Metabolic syndrome and pancreatic cancer risk: a systematic review and meta-analysis

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ABSTRACT

The aim of this study was to evaluate the association between metabolic syndrome and pancreatic cancer risk by conducting a meta-analysis. We searched the databases of Embase, PubMed, and Cochrane Central Register of Controlled Trials from inception to March 2017. We also searched clinical trial registries for ongoing trials. Studies investigating the association between metabolic syndrome and pancreatic cancer risk were included. Pooled relative risk (RR) was calculated using either a random-effects or a fixed-effects model. A total of 4 studies involving 622,694 participants were identified. The pooled data showed that metabolic syndrome was associated with a statistically significant 40% increase in pancreatic cancer risk (RR, 1.40; 95% CI, 1.06 to 1.86) with significant heterogeneity (I^2 =78.1%). A somewhat stronger association was observed in women (RR, 1.58; 95% CI, 1.36 to 1.84; I^2 = 0.0%) than in men (RR, 1.25; 95% CI, 0.77 to 2.04; I^2 =71.7%). Our findings support that patients with metabolic syndrome carry an increased risk for developing pancreatic cancer.

INTRODUCTION

Pancreatic cancer is the ninth most common form of cancer and seventh leading cause of cancer-related death worldwide [1]. Patients suffered from pancreatic cancer carry a dismal prognosis, with a 5-year survival rate roughly 2%–8%, and most deaths occur only 6 months after diagnosis [2]. Even for surgically resectable cases, the 5-year survival rate is merely 10–20% [3]. Currently, there are still no established screening methods for early detection. Therefore, the most effective way to reduce pancreatic cancer burden may be primary prevention by altering modifiable risk factors. Indeed, several unfavourable risk factors have been identified, including tobacco smoking, alcohol consumption, obesity, and chronic pancreatitis [4–7]. However, these established risk factors can explain only a small fraction of cases. Thus, it is imperative to identify other potential risk factors and high-risk populations, so that effective actions could be taken to prevent the development of pancreatic cancer.

Metabolic syndrome (MetS) is a cluster of interrelated risk factors that result in increased cardiovascular morbidity and mortality [8]. Essential components of MetS include central obesity, raised blood pressure, impaired glucose, high triglyceride and low high-density lipoprotein (HDL) [9]. To date, various definitions of MetS have been proposed, including the National Cholesterol Education Program-Adult Treatment Panel-III (NCEP-ATP-III), the International Diabetes Federation (IDF), the American Heart Association/National Heart Lung and Blood Institute (AHA/NHLBI) and the new Joint Interim Societies (JIS) [10]. Of these, the most widely accepted one was put forward by the NCEP-ATP III. According to its definition, MetS is defined having three or more of the following: 1) visceral obesity defined by waist circumference (population and country specific definitions); 2) blood pressure $\geq$ 130 and/or 85 mmHg; 3) fasting glucose $\geq$ 100 mg/dL; 4) triglycerides $\geq$ 150 mg/dL; and 5) low highdensity lipoprotein (HDL) cholesterol levels (men $\leq$ 40 mg/dL; women $\leq$ 50 mg/dL)

[11]. It has been estimated that MetS is prevalent in at least a quarter of adults in India, America and Europe [12]. Interestingly, evidence from epidemiologic investigations has suggested that MetS is a risk factor for developing several malignancies, including breast, colorectal and prostate cancer [13–15].

Some individual components of MetS are associated with increased pancreatic cancer risk, particularly obesity and diabetes [6, 16]. It seems self-explanatory that clustering of MetS components will carry a greater risk for developing pancreatic cancer than individuals. This is probably due to alterations in cancer-related signaling pathways and cytokines caused by MetS [17]. A body of epidemiologic studies identifying the association between MetS and pancreatic cancer risk has obtained controversial results. Therefore, we conducted a systematic review and meta-analysis to evaluate the association between MetS and pancreatic cancer risk based on available evidences.

