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ORIGINAL RESEARCH

The association between metabolic syndrome and bladder cancer susceptibility and prognosis: an updated comprehensive evidence synthesis of 95 observational studies involving 97,795,299 subjects

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Background: The association between metabolic syndrome (MS) and bladder cancer (BC) was not fully investigated, and most primary studies and pooled analyses were only focused on certain specific components.

Objective: To further investigate this issue and obtain more precise findings, we conducted this updated evidence synthesis of published studies, which involved not only MS components but also the MS in its entirety.

Materials and methods: We searched the PubMed, EMBASE, and Web of Science databases for observational studies on the association between BC susceptibility and/or mortality, and MS and its components. We extracted data from included studies, evaluated heterogeneity, and performed meta-analytic quantitative syntheses.

Results: A total of 95 studies with 97,795,299 subjects were included in the present study. According to the results, MS significantly increased the risk of BC (risk ratio [RR]=1.11, 95% CI=1.00–1.23); diabetes significantly increased the risk of BC (RR=1.29, 95% CI=1.19–1.39) and associated with poor survival (RR=1.24, 95% CI=1.08–1.43). Excessive body weight was associated with increased susceptibility (RR=1.07, 95% CI=1.02–1.12), recurrence (RR=1.46, 95% CI=1.18–1.81), and mortality (RR=1.17, 95% CI=1.00–1.37). As indicated by cumulative meta-analysis, sample size was inadequate for the association between BC susceptibility and MS, the association between BC recurrence and excessive body weight, and the association between BC survival and diabetes. The sample size of the meta-analysis was enough to reach a stable pooled effect for other associations.

Conclusion: Diabetes and excessive body weight as components of MS are associated with increased susceptibility and poor prognosis of BC. Uncertainty remains concerning the impact of overall MS, hypertension, and dyslipidemia on BC susceptibility and prognosis, for which further investigations are needed.

Keywords: metabolic syndrome, bladder cancer, diabetes, excessive body weight, susceptibility, prognosis, meta-analysis, cumulative meta-analysis

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Introduction

Metabolic syndrome (MS) is defined by a collection of biochemical and physiologic abnormalities associated with the development of cardiovascular disease (CVD) and type 2 diabetes. Abdominal obesity, atherogenic dyslipidemia, high blood pressure,

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and insulin resistance are major components of MS.[1] According to the US National Health and Nutrition Examination Survey data, the overall MS prevalence among adults was 21.8% during 1988–1994, and it had increased up to 34.7% by the end of 2012. The prevalence of MS also increases with age, from 18.3% among those aged 20–39 years to 46.7% among those aged 60 years or more. Almost half of the US population will be diagnosed of MS throughout their life as the population-aging continues.[2,3] The MS was previously identified as a strong contributor to cardiovascular morbidity and mortality; in addition, it has also been recognized as a potential etiologic factor for the development and progression of multiple types of cancers.[4] Bladder cancer (BC) is the most common malignancy that affects the urinary tract. Evidence from epidemiologic investigations, clinical studies, and pooled analyses suggests that the MS may increase the risk, recurrence, and mortality of BC. However, most primary studies and pooled analyses only focused on certain specific MS components, such as diabetes and excessive body weight, but not the overall MS; as a result, the impact of MS on the carcinogenesis and prognosis of BC patients remains unclear. On the other hand, the stability of pooled effects (robustness to inclusion of additional studies), which could be investigated using cumulative meta-analysis, was left unexamined in previous meta-analysis. Therefore, in order to further investigate this issue and obtain more precise findings, an updated summarization of published studies, which integrates pooled analysis and stability examination and involves not only MS components but also the MS in its entirety, needs to be performed. To this end, we conducted the present comprehensive evidence synthesis incorporating pooled analysis and cumulative meta-analysis, to summarize all published studies to date, concerning the association between MS, its components, and BC in terms of susceptibility and prognosis.

Materials and methods

Literature search strategy

To identify observational studies on the association between BC risk and prognosis, we searched literature databases including the PubMed, EMBASE, and Web of Science. All possible combinations of the following search terms were used for the search: "bladder cancer", "urothelial carcinoma", "metabolic syndrome", "diabetes", "overweight", "obesity", "hypertension", "dyslipidemia", "risk", "susceptibility", "survival", "recurrence", and "prognosis". The time limit for the search was between the establishment of the database and 31 March 2018. No language limits were applied to the search. The references of previous meta-analyses on similar topics were also screened for potential relevant studies.

