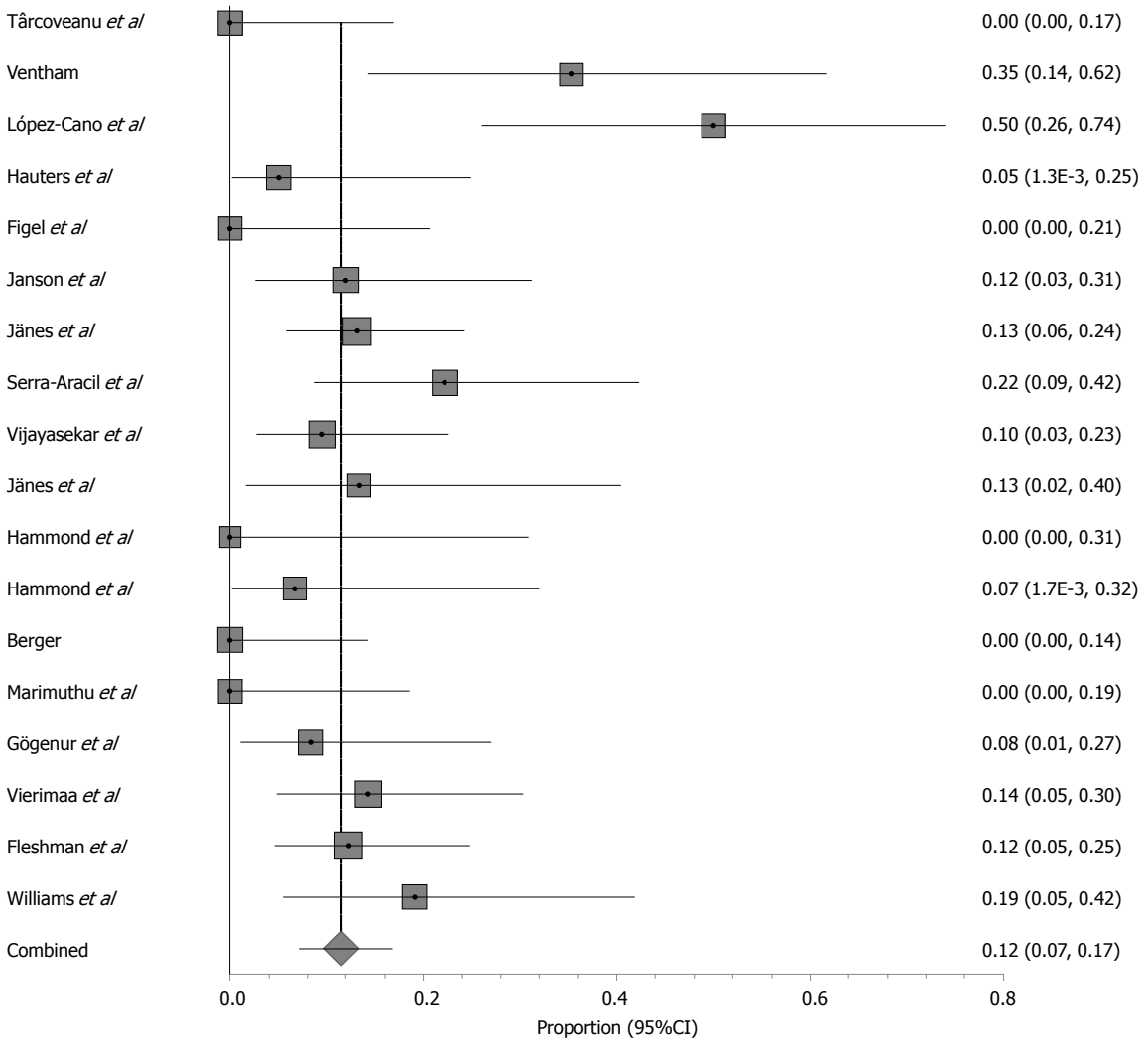


Figure 6 Proportion of hernia occurrence after prophylactic mesh placement. The square shape represents the weight of the study, and the horizontal line through the square represents the confidence interval of the effect estimate (random-effects model; Cochran's *Q* test = 45.5; I^2 = 62.7%; *P* = 0.0002).

patients who underwent reoperation involving relocation of stoma and mesh repairs[44,45]. All other reported hernia occurrences were asymptomatic and treated conservatively[6,16,22,45]. Six studies reported treatment of a wound infection[6,22,39,42,45,46]. Sixteen patients were treated conservatively, 7 patients were treated by surgical drainage, and 2 patients were treated with systemic antibiotics. Other complications were seroma (7%), cardiopulmonary event (4.7%), urinary tract infection (5.4%), cutaneous/fascial dehiscence (3.9%), stoma necrosis (12.4%), intra-abdominal/pelvic infection (1.6%) stoma-related problems (1.6%), miscellaneous (20.9%) and severe events not further specified (39.5%). All nine reported seromas were treated by surgical drainage[44].

Meta-analysis was performed on the data concerning the incidence of parastomal hernia in the seven randomized controlled trials (Figure 2). Overall, parastomal hernias occurred significantly less in the prophylactic group (weighted-pooled proportion 14.9%; 95%CI: 6.1-26.6) compared to the conventional stoma group (46.8%; 95%CI: 24.7-69.7) (OR = 0.20; 95%CI: 0.08-0.50; *P* = 0.0006). Concerning the use of prophylactic biologic mesh repair or synthetic mesh repair, there was no significant difference in parastomal hernia occurrence (OR = 0.48; 95%CI: 0.18-1.25; *P* = 0.13). Additionally, there was no significant difference found between both groups (7.8%; 95%CI: 1.8-17.5 *vs* 8.2%; 95%CI: 4.2-13.4) regarding wound infection (OR = 1.04 95%CI: 0.53-2.02; *P* = 0.91 FE).

Anatomic position of the prosthesis: Considering the surgical technique used for prophylactic mesh repair, 12 studies reported open reinforcement, and 3 studies reported laparoscopic reinforcement. Unfortunately, separate data of 2 studies combining open and laparoscopic reinforcement and 1 study combining the onlay and sublay techniques did not allow for stratification of outcomes.

Williams *et al*[41] used the stapled mesh stoma reinforcement technique (SMART) and reported 21 prophylactic mesh placements and 4 hernia occurrences.

In eleven studies, of which ten reported open and

Table 6 Study characteristics and outcomes of prophylactic mesh placement of parastomal hernia *n* (%)