RESULTS

Study selection

A total of 1021 records were identified from thorough database searching, no additional records were found from ongoing trials. After removing duplicates and screening the titles and abstracts, a total of 10 potentially relevant records were retrieved for detailed review. Of these, 6 studies were excluded for following reasons: 2 investigated the association between MetS and survival outcomes in pancreatic cancer [18, 19], 2 did not report pancreatic cancer risk [20, 21], and 2 did not have usable data [22, 23]. We did not identify any records from reference lists. Finally, 4 eligible studies were included in this meta-analysis. The flow diagram summarizing the selection process is given in Figure 1.

Study characteristics

A total of 4 non-randomized studies involving 622,694 participants were included in this meta-analysis, with 3 cohort studies [24–26] and 1 case-control study [27]. The studies were published between 2008 and 2011. Among them, 2 studies were performed in the Italy [24, 27], 1 in Austria, Norway and Sweden [26], and 1 in Japan [25]. The NOS values ranged from 5 to 9 stars: 1 study was awarded 5 stars, 1 study was award 6 stars, and 2 studies were award 9 stars. The characteristics of the included studies are shown in Table 1.

Meta-analysis

Four observational studies involving 622,694 participants investigated the association between MetS and pancreatic cancer risk [24–27]. The pooled data showed that MetS was associated with a statistically significant 40% increase in pancreatic cancer risk (RR, 1.40; 95% CI, 1.06 to 1.86). The Chi-square test resulted in a p value of 0.000, and the corresponding I^2 was 78.1%, both indicating that there was significant heterogeneity between studies (Figure 2). In sensitivity analysis, each study was excluded and its influence was evaluated by repeating the primary analysis. The analysis confirmed the stability of our result because none of the individual studies markedly affected the pooled effect.

Then, we performed a subanalysis based on sex. The pooled data in men showed a modest increase in pancreatic cancer risk but the data supporting this association was not as robust (RR, 1.25; 95% CI, 0.77 to 2.04). There was significant heterogeneity among the studies (I^2, 71.7%; $p = 0.014$) (Figure 3). In sensitivity analysis, the result did not change significantly after omitting any of the included studies. A stronger association was observed in women, with a significant 58% increase in pancreatic cancer risk (RR, 1.58; 95% CI, 1.36 to 1.84) (Figure 4). No statistically significant heterogeneity was detected ($I^2 = 0.0\%$; $p = 0.937$).

DISCUSSION

There is a long-standing debate regarding the association between MetS and pancreatic cancer risk. By permitting synthesis of data and providing an objective evaluation of the evidence, meta-analysis may be resolution of controversy and uncertainty [28]. This meta-analysis was conducted to examine the association between MetS and pancreatic cancer risk. Overall, our results provide supportive evidence for a positive association between MetS and pancreatic cancer risk. Our results are consistence with recent meta-analyses regarding the association between MetS and risk of other types of cancers. Similarly, they concluded that MetS was associated with increased risk of breast, colorectal, prostate, liver and endometrial cancer [29–33].

In subanalysis based on sex, MetS was, on average, associated with increased pancreatic cancer risk in men and women. However, a somewhat stronger association was observed in women than in men, which was in line with previous observational studies [25–27]. It is not clear why MetS is a more important risk factor in women. One possible explanation may be that, women produce higher levels of estrogens than men, which in turn increase circulating estradiol by reducing plasma level of sex hormone binding globulin (SHBG) [34]. Low plasma concentration of SHBG is linked to insulin resistance and subsequent hyperinsulinemia [35]. Preclinical studies demonstrated that insulin can stimulate proliferation, invasion and migration of pancreatic cancer cells *in vitro* [36]. It can also act synergistically with hypoxia-inducible factor-1 in pancreatic cancer cells to increase cell viability [37]. Another explanation may be that women have more adipose tissue than men. Adipose tissue produces leptin, which can affect pancreatic cancer biology [38]. Laboratory

studies showed that leptin signaling can enhance growth, invasion, migration and survival of pancreatic cancer cells [39]. Whether or not estrogen affects the development of pancreatic cancer or if it could modify other relevant risk factors and thus explain different risk factor profiles in women and men need to be clarified in future studies.