Study selection and data extraction

Eligible studies were selected according to the predefined selection criteria. Included studies should be observational studies and provided data on the association between BC susceptibility and/or survival, and MS or any of its known components. Two authors independently reviewed the literature search results and selected studies for inclusion. Any discrepancies were resolved by discussion with a third author.

The following data were extracted from the included studies: surname of the first author, year of publication, country of origin, research design, sample size, exposures examined (MS and/or its components), outcomes analyzed (susceptibility and/or prognosis), and data of effect sizes measuring the association between exposures and outcomes. Two authors independently conducted data extraction, and any discrepancies were resolved by discussion or consulting with a third author.

Statistical analysis

Quantitative evidence syntheses using a fixed effects or random effects meta-analytic model were performed. When significant heterogeneity among studies was detected, a fixed effects model was used, otherwise a random effects model was used. Leave-one-out sensitivity analysis was performed to identify influential studies for a given meta-analysis. Subgroup analysis by gender was performed concerning the association between MS and BC susceptibility, and subgroup analysis by degree of excessive body weight (overweight vs obesity) was performed for the association between excessive body weight and BC risk, recurrence, and mortality. Z-test was performed to examine if the difference between pooled effects across subgroups was significant. Cumulative meta-analyses by chronologic order were performed to examine if a stable pooled effect was reached in meta-analysis. Publication bias was investigated by funnel graphs and Egger's test, and trim-and-fill analysis was performed when significant publication bias was detected.

Results

Basic characteristics of included studies

The primary literature search identified 884 publications. After comprehensive screening according to the selection criteria, a total of 95 studies were included in the present evidence synthesis. Among the included studies, 74 were

cohort studies, 16 were case–control studies, and five were cross-sectional studies. The basic characteristics of the included studies are shown in Table S1.

Association between MS and BC susceptibility and prognosis

As to the correlation between overall MS and susceptibility of BC, a total of five studies were included, among which significant heterogeneity was detected (I^2=59.6, P=0.008).[5–9] Based on the results of pooled analysis, MS significantly increased the risk of BC (risk ratio [RR]=1.11, 95% CI=1.00–1.23; Figure 1). Sensitivity analysis showed that the study by Montella et al was influential and was a potential source of observed heterogeneity.[8] According to the subgroup analysis by gender, MS significantly increased the incidence of BC in males (RR=1.15, 95% CI=1.02–1.30; Figure 1), but not in females (RR=1.03, 95% CI=0.83–1.29; Figure 1). However, the observed subgroup difference was not statistically significant (Z=0.88, P=0.38).

Only one study that investigated the association between MS and BC mortality was found, in which a strong positive correlation between MS and BC mortality was reported (RR=4.03, 95% CI=2.03–8.01).[10]

According to the results of cumulative meta-analysis by year of publication, stable pooled effects were not yet reached in both overall meta-analysis and subgroup analysis by gender, regarding the association between MS and BC susceptibility (Figure S1).

Association between diabetes and BC susceptibility and prognosis

In terms of the correlation between diabetes and risk of BC, a total of 41 studies were included, among which significant heterogeneity was detected (I^2=89.8%; P<0.001).[11–51] Based on the results of pooled analysis, diabetes significantly increased the risk of BC (RR=1.29, 95% CI=1.19–1.39; Figure 2A). Sensitivity analysis revealed that the study by Lee et al was influential, which was a potential source of observed heterogeneity.[39]