Ref.	No. Patients (completed follow-up)		Type of stoma	Material; technique	Parastomal hernia[1]		Wound infection		Mesh infection	Other[3]		Mortality	Follow-up (mo)
	Mesh	No mesh			Mesh	No mesh	Mesh	No mesh	Mesh	Mesh	No mesh		
Târcoveanu *et al*[44]	20	22	C: 42	O: 42; Sublay; PP	0	6 (27)	0	2 (9)	0	9 (45)	11 (50)	0	9 (median)
Ventham *et al*[63]	17	24	C: 42	O: 42; Sublay; PP	6 (35)	13 (54)	2 (12%)	1 (4)	NS	0	0	0	12
López-Cano *et al*[40]	19 (18)	17 (16)	C: 36	L: 36; IPOM; SB; Proceed	9 (50)	15 (94)	8 (44)	3 (19)	0	16 (89)	5 (31)	1[2] (3)	12
Hauters *et al*[16]	20	-	C: 20	L: 17 O: 3; IPOM; SB: 20; PCM	1 (5)	-	0	-	0	6 (30)	-	0	24
Figel *et al*[62]	16	-	C: 16	O: 16; IPOM; SB: 12; K: 4; Surgisis	0	-	0	-	0	NS	-	0	38 (median)
Janson *et al*[64]	25	-	C: 25	L: 25; Sublay; ULTRAPRO	3 (15)	-	2 (8)	-	0	1 (4)	-	0	19
Jänes *et al*[42]	75 (61)	18 (12)	C: 79 I: 14	O: 93; Sublay; ULTRAPRO	8 (13)	8 (67)	6 (8)	4 (22)	0	0	0	5[2] (5)	15
Serra-Aracil *et al*[6]	27	27	C: 54	O: 54; Sublay; ULTRAPRO	6 (22)	12 (44)	4 (15)	4 (15)	0	1 (4)	1 (4)	0	29
Vijayasekar *et al*[45]	42	-	C: 33 I: 9	O: 42; Sublay; PP	4 (10)	-	1 (2)	-	0	1 (2)	-	0	31
Jänes *et al*[43]	27 (15)	27 (21)	C:54	O: 54; Sublay; Vypro	2 (13)	17 (81)	0	0	0	0	0	0	65
Hammond *et al*[68]	10	10	NS	O: 20; Sublay; Permacol	0	3 (30)	0	0	0	0	0	0	6.5
Hammond *et al*[21]	15	-	NS	O: 15; Onlay: 6; Sublay 9; Permacol	1 (7)	-	NS	-	NS	NS	-	0	7 (median)
Berger[39]	25 (24)	-	C: 24 I: 1	L: 6, O: 19; IPOM; K; DynaMesh	0	-	0	-	0	0	-	1[2] (4)	11
Marimuthu *et al*[46]	18	-	NS	O: 18; Sublay; Surgipro	0	-	1 (6)	-	0	1 (6)	-	0	16
Gögenur *et al*[22]	25 (24)	-	C: 25	O: 25; Sublay; StomaMesh	2 (8)	-	4 (17)	-	0	6 (25)	-	1[2] (4)	12
Vierimaa *et al*[23]	42 (35)	41 (32)	C: 83	L: 83; IPOM; K; DynaMesh	5 (14)	12 (38)	1 (3)	2 (6)	NS	9 (21)	10 (24)	1[2] (1)	12
Fleshman *et al*[20]	55 (49)	58 (53)	C: I:23/ C:35 I: I:19/ C:36	O: 113; Sublay; STRATTICE	6 (12)	7 (136)	2 (4)	3 (6)	0	21 (38)	30 (52)	11[2] (10)	24
Williams *et al*[41]	22 (21)	11	C: I:4/ C:7 I: I:11/ C:11	I: O = 18 L = 4 C: O = 11 SMART Onlay; Permacol	4 (19)	8 (73)	NS	NS	0	2 (9)	0	1[2] (3)	I: 18 C: 9
Weighted pooled %; (95%CI)					11.5% (7.1-16.8)	51.5% (33.7-69.1)	6.90% (3.6-11.1)	9.30% (4.8-15.1)	0% (0-2.0) FE	14.20% (5.5-26.0)	13.80% (3.0-30.7)	2.6% (1.3-4.4)	

[1]With regard to lost after follow-up; [2]Unrelated to mesh; [3]Seroma 9 (10); Cardiopulmonary event 6 (10, 436); Urinary tract infection 7 (10, 436); Cutaneous/fascial dehiscence 5 (53, 231,436); Stoma (mucosal/intestinal) necrosis 16 (53, 126, 163, 173, 227,436); Intra-abdominal/pelvic infection 2 (436, 489); Intestinal occlusion 4 (436,489); Stoma-related problems 2 (436); Other 27 (10, 53, 54, 231); Severe events not further specified 51 (488). L: Laparoscopic; O: Open; C: Colostomy; I: Ileostomy; SB: Sugarbaker; PP: Polypropylene mesh; IPOM: Intraperitoneal mesh; PCM: Parietex composite mesh; SMART: Stapled mesh stoma reinforcement technique.

one reported laparoscopic reinforcements, the mesh was placed in the sublay position, and 37 hernia occurrences with a weighted pooled proportion of 11.5% (95%CI: 6.9%-17.1%) were reported. The mesh was placed intraperitoneally in three studies. Figel *et al*[62] used the open intraperitoneal surgical technique and reported 16 stoma reinforcements without hernia occurrences. Two studies reported the laparoscopic surgical reinforcement technique. Lopez-Cano *et al*[40] used the Sugarbaker technique and reported 18 mesh placements and 9 (50%) hernia occurences. Vierimaa *et al*[23] used the keyhole technique and reported 35 mesh placements and 5 (14%) hernia occurrences.

DISCUSSION

The current study evaluated and compared all the evidence regarding the use of biologic and synthetic mesh for repair and prevention of parastomal hernia. Interestingly, the results of comparing biologic and synthetic mesh repairs showed a comparable or even superior result regarding parastomal hernia recurrence (24% *vs* 15.1%) and wound infection (5.6% *vs* 2.8%) in favour of the synthetic mesh repair. Overall, the mesh infection rate was low. Only sixteen mesh infections were reported in 753 repairs (2.1%), which resulted in fourteen mesh removals (all synthetic meshes). However, these observations should be interpreted cautiously because of the low to moderate quality of the studies.

Biologic mesh has gained widespread popularity in the context of infection and a contaminated environment because of their proposed advantages, including biocompatibility resulting in rapid vascularization and migration of host (immune) cells. It is thought that biologic prostheses are therefore less susceptible to infection than their synthetic counterparts. The ventral hernia working group regards parastomal hernia repair as potentially contaminated (grade 3) and therefore recommends biologic mesh repair[47]. Many authors believe that synthetic mesh should not be used in a contaminated environment or in close proximity to the bowel and stoma due to the risk of erosion and fistula formation. However, studies with high-level evidence are lacking, and the exact origins of these concerns are difficult to identify, are mostly anecdotal or reference old reports using inferior materials and techniques[48-50]. Primus and Harris criticized the surgical literature on the use of biologics in contaminated fields, arguing that cumulative data do not support the claim that biologics are indicated for use in contaminated fields. The primary literature varies widely in terms of sample size, diagnosis of (recurrent) PSH, methods of mesh placement, follow-up period, reported hernia recurrences and surgical site infection[51]. Rosen *et al*[52] reported a critical review of the surgical literature on biologic mesh repair, which revealed that the majority of the studies evaluating the outcomes of biologic mesh are actually reporting the repair of clean defects. This finding is very surprising given the high costs of biologic mesh, whereas the position of synthetic mesh in "clean" hernia repair has been proven. Despite the lack of high-grade evidence, biologic meshes are still preferred above synthetic mesh in contaminated fields as noted by Bondre *et al*[53], who conducted a multicentre study about practice patterns in contaminated ventral hernia repair. This review shows a comparable to superior result of synthetic mesh over biologic mesh concerning parastomal hernia recurrence. This finding is confirmed by Lee *et al*[54] in a systematic review on ventral hernia mesh repair in contaminated fields. Mesh removal due to infection is a much-feared complication. The literature suggest that biologic mesh does not prevent infection but can be more easily salvaged when infection arises[55]. This review challenges the concept that contaminated hernias should be repaired with expensive biologic mesh. Only sixteen mesh infections were seen in this current review, resulting in mesh removal from 14 patients. Concerning parastomal hernia repair, surgeons should carefully balance the risks and costs with the benefits when deciding on the choice of mesh for parastomal hernia repair.

Similar to ventral hernia repair, the prosthesis is placed in either the inlay, onlay, sublay, or underlay (intraperitoneal) position during parastomal hernia repair. None of the included studies used an inlay placement of the prosthesis. Onlay mesh repair showed the highest recurrence rate, whereas the sublay technique showed the lowest in the current study. There was no difference in wound and mesh infection rates between the various anatomic positions. However, firm conclusions cannot be drawn based on this subanalysis because these results were obtained from small groups. Each method of mesh repair has its own theoretical advantages and disadvantages. Laparotomy is avoided with the onlay technique, but it requires extensive dissection of subcutaneous tissue, which predisposes patients for haematoma and seroma formation. Disruption of skin vascularization may lead to impaired wound healing. Additionally, intra-abdominal pressure may lead to lateral detachment of the prosthesis, resulting in the higher recurrence rates. The sublay mesh technique protects the mesh from bacterial contamination while minimizing contact with the bowel because the mesh is enveloped in well-vascularized tissue, whereas the fascia and peritoneum form a natural barrier between prosthesis and abdominal organs. This technique reduces the risk of infection, adhesion or fistulation. The anatomic positions of the sublay and intraperitoneal mesh technique are more attractive because of the benefits from intra-abdominal pressures, which help to keep the mesh in place.