Generally, meta-analysis based on randomized studies is more likely to provide unbiased results and thus allows for a more objective appraisal of evidence than that of non-randomized studies. However, for those specific questions which cannot be answered by reviews of randomized studies, such as limited number of studies, non-randomized studies should be retrieved for meta-analysis. To date, no randomized studies has investigated the associated between MetS and pancreatic cancer risk. Therefore, we conducted this meta-analysis by pooling the results from 4 non-randomized studies.

Although the exact roles of MetS in pancreatic cancer remains elusive, several possible biological mechanisms linking MetS with increased pancreatic cancer risk have been proposed. First, hyperinsulinemia, which is a common phenomenon in MetS patients, may stimulate cell proliferation and promote pancreatic cancer development through increasing the production of insulin-like growth factor-1 (IGF-1) [40]. Second, MetS is frequently associated with inflammation and the malignant transformation of pancreas may due to increased oxidative stress and a subsequent reduced intracellular antioxidant capacity [41]. Reactive oxygen species generated by oxidants can lead to accumulation of mutations by causing deoxyribonucleic acid (DNA) damage, disturbing DNA repair and altering intracellular homeostasis [42]. Third, hypoadiponectinemia is a common characteristic of MetS [43]. Adiponectin level is negatively associated with insulin concentration and plasma glucose, whether this is a consequence or a cause of insulin resistance is not clear [44]. Previous studies found that adiponectin could inhibit proliferation of endothelial cells and stimulate apoptosis of cancer cells [45, 46] and might play crucial roles in the etiology of several types of cancers, including gastric, colorectal, liver and pancreatic cancer [47–49].