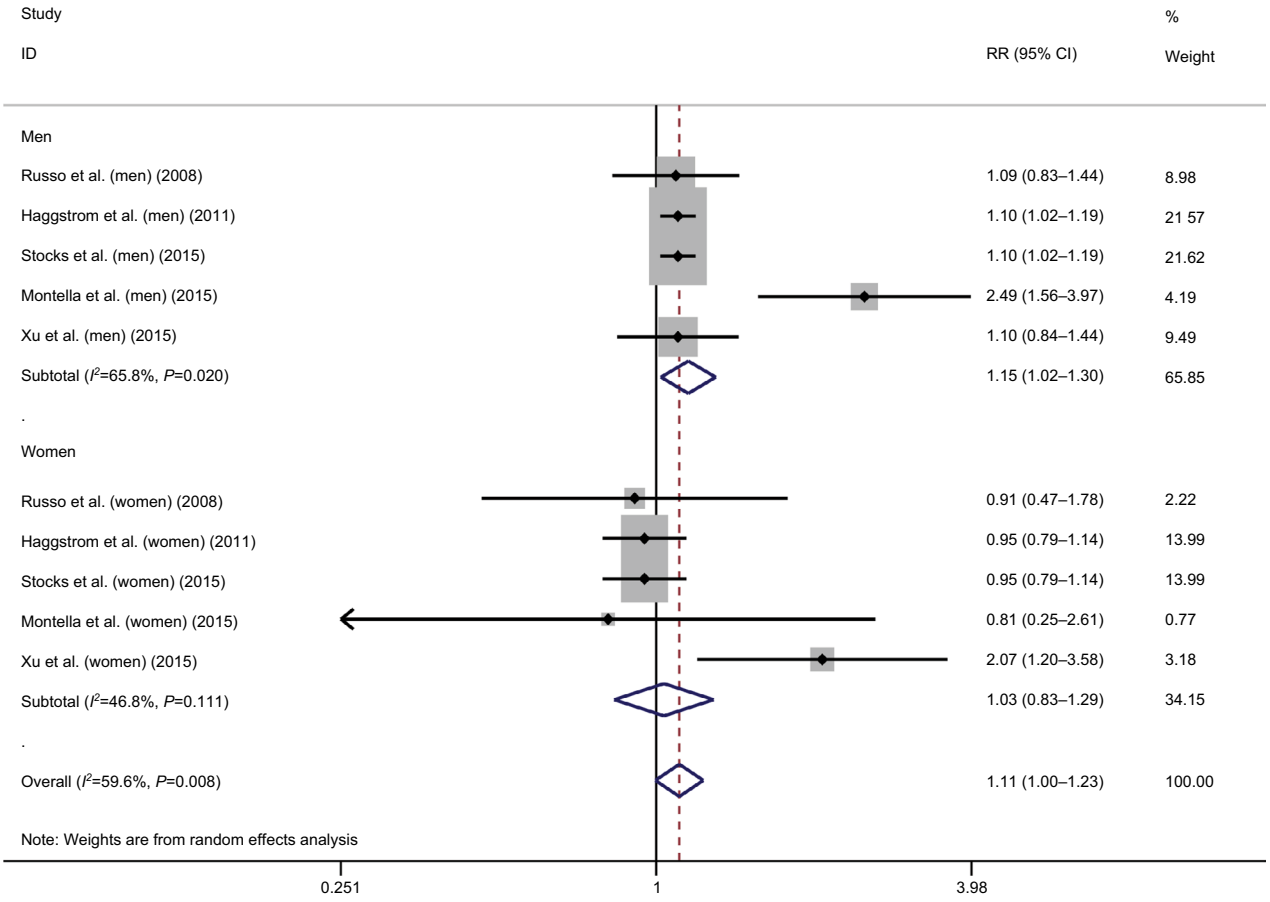

Figure 1 Meta-analysis on the association between bladder cancer susceptibility and metabolic syndrome.
Abbreviation: RR, risk ratio.