Concerning laparoscopic *vs* open parastomal hernia repair, this review shows similar results regarding hernia recurrence (18% *vs* 13.5%; $P = 0.37$), wound infection (2.4% *vs* 3%; $P = 0.79$) and mesh infection (3.6% *vs* 2.3%; $P = 0.50$). However, a significantly lower rate of other complications was seen with open repair

(23.8% *vs* 12.8%; $P < 0.0001$), which was mostly due to the high occurrence of seroma formation in three laparoscopic repair studies[5,8,31].

When performing laparoscopic intraperitoneal repair there was a significantly lower recurrence rate of parastomal hernia using the Sugarbaker technique compared to the keyhole technique (10.9% *vs* 35.6%, OR = 0.35; 95%CI: 0.21-0.59; $P \leqslant 0.0001$). Remarkably, it appears that all failures using the keyhole technique were related to the use of an e-PTFE-mesh. As noted by Hansson *et al*[9], using the keyhole technique estimation of the size of the hole is difficult as mesh shrinkage may result in enlargement of the central hole and reherniation.

Unfortunately, the recurrence rate is still up to one third after mesh repair of parastomal hernias. Our systematic review with meta-analysis shows that prevention of parastomal hernia by the use of mesh at the time of stoma formation reduces the incidence of parastomal hernia significantly compared to the conventional stoma group (14.9% *vs* 46.8% OR = 0.20; 95%CI: 0.08-0.50; $P \leqslant 0.0006$). Interestingly, placement of preventive mesh did not result in increased wound infection or mesh infection. Recently published reviews also confirm our conclusion that prophylactic insertion of a mesh when forming a stoma prevents parastomal hernia without increasing the incidence of wound infections or other mesh-related complications[56,57].

One point of discussion remains whether universal reinforcement is expedient and cost-effective. Other non-mesh prophylactic measures can be considered, such as lateral rectus abdominis positioned or extra-peritoneal positioned stomas[58,59]. Most patients who develop a parastomal hernia are asymptomatic. However, complications due to an untreated parastomal hernia (incarceration, obstruction, strangulation) can be severe and are associated with significant morbidity and mortality. Identification of patients in whom reinforcement is beneficial is essential as the patient can avoid unnecessary longer operative time, costs and possible long-term complications associated with mesh placement. As noted by Hotouras *et al*[60], risk factors for parastomal hernia formation include abdominal obesity, increasing age, corticosteroid use, poor nutritional status, increased intra-abdominal pressure, connective tissue disorders and other disorders that predispose patients to wound infection such as diabetes. Factors that need to be considered include the reason for the stoma (temporary or permanent stoma), patient co-morbidity, chance of reoperations and risk factors concerning parastomal hernia formation. Patients undergoing stoma formation with short life expectancies will often not survive long enough to develop a parastomal hernia, and patients who are healthy enough to undergo stoma reversal before hernia occurrence would not benefit from prophylactic mesh placement.

Median direct costs for complex ventral hernia repairs with biologic mesh ($16970) is more than twice the amount compared to repairs with synthetic mesh ($7590)[61]. Parastomal hernia repair probably costs less due to the need for smaller meshes; however, a substantial cost difference is expected to remain. Figel *et al*[62] calculated that by using a bio-prosthetic and considering a 30% incidence of surgical management of parastomal hernia repair, it would be cost-effective if the prosthesis cost less than $4312. The decision to place prophylactic mesh after stoma formation must be patient tailored and may certainly be justified in selected patients. However, standard application in all patients does not seem warranted. More randomized controlled trials with adequate power for risk stratification and subsequent costs of usage of biologic and synthetic mesh are needed.

Most of the studies that were included are retrospective cohorts (level 3 evidence), which could introduce selection and information bias and are affected by heterogeneity. Most study populations were diverse with different types of stomas and indications for the initial surgery. The high recurrence rate regarding biologic parastomal mesh repairs was mostly determined by one study: A 75% recurrence rate of 16 stoma repairs lateral to the rectus sheath compared to a 27% rate when the repair was within the rectus sheath. As noted by Smart *et al*[4], parastomal hernia repairs where the stoma is lateral to the rectus sheath had a significantly higher risk of recurrence and suggested that this higher risk was likely due to the inherent strength of the tissue onto which the onlay mesh was sutured.

Unfortunately, reporting was insufficient to allow proper stratification for individual risk factors for parastomal hernia. Follow-up time and diagnostic modalities used for determining recurrence rates had a strong impact on the outcome. The longer the follow-up period was, the more recurrences were found. In addition, the diagnostic modalities differ in terms of sensitivity and specificity. Some recurrences found may be of no clinical relevance. Reported follow-up periods within and between studies varied from 7 mo to 51 mo. As recurrence occurs mostly in the first years after operation a minimum follow up of 12 mo seems appropriate.

Definitions of parastomal hernia, wound infection and mesh infection were ill-defined in most studies, and the modality of determining hernia recurrence (*e.g.*, clinical evaluation or CT imaging) was often not clearly stated. Therefore, the results of this review should be interpreted with care.

In an effort to reduce the effect of low quality studies, we excluded the high risk of bias randomized controlled trials for the prophylactic mesh meta-analysis. Only three studies considered of sufficient methodological quality remained, and a second meta-analysis was performed[20,23,40]. No significant difference was found in the occurrence of parastomal hernia when comparing the prophylactic group to the conventional

group (OR = 0.33; 95%CI: 0.09-1.20; *P* = 0.09).

However, provided the large amount of parastomal hernia repairs included in the current report, meaningful conclusions may be drawn regarding optimal surgical management of synthetic and biologic mesh repair in parastomal hernia recurrence.

Clinical implications

The current evidence suggests there is no superiority of (more expensive) biologic mesh over synthetic mesh for parastomal hernia repairs after parastomal hernia recurrence, wound infection and mesh infection. In the context of cost-effective healthcare, careful consideration must be taken in choosing the types of materials to use[55]. Sublay seemed to be the most advantageous anatomic position of the mesh, as this position resulted in the lowest recurrence and protects the mesh from bacterial contamination while minimizing contact with the bowel. No difference was found for parastomal hernia recurrence between open or laparoscopic parastomal hernia repairs. When performing laparoscopic repair, the keyhole technique should be abandoned in favour of the Sugarbaker technique when using an ePTFE-mesh because of much higher recurrence rates. As shown by Wara *et al*[5], the keyhole technique can be considered when using a polypropylene-based mesh or with open parastomal keyhole hernia repairs.

Prophylactic mesh placement at the initial surgery significantly reduced parastomal hernia occurrence on the mid-long term without increasing wound infection or mesh infection. However, it has yet to become clear what the long-term results will be. The number of recurrences will increase over time, though at a slower pace than in the first few years after mesh placement. The same applies to some specific long-term side effects such as mesh infection and mesh-related fistulas. Although their incidence may be low, their impact is disproportionately high.

Identification of patients in whom reinforcement is mandatory is essential, as the patient can avoid unnecessary longer operative time, costs and possible long-term complications associated with mesh placement.

Altogether there is still not enough evidence to recommend the use a biologic mesh over synthetic mesh under contaminated conditions in general and specifically not for parastomal hernia repair. Prophylactic mesh reinforcement during stoma formation significantly reduces parastomal hernia occurrence regardless of mesh type. Yet, a significant number of patients will develop asymptomatic parastomal hernia and there are no data on long term effects of preventive mesh placement. Therefore, it is essential to select the right patient for whom prophylactic reinforcement is mandatory.