Given the striking rise in the number of MetS patients and its association with pancreatic cancer, it is imperative to establish public health strategies for better
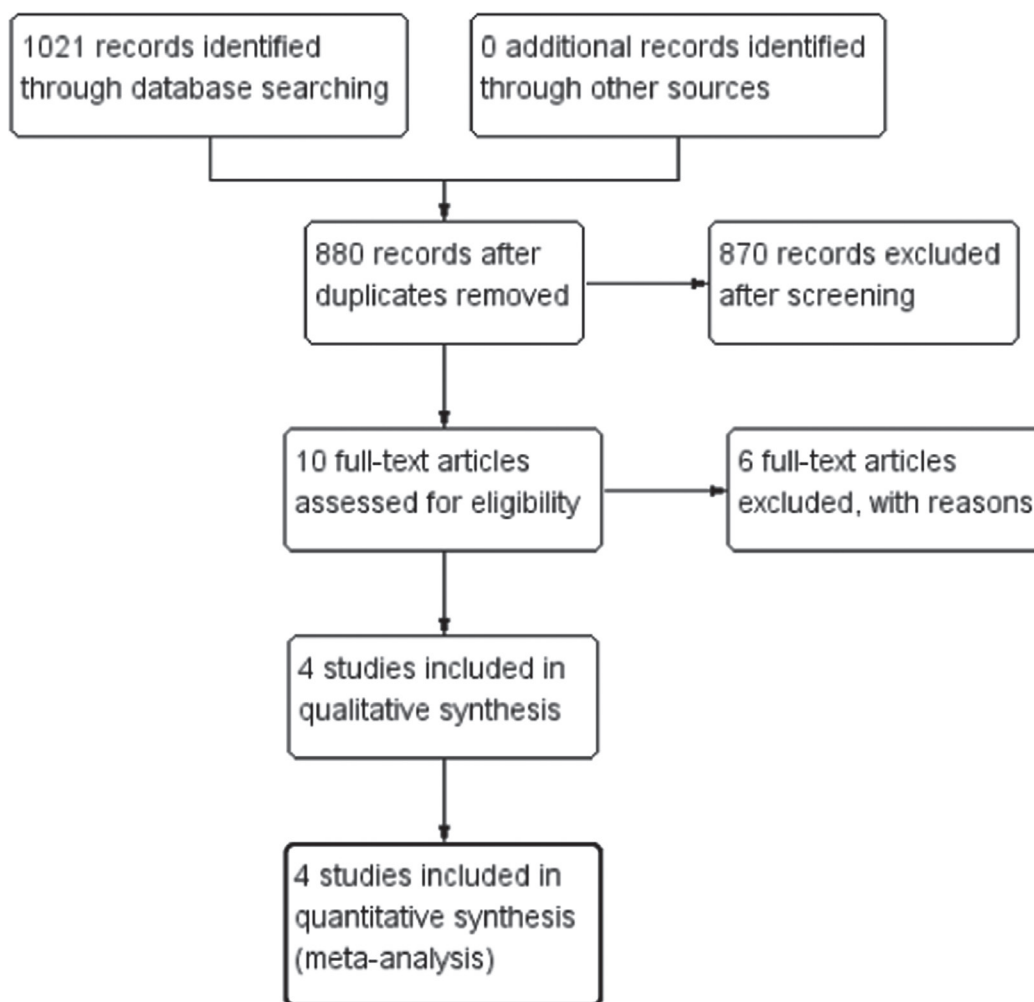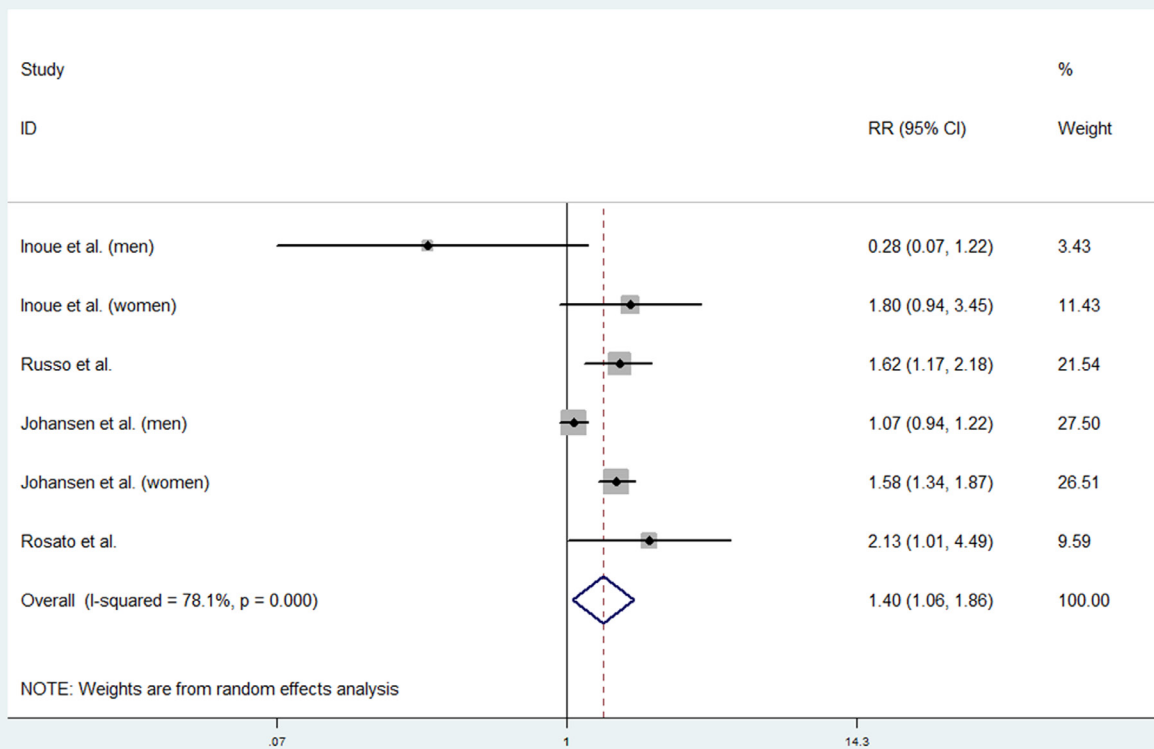

Figure 1: Study flow diagram.