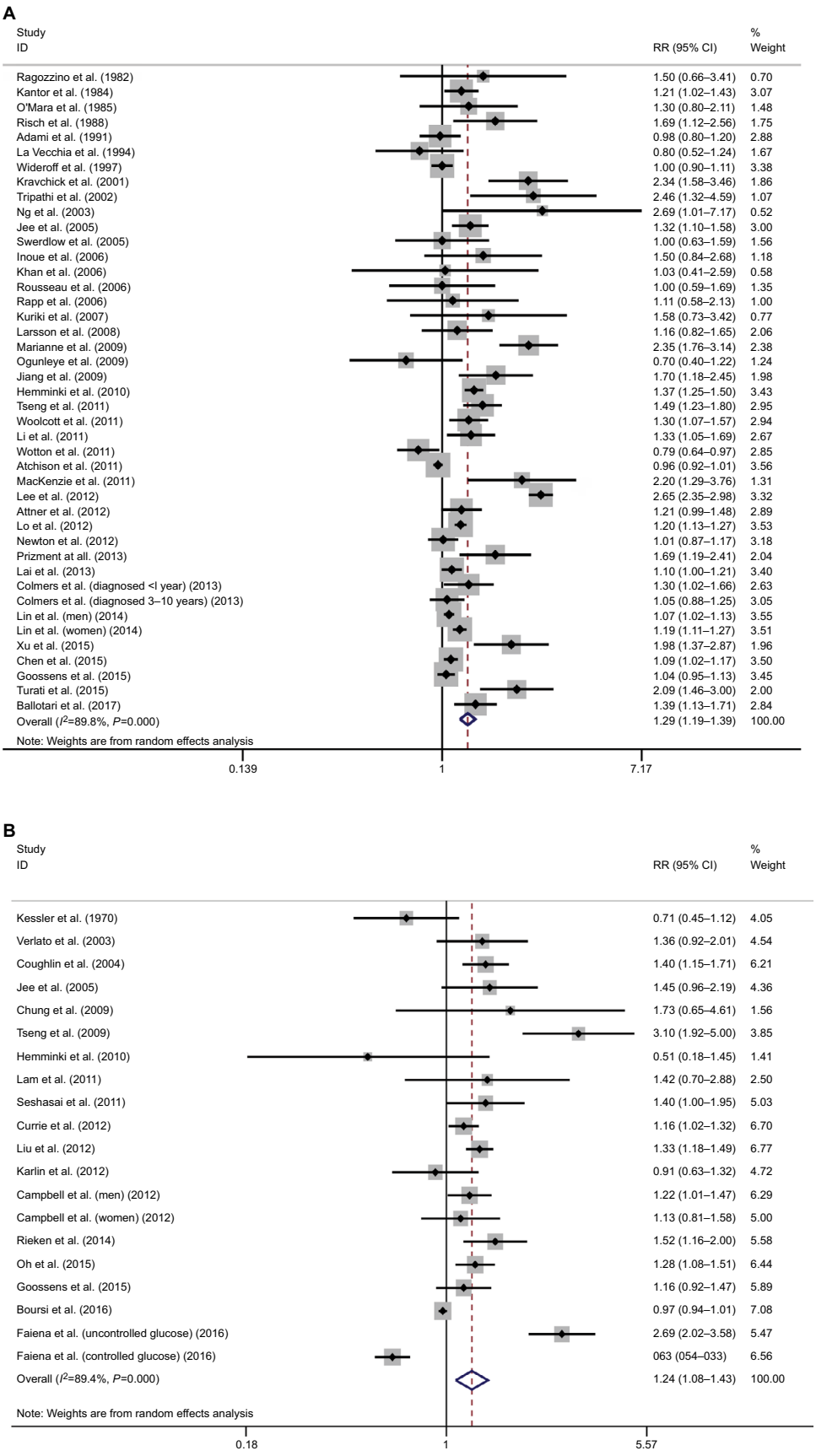

Figure 2 Meta-analysis on the association between bladder cancer susceptibility (**A**), mortality (**B**), and diabetes.
Abbreviation: RR, risk ratio.

In terms of the correlation between diabetes and mortality of BC patients, a total of 18 studies were included.[21,32,49,52–67] Significant heterogeneity was detected (I^2=89.4%; P<0.001). The results of pooled analysis showed that diabetes was significantly associated with poor survival in BC patients (RR=1.24, 95% CI=1.08–1.43; Figure 2B). Sensitivity analysis revealed that the studies by Faiena et al[66] and Tseng et al[55] were influential, as potential sources of observed heterogeneity.

According to the results of cumulative meta-analysis by year of publication, a stable pooled effect was reached in meta-analysis regarding the association between diabetes and BC susceptibility (Figure S2A), but not the association between diabetes and BC mortality (Figure S2B).

Association between excessive body weight and BC susceptibility and prognosis

In terms of the association between excessive body weight and risk of BC, a total of 18 studies were included in the overall meta-analysis of both overweight and obesity, among which significant heterogeneity was detected (I^2=64.6, P<0.001).[6,19,28,68–82] Excessive body weight was significantly associated with increased risk of BC (RR=1.07, 95% CI=1.02–1.12; Figure 3A). Sensitivity analysis revealed that the studies by Samanic et al[72], Koebnick et al[77], and Häggström et al[6] were influential and were potential sources of observed heterogeneity. The overall meta-analysis investigating the association between excessive body weight and BC recurrence indicated increased risk of recurrence in BC patients with excessive body weight (RR=1.46, 95% CI=1.18–1.81; Figure 3B). Significant heterogeneity was detected (I^2=85.5, P<0.001) among the included 11 studies.[83–93] Sensitivity analysis revealed that the study by Kluth et al was influential, a potential source of observed heterogeneity.[90] The overall meta-analysis investigating association between excessive body weight and BC survival indicated unfavorable survival of BC patients with excessive body weight (RR=1.17, 95% CI=1.00–1.37; Figure 3C). Significant heterogeneity was detected (I^2=88.2, P<0.001) among the included six studies.[87,90,92,94–96] Sensitivity analysis revealed that the studies by Chromecki et al and Dabi et al were influential and were potential sources of observed heterogeneity.[87,92]