COMMENTS

Background

Parastomal hernia develops in 50% of patients. Hernias are often asymptomatic and managed with conservative treatments; however, 11% to 70% of patients undergo surgery due to discomfort, pain, obstructive symptoms and cosmetic dissatisfaction. Although standard care is mesh repair, prevention by prophylactic mesh placement is gaining popularity. The use of biologic mesh is becoming more popular as it claims less infections with sustained durability of the repair compared to synthetic mesh. The primary aim of the current study was to compare biologic and synthetic mesh use for the treatment and prevention of parastomal hernia by systematic review and meta-analysis of available data in the literature. The secondary aim was to evaluate different anatomical positions and surgical techniques concerning parastomal hernia repair.

Research frontiers

The recurrence rate of parastomal hernia is the lowest after mesh repair (0%-33%), whereas primary fascial closure (46%-100%) and relocation of the stoma (0%-76%) result in much higher rates. Although low recurrence rates are reported after synthetic mesh repair, concerns have been raised regarding the safety of synthetic meshes in (potentially) contaminated fields due to the risk of mesh infection and subsequent removal.

Innovations and breakthroughs

Biologic mesh was first introduced in the 1980s and was developed with the concept that due to its bio-degradable nature, it has the potential to ameliorate problems in infected and contaminated fields. No clear answer can be given as to whether there is a difference in the clinical outcomes between synthetic and biologic mesh repairs. The high prevalence of parastomal hernia and difficulty of repair have led to a shift of focus from repair towards prevention using prophylactic mesh reinforcement at the time of stoma formation.

Applications

This review and meta-analysis suggests there is no superiority of biologic over synthetic mesh for parastomal hernia repair after parastomal hernia recurrence, wound infection and mesh infection. Prophylactic mesh reinforcement during stoma formation significantly reduces parastomal hernia occurrence regardless of the mesh type. Identification of patients for whom reinforcement is mandatory is essential, and mesh reinforcement should be reserved for selected patients.

Terminology

Ostomy formation requires the creation of a full-thickness defect within the abdominal wall. Parastomal hernia is a type of incisional hernia that allows protrusion of abdominal contents through an abdominal wall defect that is created. Both synthetic mesh and biologic mesh (acellular collagen matrix) are used in parastomal hernia repair. There are various approaches regarding the anatomic position of the mesh during parastomal hernia repair. Meshes can be implanted in an inlay (between the fascia), onlay (over the fascia), sublay (below the anterior fascia and muscular level but above peritoneum) or underlay (intraperitoneal) position. Laparoscopic repair involves the intraperitoneal technique, and open repair may involve any of the anatomical planes of the mesh. When performing intraperitoneal repair, the choice can be made between the Sugarbaker and keyhole repair technique.

Peer-review

In this systematic review, the authors have presented a thorough and critical analysis of biologic and synthetic mesh use for the treatment and prevention of parastomal hernias. With a focus on hernia recurrence in the absence of rigorous data in the literature, the current review contributes to the increased understanding of parastomal hernias.

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META-ANALYSIS

Complete revascularization reduces adverse outcomes in patients with multivessel coronary artery disease

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Abstract

AIM

To investigate the influence of complete and incomplete revascularization (ICR) in patients with multivessel coronary artery disease undergoing coronary artery bypass or percutaneous coronary intervention.

METHODS

We searched PubMed using the keywords "complete revascularization", "incomplete revascularization", "coronary artery bypass", and "percutaneous coronary intervention". We selected randomized controlled studies (RCT) and observational studies only for review. The main outcomes of interest were mortality, myocardial infarction (MI) and repeat revascularization. We identified further studies by hand searching relevant publications and included those that met with the inclusion criteria in our final analysis and performed a systematic review.

RESULTS

Ten studies were identified, including 13327 patients of whom, 8053 received complete revascularization and 5274 received ICR. Relative to ICR, CR was associated with lower mortality (RR: 0.755, 95%CI: 0.66 to 0.864, P = 0.765, I^2 = 0.0%), lower rates of MI (RR: 0.759, 95%CI: 0.615 to 0.937, P = 0.091, I^2 = 45.1%), lower rates of MACCE (RR: 0.731, 95%CI: 0.668 to 0.8, P = 0.453, I^2 = 0.0%) and reduced rates of repeat coronary revascularization (RR: 0.691, 95%CI: 0.541 to 0.883, P = 0.0, I^2 = 88.3%).

CONCLUSION

CR is associated with lower rates of adverse outcomes. CR can be used as a standard in the choice of any particular revascularization strategy.

Key words: Complete revascularization; Percutaneous coronary intervention; Coronary artery bypass grafting;

Incomplete revascularization

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Core tip: Completeness of revascularization has been documented to have lesser adverse post-operative/post-procedural outcomes as compared to incomplete revascularization (ICR). We conduct a systematic review with meta-analysis to analyze the outcomes in patients undergoing CR *vs* ICR, using any or both techniques. Ten studies were identified, including 13327 patients of whom, 8053 received CR and 5274 received ICR. CR is associated with lower rates of mortality, MI, repeat coronary revascularization procedures, and MACCE. Subgroup analysis also showed reduced rates of adverse events. CR can be used as an aim for any myocardial revascularization procedure.

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INTRODUCTION

Complete revascularization arose from early studies on coronary artery bypass grafting (CABG) surgery whereby some studies demonstrated that patients who were completely revascularized enjoyed a mortality benefit over those who were incompletely revascularized[1-3]. Data from the coronary artery surgery study (CASS) registry show that patients with multi-vessel coronary artery disease (CAD) and severe angina that received three or more grafts had better survival relative to patients who received one or two grafts[4]. Although CR is often easier to achieve with CABG than with percutaneous coronary intervention (PCI), with recent developments in percutaneous transluminal coronary angioplasty procedures, such as the new era of drug eluting stents (DES), the previous barriers of PCI in the treatment of multi-vessel disease are no longer insurmountable, and favorable outcomes have been recorded across multiple centers using this revascularization approach[5].

Different established standards are used to determine the degree of completeness of revascularization. Conventionally, perfusion districts are divided into three areas according to the supply of the coronary artery branches namely the left anterior descending (LAD), the left circumflex (LCX) and the right coronary artery (RCA). The most commonly used definition across studies is the (1) anatomical definition, and was used in 90% of the studies included in our meta-analysis. According to this definition, CR has been achieved if all diseased arterial segments with a vessel size (greater/equal to 1.5 mm for a graft and 2.0-2.25 mm for a stent) with at least one significant stenosis greater than or equal to 50% receive a graft or a stent. A second definition of CR is (2) numerical whereby the number of distal anastomoses is greater or equal to the number of diseased coronary segments/systems and was used in 10% of the studies included in our meta-analysis. Other definitions include the (3) functional definition whereby all ischemic myocardial territories are grafted (or stented); areas of old infarction with no viable myocardium are not required to be perfused, the (4) score-based definition whereby the stenosis in different vessels is scored and different weights are given to different vessels according to number of myocardial segments supplied (A residual score of 0 is usually considered equivalent to CR) and the (5) physiology-based definition whereby all coronary lesions with fractional flow reserve of less than equal to 0.75-0.80 receive a graft or stent.

Due to procedural difficulties associated with each technique (CABG and PCI), complete revascularization is not always achieved. Previous studies have tried to assess the outcomes following incomplete revascularization (ICR). However, since there is no specific definition for ICR, which is essentially defined as "failure to achieve complete revascularization", it lacks objectivity as it relies on post-procedural classification of CR by the treating surgeon/physician. The SYNTAX trial, which used a more accurate method to determine the completeness of revascularization (patients were categorized as incompletely revascularized when the number of diseased segments that were treated did not match the heart team decision), and the BARI trial reported no increase in adverse outcomes in incompletely revascularized patients.

There is discrepancy between the results of different studies concerning the superiority of CR over ICR. In our meta-analysis, we aim to determine whether CR, is associated with improved post-procedural outcomes. In a subgroup analysis, we also investigate the mid/long-term outcomes of CR, along with outcomes in a > 60 years old patient population.