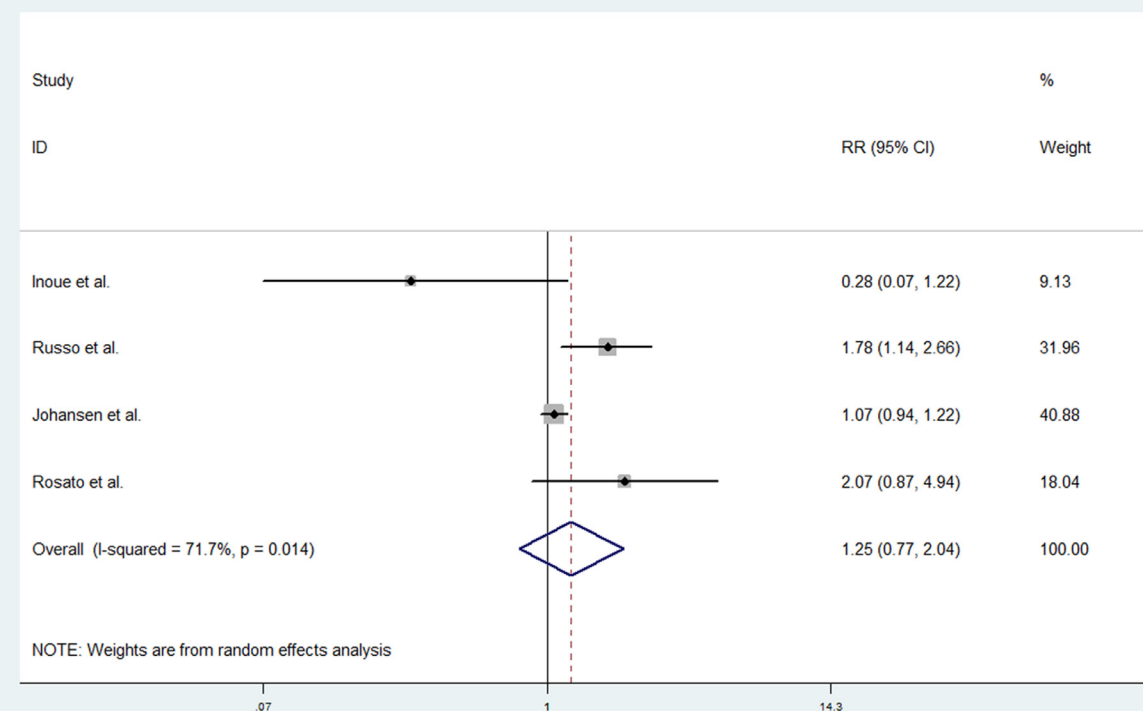**Figure 2: Forest plot of association between metabolic syndrome and pancreatic cancer risk.**

Figure 3: Forest plot of association between metabolic syndrome and pancreatic cancer risk in men.

Table 1: Characteristics of the included studies

Study	Study location	Study design	No. of paticipants	No. of PaC patients	Definition of MetS	Adusting factors	NOS value
Russo et al. 2008	Italy	Cohort	16,677	43	Comebined therapy for antihypertensive, hypolipid, and hypoglycemic drugs	NA	6
Inoue et al. 2009	Japan	Prospective cohort	27,724	65	Three or more than three factors (high blood pressure, high glucose, low HDL-cholesterol, high triglycerides, and being overweight)	Age, study area, smoking status, weekly ethanol intake, daily total physical activity level, total cholesterol	9
Johansen et al. 2010	Austria, Norway, and Sweden	Prospective cohort	577,315	862	Metabolic factors (Z score of the following components: (a) glucose, (b) mid-blood pressure,(c) cholesterol, (d) triglycerides, and (e) oerweight)	Age, smoking status;	9
Rosato et al. 2011	Italy	Case-control	978	326	At least 3 conditions among diabetes, drug-treated hypertension, hyperlipidemia, and overweight at age 30 years.	Age, study area, smoking status, year of interview, education.	5

Abbreviations: PaC, pancreatic cancer; MetS, metabolic syndrome; NOS, Newcastle-Ottawa Scale.

management of MetS. The increasing prevalence of MetS and large global burden of pancreatic cancer indicate that even a moderate association between MetS and pancreatic cancer could have a substantial effect on public health. In order to better identify high-risk populations for primary prevention, risk assessment tools incorporating MetS as a risk factor for pancreatic cancer should be established.