According to subgroup analysis by the degree of excessive body weight, overweight did not have a significant impact on the susceptibility of BC (RR=1.04, 95% CI=0.96–1.13), but obesity was significantly associated with increased risk of BC (RR=1.09, 95% CI=1.03–1.16). Similar results were revealed in subgroup analysis for prognosis. Overweight did not have a significant impact on recurrence and mortality of BC (recurrence: RR=1.15, 95% CI=0.95–1.39; mortality: RR=1.01, 95% CI=0.87–1.18), but obesity was associated with an increased recurrence risk and poor survival in BC patients (recurrence: RR=1.46, 95% CI=1.18–1.81; mortality: RR=1.38, 95% CI=1.03–1.84). However, the observed subgroup differences were all statistically nonsignificant (susceptibility: Z=0.93, P=0.35; recurrence: Z=1.64, P=0.10; mortality: Z=1.88, P=0.06). Significant heterogeneity was detected in each subgroup analysis (Figure 3A–C).

According to the results of cumulative analysis by chronologic order, a stable pooled effect was reached in meta-analysis regarding the association between excessive body weight and BC susceptibility (Figure S3A) and subgroup analysis by severity (Figure S3B). In contrast, instability was detected for recurrence (Figure S3C, D). An almost stable pooled effect was reached in meta-analysis for mortality (Figure S3E, F).

Association between hypertension, dyslipidemia, and BC susceptibility and prognosis

A quantitative evidence synthesis regarding the association between hypertension and BC risk or mortality cannot be performed due to limited number of relevant studies. Stocks' study revealed that every 10 mmHg blood pressure increment brought significant increase in BC susceptibility and mortality in males (susceptibility: RR=1.12, 95% CI=1.04–1.21; mortality: RR=1.26, 95% CI=1.05–1.51); in contrast, similar effects were not observed among females (susceptibility: RR=0.95, 95% CI=0.81–1.11; mortality: RR=1.14, 95% CI=0.82–1.59).[97] Batty's study reported no significant association between increased systolic or diastolic blood pressure BC (high systolic blood pressure: RR=1.06, 95% CI=0.96–1.18; high diastolic blood pressure: RR=1.08, 95% CI=0.92–1.27).[98] In Tai's study, investigators reported a nonsignificant association between hypertension and BC recurrence (HR=1.3, 95% CI=0.88–1.93).[99]

Concerning the association between dyslipidemia and BC, only two studies were identified in our literature search, in which inconsistent findings were reported. A retrospective study with 2,070 Chinese participants revealed a nonsignificant correlation between hypertriglyceridemia and BC susceptibility (adjusted OR=1.3, 95% CI=0.88–1.93).[9] However, another study by Stocks et al reported a significant