MATERIALS AND METHODS

We identified four types of studies on the PubMed database: Randomized controlled trials, observational studies, controlled clinical trials and clinical trials. The study was conducted in March 2016, using the keywords "coronary artery bypass", "percutaneous coronary intervention", "complete revascularization", "incomplete revascularization". The total number of records identified was fifty-four. We limited our search to the specific above-mentioned study types. Six of these studies met with our inclusion criteria. Through Hand-search (a methodological approach previously validated), we searched through journals related to our subject-matter and identified relevant studies and also searched the latter's references. An additional four manuscripts were selected using the above-mentioned method[6]. A total of

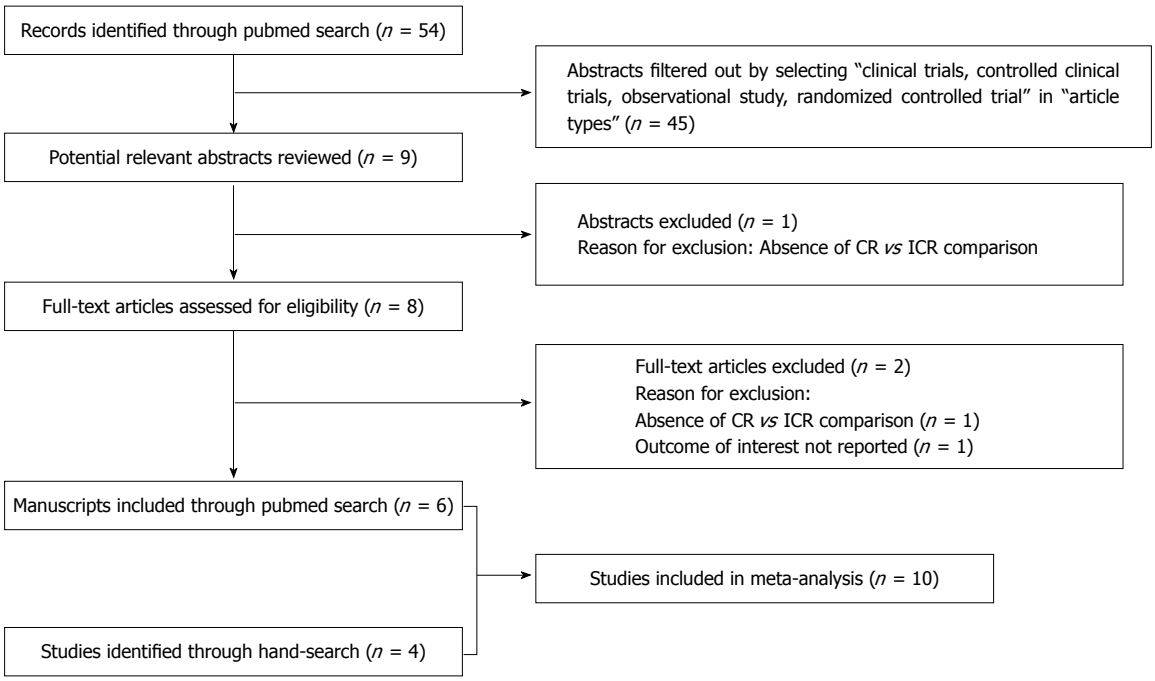


Figure 1 Flow diagram of literature search and study selection. ICR: Incomplete revascularization.

ten studies were included in our final analysis.

Data sources and study search strategy

We included two types of studies in our meta-analysis, namely randomized controlled trials and observational studies in which: (1) Patients with multi-vessel CAD were enrolled for either CABG or PCI; (2) the outcomes of interest between CR and ICR were compared using any of the definitions of CR (see introduction for definitions of CR used); and (3) the outcomes included the primary outcome of interest and/or the secondary outcomes. We excluded studies in which: (1) multiple grafts were used for treatment of multi-vessel CAD without any reference to CR and/or ICR; (2) PCI was used for the treatment in the setting of ST-elevation acute myocardial infarction (MI); (3) outcomes of interest were not reported unless there was reference to CR and ICR; (4) the patients included were undergoing repeat CABG surgery; and (5) the sample size was small (< 100 patients).

Study selection

Our initial search using the keywords: Complete revascularization, ICR, coronary artery bypass, PCI yielded fifty-four citations on PubMed. Using the filter for article types, we selected clinical trials, controlled clinical trials, observational studies and randomized controlled trials only. Of the fifty-four citations, nine citations remained, and the abstracts from these nine citations were reviewed. Of these, one abstract was excluded due to absence of comparison between complete and ICR. The remaining eight full text manuscripts were reviewed for eligibility. Of these eight manuscripts, six met with our inclusion criteria. We hand-searched references cited in relevant publications and an additional four manuscripts that fit our inclusion criteria were included. A total of ten studies were selected and included in this meta-analysis (Figure 1).

Data extraction

The data was extracted by Merveesh L Auchoybur using standardized extraction forms. Extracted information included study design, method of revascularization and definition of CR used by each study, follow-up time, patient characteristics pre-operatively, and outcomes relevant to this meta-analysis. The subjects were divided into two groups, namely the complete revascularization group for those subjects who received complete revascularization and the ICR group for those subjects who were not completely revascularized. In studies where complete revascularization through CABG and PCI were reported separately, the sum total of completely revascularized patients was used for the complete revascularization group and the remaining patients were added to the ICR group.

Outcomes

The primary outcome used in this systematic study was all-cause mortality. Secondary outcomes were MI and repeat revascularization. Major adverse cardiovascular and cerebral events were also analyzed where present.

Methodological quality

In this meta-analysis, both χ^2 based *Q*-statistic test and I^2 test were considered to assess the heterogeneity across studies, and *P*-value less than or equal to 0.05 was considered significant. I^2 is a description of the variation present across studies that is due to heterogeneity

Table 1 Studies included in meta-analysis

Ref.	Type of search	Method of revascularization	Study design	Year	Definition of CR used	Follow-up (yr)
Bell *et al*[24]	Hand	PCI	Post hoc analysis, non-RCT	1990	Anatomical	2.2
Approach/catherine Mclellan *et al*[25]	Hand	PCI	Post hoc analysis, non-RCT	2005	Anatomical	9
ARTS II/Sarno *et al*[26]	PubMed	CABG/PCI	Post hoc analysis, non-RCT	2010	Anatomical	5
ARTS trial/van den Brand *et al*[14]	PubMed	CABG/PCI	Post hoc analysis, RCT	2002	Anatomical	1
SYNTAX trial/Farooq *et al*[27]	PubMed	CABG/PCI	Post hoc analysis, RCT	2013	Anatomical	4
BARI/Bourassa *et al*[28]	PubMed	CABG/PCI	Post hoc analysis, RCT	1999	Anatomical	5
Bourassa *et al*[29]	Hand	PTCA	Post hoc analysis, non-RCT	1998	Anatomical	9
Head *et al*[30]	PubMed	CABG/PCI	Post hoc analysis, RCT	2012	Anatomical	3
BARI 2D/Schwartz *et al*[31]	PubMed	CABG/PCI	Post hoc analysis, non-RCT	2012	Numerical	5.3
Mohammadi *et al*[32]	Hand	CABG	Post hoc analysis, non-RCT	2012	Anatomical	5.4 ± 3.0

CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; CR: Complete revascularization; RCT: Randomly controlled trial.