This meta-analysis has some limitations. First, all studies included in this meta-analysis were non-randomized studies due to a lacking of RCTs in the literature to date. Second, the limited number of included studies made it impractical to evaluate potential publication bias or explore the sources of heterogeneity by conducting subgroup analysis and meta-regression. Third, adjustment method for potential confounding factors was not consistent in all studies, which might introduce excessive heterogeneity among studies. Even though the multivariate Cox proportional hazards model was employed in most studies, for those studies without such data, univariate analysis was applied.
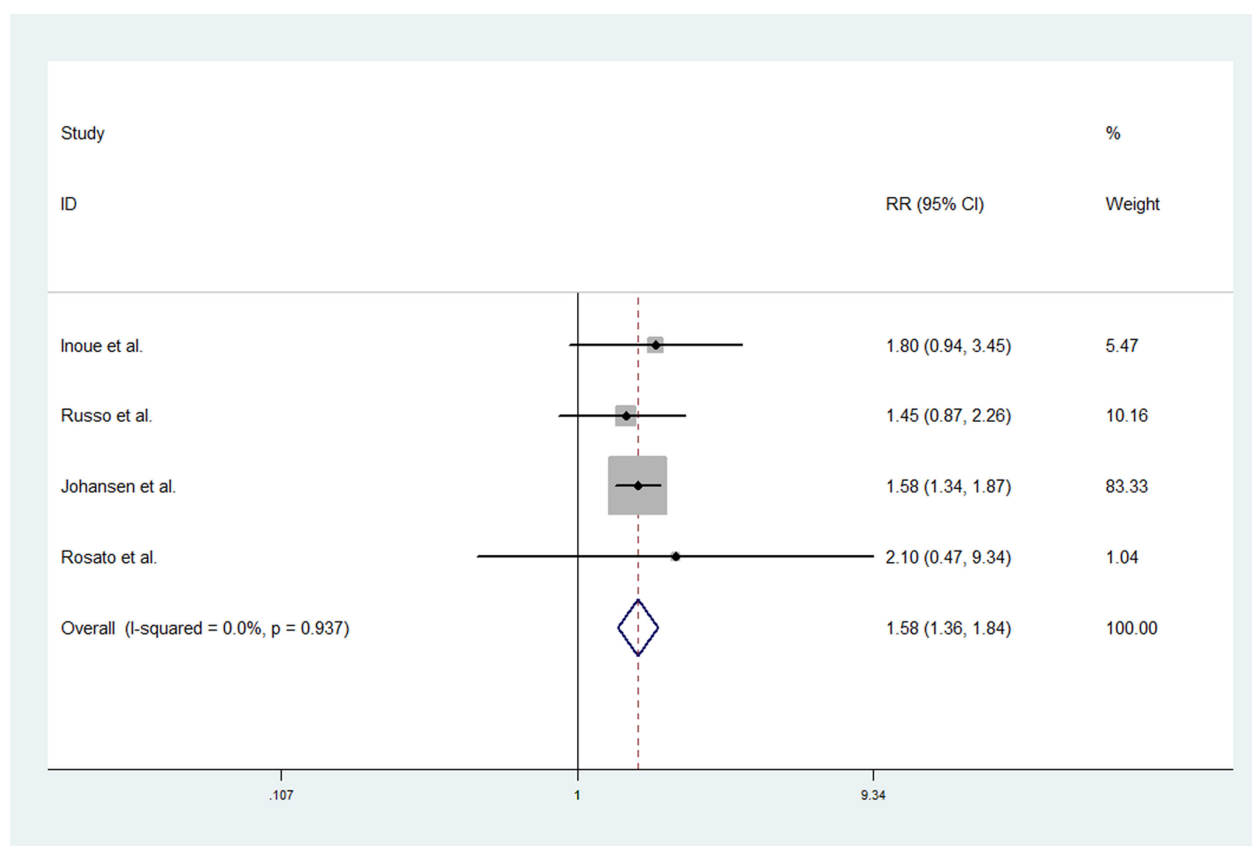
Figure 4: Forest plot of association between metabolic syndrome and pancreatic cancer risk in women.