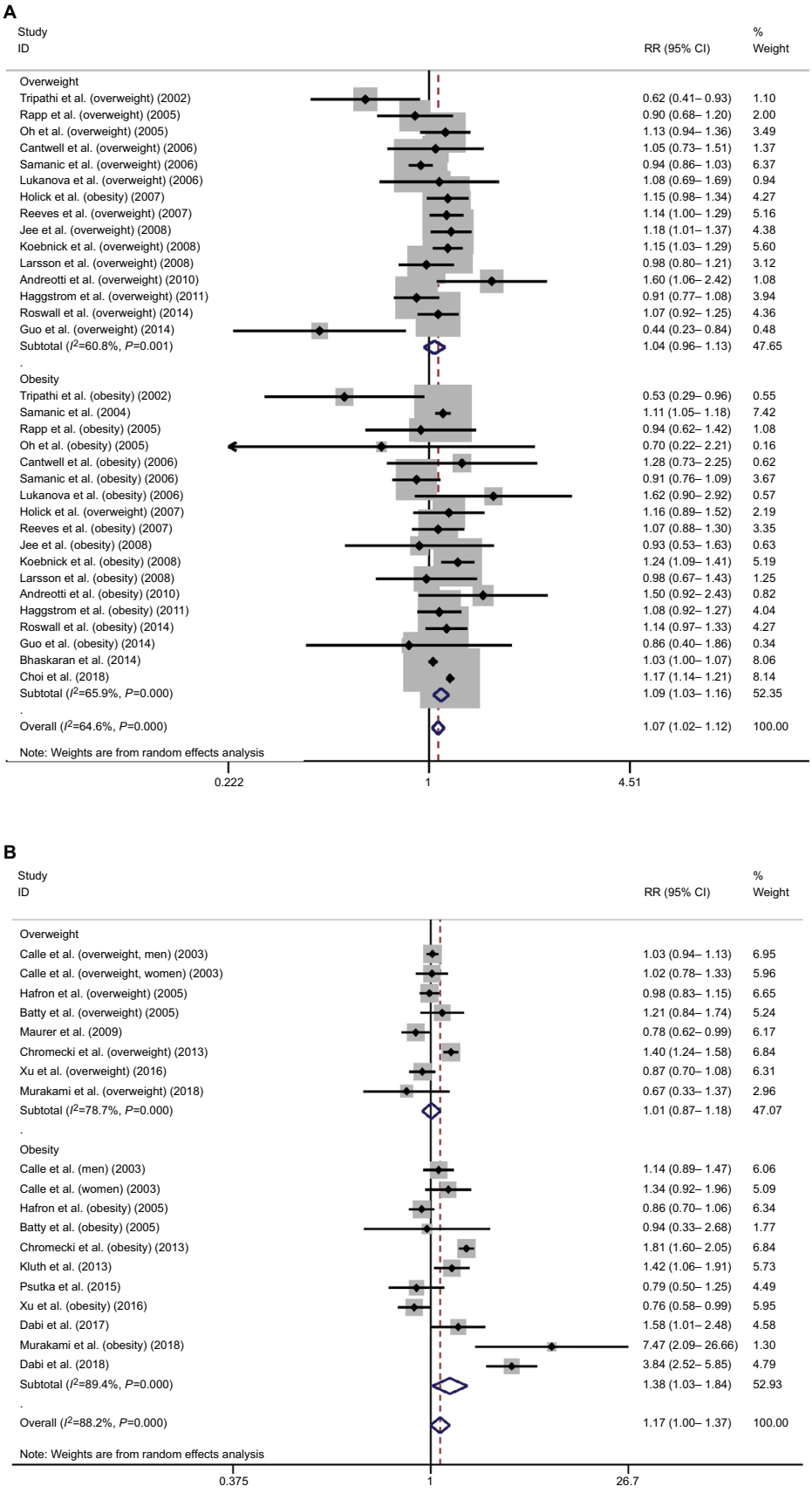

Figure 3 (*Continued*)

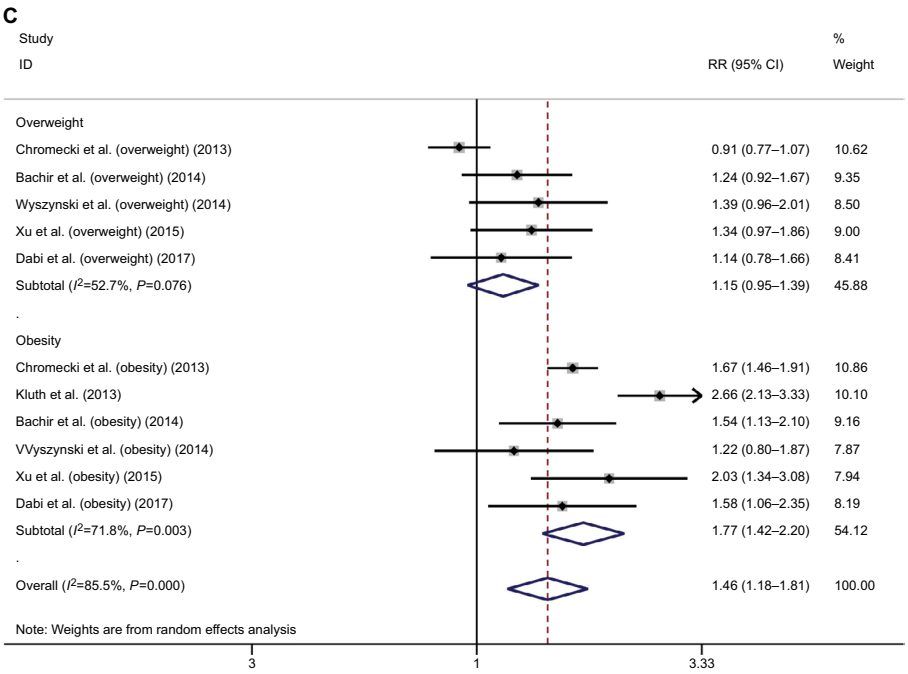

Figure 3 Meta-analysis on the association between bladder cancer susceptibility (**A**), recurrence (**B**), mortality (**C**), and excessive body weight.
Abbreviation: RR, risk ratio.

association between hypertriglyceridemia and both BC susceptibility (HR=1.18, 95% CI=1.06–1.32) and mortality (HR=1.72, 95% CI=1.39–2.12).[7]

Publication bias

No significant publication bias was detected except for the meta-analyses regarding the association between diabetes and BC susceptibility (P=0.015; Figure 4A) and mortality (P=0.036; Figure 4B). The trim-and-fill adjusted pooled RR and 95% CI was 1.28 (1.19–1.38) and 1.11 (0.97–1.28), respectively.