Table 2 Characteristics of patients undergoing complete revascularization

Ref.	Prevalence of CR (%)	Mean age (yr)	Previous MI	No previous MI	Diabetes	No diabetes	Hypertension	No hypertension
Bell *et al*[24]	41.0	60.0	122	234	46	319	148	217
Approach/catherine Mclellan *et al*[25]	66.9	62.1	802	506	244.6	1063.4	725.94	582.06
ARTS II/Sarno *et al*[26]	72.5	61.5	149	688	163	674	440	397
ARTS trial/van den Brand *et al*[14]	77.2	61.0	385	498	143.93	739.07	-	
SYNTAX trial/Farooq *et al*[27]	61.8	65.3	521	1088	429.6	1179.4	759.45	849.55
BARI/Bourassa *et al*[28]	65.4	61.3	612	584	204.52	991.48	578.86	617.14
Bourassa *et al*[29]	17.4	56.6	62	70	15.05	116.95	55.97	76.03
Head *et al*[30]	59.9	64.9	328	713	300	438	702	356
BARI 2D/Schwartz *et al*[31]	37.9	61.21	-		-		-	
Mohammadi *et al*[32]	82.1	82.1	224	167	107.92	283.08	286.21	104.79

CR: Complete revascularization; MI: Myocardial infarction.

instead of chance (I^2 value less than 50% indicates no or little heterogeneity)[7]. Weighted relative risk (RR) and its 95% confidence interval were calculated to evaluate the effect size. A fixed effect model using Mantel-Haenszel method were used to combine values from studies when heterogeneity was absent, otherwise, a random-effects model using the DerSimonian and Laird method was used[8]. Egger's test and inverted funnel plots were utilized to provide a diagnosis of publication bias[9]. Automatic "zero cell" correction was used for studies with no events for a particular outcome. All analyses were performed using Stata version 11.1 software (Stata, College Station, TX, United States). All statistical evaluations were made assuming a two-sided test with a significance level of 0.05, unless stated otherwise.

RESULTS

Study and patient characteristics

The list of the ten studies that met with our inclusion criteria are listed in Table 1. Of the studies included, four were RCTs and six were non-RCTs. All the RCTs reported both CABG and PCI as revascularization strategies. Of the six non-RCTs included, three reported PCI, two reported both CABG and PCI simultaneously, and one reported CABG only. Of the studies comprising our analysis, nine use an anatomical definition of CR and one uses a numerical definition of CR. The current analysis includes 13327 patients of whom, 8053 (60.4%) received complete revascularization (CR) and 5274 (39.6%) received ICR. The mean age of the patients undergoing CR was 63.6 years, 20.5% had diabetes mellitus, 39.8% had suffered from previous MI, 43.5% had hypertension (Table 2). The mean age of the patients undergoing ICR was 65.1 years, 22.4% had diabetes mellitus, 46.1% had previously suffered from MI, and 52.6% had hypertension (Table 3). The mean follow-up time of the patients was 4.9 years.

Mortality

Of the ten studies included, eight reported mortality and were used for this analysis. CR is associated with reduced overall mortality relative to ICR (RR: 0.755, 95%CI: 0.66 to 0.864, P = 0.765, I^2 = 0.0%) (Figure 2). In a subgroup analysis: Mid-term follow-up of < 5 years shows that CR has lower mortality (RR: 0.710, 95%CI: 0.595 to 0.847, P = 0.701, I^2 = 0.0%). Long-term follow-up of > 5 years is associated with reduced mortality (RR: 0.824, 95%CI: 0.669 to 1.016, P = 0.660, I^2 = 0.0%). In the age group of > 60 years, CR is associated with reduced mortality (RR: 0.742, 95%CI: 0.641 to 0.859, P = 0.706, I^2 = 0.0%) (Figure 3).

Table 3 Characteristics of patients undergoing incomplete revascularization

Ref.	Prevalence of CR (%)	Mean age (yr)	Previous MI	No previous MI	Diabetes	No diabetes	Hypertension	No hypertension
Bell *et al*[24]	41.0	60.0	122	234	46	319	148	217
Approach/catherine Mclellan *et al*[25]	66.9	62.1	802	506	244.6	1063.4	725.94	582.06
ARTS II/Sarno *et al*[26]	72.5	61.5	149	688	163	674	440	397
ARTS trial/van den Brand *et al*[14]	77.2	61.0	385	498	143.93	739.07	-	
SYNTAX trial/Farooq *et al*[27]	61.8	65.3	521	1088	429.6	1179.4	759.45	849.55
BARI/Bourassa *et al*[28]	65.4	61.3	612	584	204.52	991.48	578.86	617.14
Bourassa *et al*[29]	17.4	56.6	62	70	15.05	116.95	55.97	76.03
Head *et al*[30]	59.9	64.9	328	713	300	438	702	356
BARI 2D/Schwartz *et al*[31]	37.9	61.21	-		-		-	
Mohammadi *et al*[32]	82.1	82.1	224	167	107.92	283.08	286.21	104.79

CR: Complete revascularization; MI: Myocardial infarction.

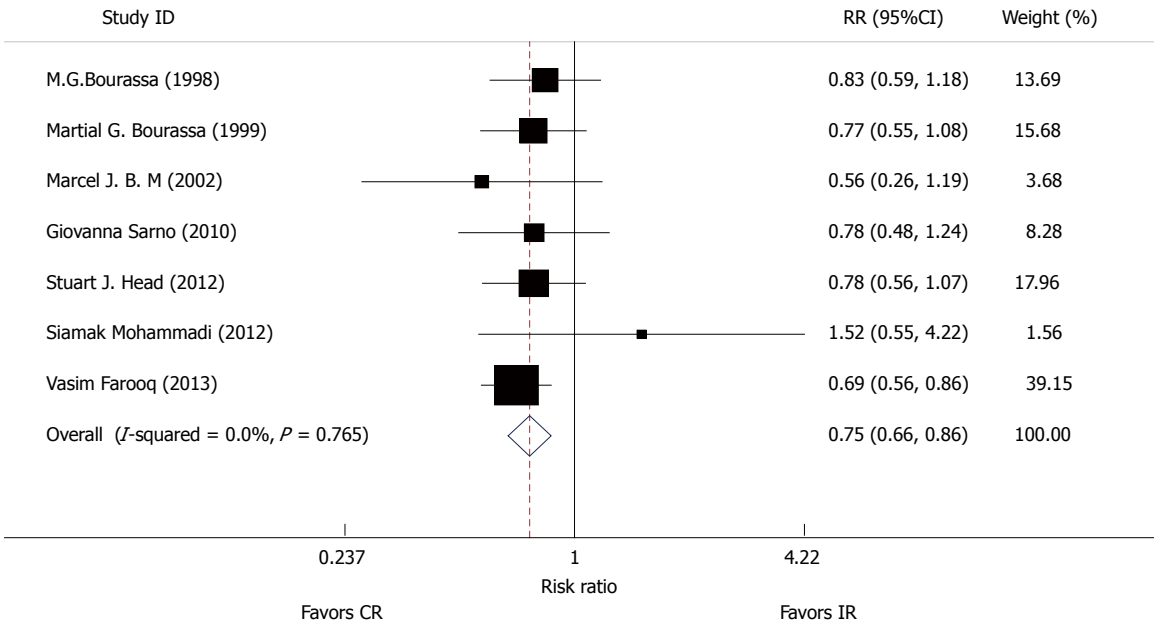


Figure 2 Pooled analysis with risk ratio and 95%CI for the occurrence of total mortality. Boxes are relative risk estimates from each study. The horizontal bars are 95%CI. The size of the box is proportional to the weight of the study in the pooled analysis. CR: Complete revascularization.

MI

Of the ten studies, seven reported MI and were used for this analysis. CR is associated with reduced rates of post-operative MI as compared to ICR (RR: 0.759, 95%CI: 0.615 to 0.937, $P = 0.091$, $I^2 = 45.1\%$) (Figure 4). In a subgroup analysis: mid-term follow-up of < 5 years group, occurrence of MI is less with CR as compared to ICR (RR: 0.608, 95%CI: 0.484 to 0.763, $P = 0.388$, $I^2 = 0.0\%$). Long-term follow-up of > 5 years shows that CR is associated with reduced rates of MI (RR: 0.894, 95%CI: 0.731 to 1.095, $P = 0.419$, $I^2 = 0.0\%$). In the age group of > 60 years, CR is associated with reduced MI (RR: 0.758, 95%CI: 0.589 to 0.974, $P = 0.053$, $I^2 = 54.1\%$).