In summary, findings of this meta-analysis demonstrate that MetS patients carry an increased pancreatic cancer risk. The association between MetS and pancreatic cancer risk is stronger in women than men. Future studies should be conducted to clarify exact mechanisms and identify high-risk populations in order to better prevent the development of pancreatic cancer.

MATERIALS AND METHODS

This systematic review and meta-analysis was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [50].

Search strategy

A systematic search was performed using the databases of Embase, PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) to identify all relevant articles from inception to March 2017. We used both subject headings and free text words in the search. The following search terms were used: "metabolic syndrome OR metabolic abnormalities OR insulin-resistance syndrome OR syndrome X" AND "pancreatic neoplasms OR pancreatic carcinoma OR pancreatic malignancy OR pancreatic cancer OR pancreatic tumor OR pancreatic tumour OR pancreatic adenocarcinoma". The following trial registers were also searched electronically to find potentially relevant ongoing trials: ISRCTN registry (http://www.isrctn.com/mrct/), World Health Organization International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/), and ClinicalTrials.gov (https://clinicaltrials.gov/). Additionally, we screened the reference lists from all retrieved articles for eligible studies. No language restriction was used in our search strategy.

Eligibility criteria

After conducting the search, two reviewers removed duplicates and screened the titles and abstracts independently. All potentially relevant references were evaluated detailedly to determine their eligibility. Studies meeting the following inclusion criteria were included in this meta-analysis: (1) randomized controlled trials (RCTs) or non-randomized studies; (2) evaluated the association between MetS and pancreatic cancer risk; (3) reported relative risk (RR) and a 95% confidence interval (CI) or provided data for their calculation. Articles were excluded if they were: (1) reviews, letters, editorials and case reports; (2) studies without appropriate data that could be extracted or calculated. For multiple publications from the same population, only the most comprehensive ones were included. Any disagreements in study selection were settled by discussion between the two reviewers and, if needed, in consultation with a third reviewer.

Data extraction and quality assessment

Data was extracted by two reviewers independently. The following data were collected from each study: publication data (ie, first author's name, publication year, and study location), study design, sample size, definition of MetS, follow-up, RR and 95% CI, and adjusting factors. When multiple estimates of effect (RR) were presented, the most adjusted one was extracted; when adjusted estimate was not available, crude estimate was extracted. Studies reporting different measures of RR, including odds ratio, hazard ratio, and standardized incidence ratio, were included in this meta-analysis. Actually, these effect measures yield similar estimates of RR because of the low prevalence of pancreatic cancer.

The methodological quality of included studies was evaluated by three reviewers independently. Since all included studies were non-randomized studies, their methodological quality was assessed using the Newcastle–Ottawa scale (NOS) [51], which uses a star system ranging from 0 to 9 stars. Studies that awarded 7 or more stars were considered high quality.

Statistical analysis

The RRs from individual eligible studies were combined to give a pooled RR. The Chi-square (χ^2, or Chi^2) and I^2 test were used to measure heterogeneity. When significant heterogeneity (p value < 0.10 or I^2 > 50 %) was found, a random-effects model was used to calculate the pooled effect; otherwise, a fixed-effects model was applied. To assess the stability of the results, we performed the leave-one-out sensitivity analysis. Publication bias was not evaluated in this meta-analysis given the limited number of studies [52, 53]. All analyses were performed using Stata version 12.0 software (Stata Corporation, College Station, TX). For all tests, a two-sided p value less than 0.05 was considered statistically significant.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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