Discussion

The prevalence of MS continues to increase worldwide. According to the US National Cholesterol Education Program's Adult Treatment Panel III report, MS has been identified as a multiplex risk factor for CVD that deserves more clinical attention.[1] On the other hand, we should also spare attention on the probable association between MS and BC, which is a common and costly malignancy.[100] In this comprehensive evidence synthesis of 95 studies involving 97,795,299 participants, we confirmed that MS and its components did confer contributing effects on the development and mortality of BC. In a Northern Italy prospective cohort of 407,157 subjects in the Reggio Emilia diabetes registry project, diabetes was associated with increases in the incidence of all cancers, including BC.[101] Our pooled analysis also reported a positive association between diabetes and BC. Our findings indicated that diabetes was the strongest single risk factor among the components of MS, which significantly increased the risk of BC and overall mortality. Our findings were similar to those reported in Fang et al's meta-analysis and identified a stronger association compared with Xu et al's meta-analysis.[102,103] The underlying mechanisms between this association have been proposed. First, insulin may play a role as growth factor by exerting mitosis-promoting effects. Insulin binds and activates the insulin-like growth factor-1 (IGF-1) receptor and triggers the downstream pathways having potent mitogenic and transforming activity.[104] Increased insulin and IGF-1 in patients with MS may contribute to cancer progression and facilitate the growth of tumors by binding to the overexpressed insulin receptor in many cancers.[105] In addition, an association between insulin resistance and aberrant level of proinflammatory cytokine tumor necrosis factor a, which may induce development and progression of many tumors, has been reported.[106,107] This could explain the increased cancer risk in adults with type 2 diabetes.[108,109] Second, diabetes was associated with mitochondrial malfunction, which will lead to insufficient DNA repair. Moreover, mitochondria malfunction will increase the production of ROS, raising oxidative stress.[110] Third, diabetes, especially under conditions of poor metabolic control,

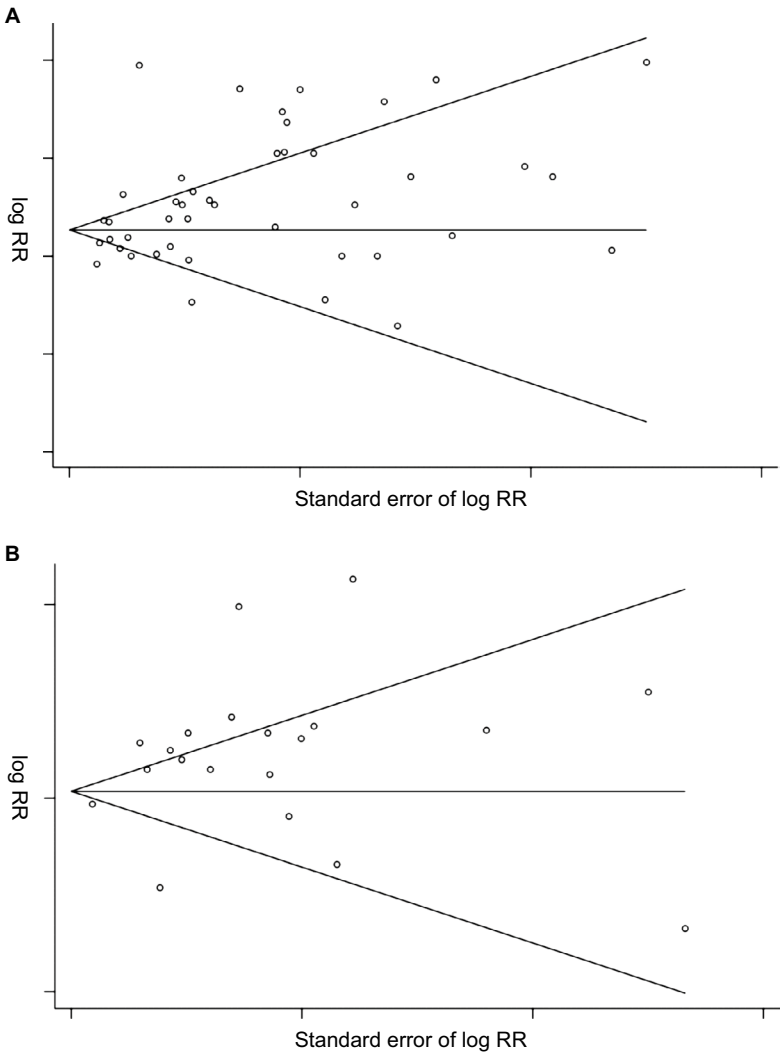

Figure 4 Funnel plot for the meta-analyses regarding the association between bladder cancer susceptibility (**A**), mortality (**B**), and diabetes.
Abbreviation: RR, risk ratio.