Repeat coronary revascularization

Of the ten studies, six reported repeat revascularization and were consequently used in this analysis. CR is associated with reduced rates of revascularization (PCI and/or CABG) relative to ICR (RR: 0.691, 95%CI: 0.541 to 0.883, $P = 0.0$, $I^2 = 88.3\%$). In a subgroup analysis: Mid-term follow-up of < 5 years shows that CR is associated with less repeat revascularizations (RR: 0.827, 95%CI: 0.651 to 1.052, $P = 0.323$, $I^2 = 11.6\%$). Long-term follow up of > 5 years shows that CR is associated with less repeat revascularizations (RR: 0.827, 95%CI: 0.651 to 1.052, $P = 0.009$, $I^2 = 78.9\%$). In the age group > 60 years, CR is associated with reduced rates of repeat revascularization (RR: 0.646, 95%CI: 0.484 to 0.863, $P = 0.0$, $I^2 = 89.2\%$).

MACCE

Of the ten studies, five reported MACCE and were used in this analysis. CR is associated with reduced MACCE relative to ICR (RR: 0.731, 95%CI: 0.668 to 0.8, $P = 0.453$, $I^2 = 0.0\%$). In a subgroup analysis of MACCE: Mid-term follow-up of < 5 years shows that CR is associated with lower MACCE rates as compared to ICR

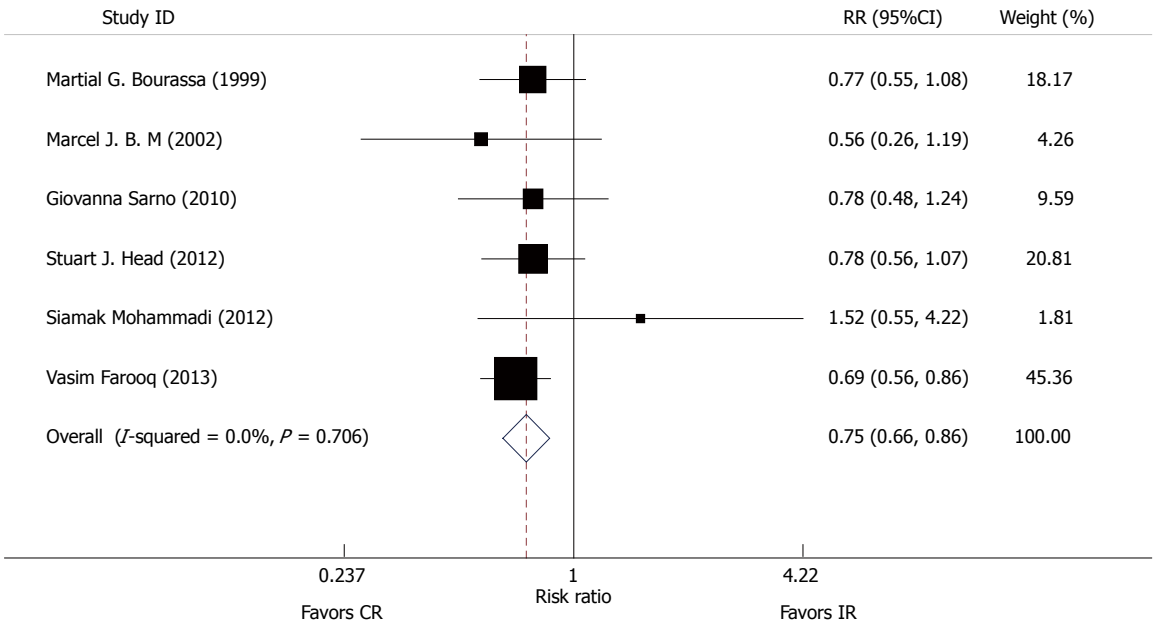


Figure 3 Pooled analysis with risk ratio and 95%CI for the occurrence of mortality in the > 60 age group. Boxes are relative risk estimates from each study. The horizontal bars are 95%CI. The size of the box is proportional to the weight of the study in the pooled analysis. CR: Complete revascularization.

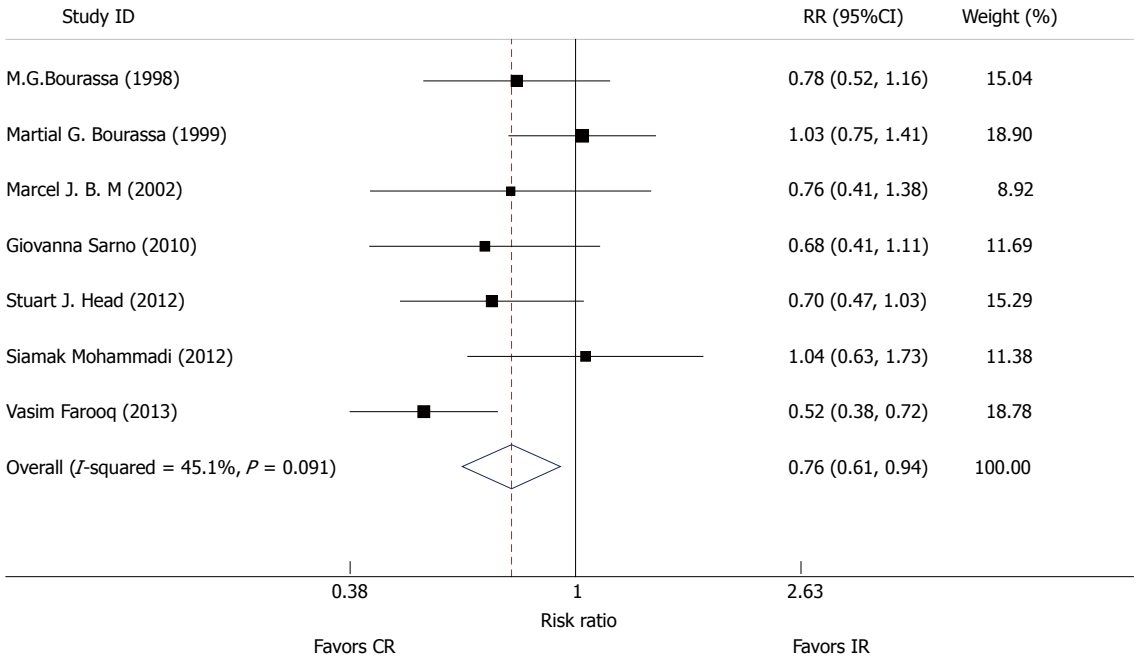


Figure 4 Pooled analysis with risk ratio and 95%CI for occurrence of myocardial infarction. Boxes are relative risk estimates from each study. The horizontal bars are 95%CI. The size of the box is proportional to the weight of the study in the pooled analysis. CR: Complete revascularization.

(RR: 0.717, 95%CI: 0649 to 0.792, P = 0.427, I^2 = 0.0%). Long-term follow-up of > 5 years shows that CR is associated with reduced rates of MACCE (RR: 0.799, CI: 0.644 to 0.990, P = 0.427, I^2 = 0.0%). In the age group of > 60 years, CR is associated with less MACCE (RR: 0.731, 95%CI: 0.668 to 0.8, P = 0.453; I^2 = 0.0%).

DISCUSSION

The results of our study comparing the outcomes of CR *vs* ICR show that CR is associated with a 25% reduction in overall mortality, 24% reduction in MI, 27% reduction in MACCE, and 31% reduction in repeat revascularization procedures. Our findings are quite similar to the paper published by Santiago *et al*[5] where they reported a 30% reduction in long term mortality, a 22% reduction in MI, and a 26% reduction in repeat coronary revascularization procedures. Moreover, the results of our subgroup analysis show that independent of the modality of revascularization, CR is associated

with better mid-term (< 5 years), long-term (> 5 years) outcomes and is also associated with lesser adverse outcomes in the > 60 years old patient population.

Conventionally, there are two distinct approaches to coronary artery revascularization, one of them being CABG and the other being PCI. Both of these revascularization strategies have their set of advantages and disadvantages. The advantages of PCI include use of local anesthesia, minimal post-procedural morbidity, and shorter hospital stay. New advancement in the form of DES has also allowed effective treatment of long diffuse stenosed segments. Despite these numerous advantages, PCI remains restricted with respect to its inability to overcome chronic total occlusions, whereby success rates vary and symptomatic failures eventually require CABG. CABG surgery, on the other hand, despite having the ability to overcome chronic occlusions, and necessitating fewer repeat revascularization procedures, is nevertheless associated with substantial postoperative morbidity, longer periods of hospitalization, and a slower return to normal activities. Multiple diseased vessel segments are challenging, requiring multiple grafts and longer operative times which translate into longer periods of CPB, and are associated with higher morbidity[10]. Among the main adverse outcomes, PCI is associated with higher rates of MI and repeat revascularization while CABG is associated with higher morbidity and risk of stroke[11]. Many variables have to be considered when selecting a patient for any procedure, which might be a cause for dissimilarities between the outcomes from different studies. Although SYNTAX reported a higher incidence of MACCE at 5 years, data concerning the incidence of death, MI and stroke at 5 years was inconsistent between these studies, even in the diabetic subgroup. In SYNTAX there was no significant difference reported at 5 years in any of the individual outcomes of death, MI, or stroke between PCI and CABG in either the diabetic or non-diabetic subgroups[12]. On the other hand, in the FREEDOM trial PCI was associated with higher incidence of death and MI with a lower incidence of stroke when compared to CABG[10]. Past studies have compared post-procedural outcomes of these two revascularization approaches[13-15]. The primary focus of our study is the clinical outcome(s) of complete revascularization as compared to ICR, achieved by any particular method of revascularization, or both methods simultaneously (hybrid procedures), rather than a comparison of CABG *vs* PCI.

Benefits of CR

The association between CR and lower risk for subsequent cardiovascular events has been documented in some studies in which the benefits of complete revascularization are reduction and often elimination of myocardial ischemia (which has been linked to worse prognosis especially when large), improvement in left ventricular function with preserved ejection fraction in heart failure patients, reduction of arrythmias, improved exercise capacity, and better tolerance to future acute myocardial ischemic events[12,16]. More importantly, the mortality benefit of CR is independent of revascularization modality and definition of CR used[17]. In a study by An Den Brand *et al*[14], the authors reported that the frequency with which CR was achieved was greater in CABG treated patients (84.1%) as compared to stented patients, despite the potential for equivalent revascularization. Although no difference in mortality or the combined endpoint of death/stroke/MI were seen, overall MACCE rates were significantly higher in the incompletely revascularized stented group, driven by an increased need for CABG within the first year of follow up.

Over the past decades, CABG has evolved to better peri-operative management, more frequent use of arterial grafting and off pump surgery, and development of minimally invasive direct coronary artery bypass grafting (MIDCAB) and robot-assisted totally endoscopic coronary artery bypass (TECAB) grafting as genuine options. PCIs, especially percutaneous transluminal coronary angioplasty (PTCA), initially developed as a strategy in the treatment of single-vessel disease. Currently, particularly with the advent of DES and new devices to treat chronic total occlusions, it is considered an alternative to CABG in the treatment of multiple vessel disease in certain cases[18,19]. These improvements in technique have increased the feasibility and practicability of complete revascularization. Although CABG and PCI have their own sets of inclusion and exclusion criteria, overlapping in selection criteria exist, where the decision to proceed with a particular technique is generally made by a heart team, consisting of both cardiac surgeons and cardiologists among others. All other factors excluded, we propose that CR/IR should influence a decision to proceed with any specific surgical approach of coronary artery revascularization.

Mid/long-term outcomes

The short-term, mid-term, and long-term outcomes of a strategy of revascularization are as important to the patient as it is to the doctor, and we consider it a pivotal factor in the decision making process. In our study, we sub-divided the follow-up time at the 5-year mark, and obtained the two sub-groups, namely the mid-term follow-up group (< 5 years) and long-term follow-up group (> 5 years). Statistical analysis was separately performed on each of the subgroups. CR was found to be associated with less mortality, post-op MI, reduced MACCE, and repeat revascularization procedures.

> 60 years old

There has been a gradual increase in the average age of patients now referred for CABG. Contemporary cohorts consist of a greater proportion of octogenarians[15,20]. The BARI trial reported no survival disadvantage associated with IR, where non-LAD territories were left ungrafted. Siamak Mohammadi *et al*[32] in their study of octogenarians undergoing CABG reported that short-term and long-term

mortality were not negatively affected by a strategy of ICR during CABG. Due to the greater number of grafted vessels, CR is associated with longer procedural times. This translates into increased duration of general anesthesia, longer cardiopulmonary bypass times, which increase the incidence of negative post-procedural complication and delay discharge from the hospital. Hence, some surgeons have advocated the concept of incomplete "reasonable" revascularization[21-23]. The results of our subgroup analysis show that there is a reduction across all negative outcomes associated with CR in patients who are > 60 years old. Despite the general trend in the elderly population, we propose CR as a precautionary measure against leaving potential myocardial regions and graftable target coronary arteries un-revascularized.

Study limitations

There are several limitations to our meta-analysis. The results are affected by variation in study design, end-point definitions and reporting and possible publication bias. Moreover, our results and analysis are limited to the papers found on the Pubmed database and those added by hand-search.

Our study is concordant with similar studies from the past, whereby CR is associated with lower mortality, reduced post-op MI and MACCE, and lower rates of repeat procedures for revascularization. Furthermore, our study shows that CR is also associated with better mid-term and long-term outcomes, and less adverse outcomes in the > 60 years of age patient population. In our experience, CR acts as a buffer between CABG and PCI, and reduces the adverse outcomes associated with any one particular technique. With this in mind, and as dictated by the patient's condition, the technique with which CR is most likely to be accomplished should be used, and hybrid techniques can be emphasized for complicated cases, thus maximizing the gains from both techniques while minimizing the drawbacks. Given the obvious benefits, CR should be considered as the standard to determine the strategy of revascularization in patients with multi-vessel CAD.

ARTICLE HIGHLIGHTS

Research background

Two strategies are used in the treatment of multivessel coronary artery disease (CAD), namely percutaneous coronary intervention with stenting and coronary artery bypass grafting. Previous studies have proved the importance of complete revascularization. However, the extent to which completeness of revascularization influences the outcomes is still unclear.

Research motivation

Nowadays with new improvements in technology and technique, the feasibility of complete revascularization is less of an issue. Hence, a thorough understanding of how complete revascularization affects post-procedural outcomes is mandatory.

Research objectives

To investigate the influence and outcomes of complete *vs* incomplete myocardial revascularization in patients with multivessel CAD.

Research methods

Database (pubmed) search coupled with hand search was performed for the identification and collection of relevant studies. Filters, inclusion and exclusion criteria were used to ensure quality and homogenecity of studies. Standard tables were used for data extraction. The data was analyzed and subjected to the appropriate tests by a statistician. A systematic review was then performed.

Research results

Ten studies were identified, including 13327 patients of whom, 8053 received complete revascularization and 5274 received ICR. Relative to ICR, CR was associated with lower mortality (RR: 0.755, 95%CI: 0.66 to 0.864, $P = 0.765$, $I^2 = 0.0\%$), lower rates of MI (RR: 0.759, 95%CI: 0.615 to 0.937, $P = 0.091$, $I^2 = 45.1\%$), lower rates of MACCE (RR: 0.731, 95%CI: 0.668 to 0.8, $P = 0.453$, $I^2 = 0.0\%$) and reduced rates of repeat coronary revascularization (RR: 0.691, CI: 0.541 to 0.883, $P = 0.0$, $I^2 = 88.3\%$).

Research conclusions

Completeness of revascularization is not mandatory for the treatment of multivessel CAD. The results of our study show that CR is associated with lower rates of adverse outcomes. The results propose that the extent to which a technique can achieve complete revascularization should be a major deciding factor in the choice of any one particular technique.

Research perspectives

Complete revascularization is an alternative standard to decide the choice of a particular technique of revascularization. With emerging techniques of coronary revascularization, new retrospective cohort studies can be performed. Further research is needed to better understand the benefits of complete revascularization with a particular technique.

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