causes a permanent proinflammatory state. This will consume intracellular antioxidant capacity, predisposing susceptible cells to carcinogenesis and cancer progression.[111] This could explain why uncontrolled diabetes was significantly associated with higher overall mortality, as reported in both Tai and Faiena's studies.[66,99] On the other hand, it has been suggested that antidiabetic drugs, such as metformin, may influence cancer risk among diabetic patients.[108]

Obesity has been previously reported to be associated with a higher incidence and mortality of cancer.[112,113] In the present meta-analysis, we observed a positive correlation between obesity and BC risk, BC survival, and recurrence; in contrast, overweight was not significantly associated with BC risk, BC survival, or recurrence. Overall, it seems that there was a positive correlation between body weight and BC risk, jBC survival or recurrence, with a possible dose–response effect. Similar to our findings, previous meta-analyses had revealed that each 1 kg/m^2 increase in body mass index (BMI) was related to a 1.3% increase in risk of BC recurrence and each 5 kg/m^2 increase in BMI was related to a 4.2% increase in BC incidence.[114,115] A meta-analysis by Qin et al also confirmed that obesity was associated with an increased risk for BC, which was consistent with our results.[116] However, a meta-analysis by Lin et al reported that obesity was not significantly associated with BC overall survival, which was partially different from our observations.[115] The mechanism for the potential effects of excessive body weight on the BC risk and outcome has not been fully clarified. A frequently proposed hypothesis is that excessive body weight may cause metabolic and hormone changes, including hyperinsulinemia, leptin level elevation, and adiponectin reduction, which may promote carcinogenesis and progression of certain

cancers.[117,118] Moreover, obesity is generally accompanied by unrestrained diet and physical inactivity, and previous studies have proved that excessive calorie intake and physical inactivity may influence cancer development and progression.[113]

Unlike obesity and diabetes, the role of hypertension and hyperlipidemia in BC development and progression has not been well investigated. Existing studies concerning hypertension and BC have not reached an unified conclusion. In Stocks et al's study, blood pressure increment was significantly associated with BC incidence and mortality in men, whereas other studies did not find a significant association between hypertension and BC. Interestingly, even Stocks et al did not find the same correlation in women.[97–99] A link between hypertension and cancer may be mediated via proliferative abnormalities in vascular smooth muscle cells. However, it needs more proof to clarify the correlation between hypertension and BC, and the underlying mechanism as well.[119] A case–control study in China revealed that hypertriglyceridemia was significantly associated with BC risk, while there was no positive correlation between low high-density lipoprotein-cholesterol and BC risk.[120] The association between hypertriglyceridemia and BC also needs further investigations.

In our meta-analysis, we found overall that MS significantly increased the risk and mortality of BC, but this effect was only observed among male subjects. This finding is consistent with those of Esposito et al's and Cantiello et al's meta-analyses, which also indicated that MS was associated with higher risk of BC in men.[4,121] However, Cantiello et al's work reported a nonsignificant association between MS and BC prognosis, and this was different from our observation.[121]

For the first time we investigated whether the sample size was large enough to support conclusions with confidence. We need additional samples (primary studies) for the association between BC susceptibility and MS, the association between BC recurrence and excessive body weight, and the association between BC survival and diabetes. The sample size was adequate to reach a stable pooled effect regarding other associations. To the best of our knowledge, the present study is the most recent evidence synthesis connecting BC and MS, which included nearly 100 studies with nearly 100,000,000 participants, examined the overall MS and individual components, evaluated both susceptibility and prognosis, and explored adequacy of sample size by cumulative meta-analysis; however, our work also has certain limitations. First, significant heterogeneity was detected for most of the pooled analysis. In addition to the effect by influential studies identified by sensitivity analysis, the variation in race, sample size, and study design could also be the potential sources of the observed heterogeneity. Second, the publication bias was detected for certain analyses, and we performed trim-and-fill adjustment as complementary information.

Conclusions

Certain components of MS, that is, diabetes and excessive body weight, are associated with increased susceptibility and poor prognosis of BC. Uncertainty remains concerning the impact of overall MS, hypertension, and dyslipidemia on BC susceptibility and prognosis, for which further investigations are needed.

Disclosure

The authors report no conflicts of interest in this work.

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