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ORIGINAL ARTICLE

Association of obesity and other anthropometric characteristics with bladder cancer risk: a systematic review and meta-analysis of longitudinal cohort studies

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Summary

Purpose: *The purpose of this systematic review and meta-analysis was to evaluate the potential associations between anthropometric characteristics and bladder cancer risk, synthesizing longitudinal cohort studies.*

Methods: *Literature search across MEDLINE, EMBASE, Scopus, Google Scholar and Cochrane Central was performed up to December 31, 2019 and data abstraction was performed independently by two authors. Random-effects (DerSimonian-Laird) models were used to estimate pooled relative risks (RR) and 95% confidence intervals (95%CI); subgroup analyses were performed in geographical region, mean age, publication year, length of follow-up, sample size, method of body mass index (BMI) estimation and adjustment for smoking.*

Results: *27 studies were included (88 593 bladder cancer cases in a total cohort of 49 647 098 subjects). Increased bladder cancer risk was noted in overweight men (pooled RR=1.12, 95%CI: 1.04-1.21) but not in overweight women. Both obese men (pooled RR=1.14, 95%CI: 1.06-1.22) and women (pooled RR=1.19, 95%CI: 1.02-1.38) showed increased risk. Interestingly, height increase per 5 cm did not seem to affect risk of bladder cancer in men (pooled RR=1.03, 95%CI: 0.99- 1.06) and women (pooled RR=1.02, 95%CI: 0.97-1.06). Larger waist circumference was associated with bladder cancer risk in men (pooled RR=1.18, 95%CI: 1.09-1.26) but not women.*

Conclusion: *Bladder cancer risk seems to be related with obesity overall and central obesity in men. In contrast to other cancer types, height does not seem to affect risk, but more studies are needed to extract safe conclusions.*

Key words: *BMI, cohort studies, meta-analysis, obesity, urinary bladder cancer, waist circumference*

Introduction

Bladder cancer is the ninth most common cancer worldwide, and sixth most common in developed countries [1,2]. The natural course of this disease is considered a major healthcare economic burden in Western countries [3] with the majority of costs being directed to surveillance procedures and management of complications [4]. Most cases represent non-muscle invasive disease (70-75%), while the remaining 25% are muscle-invasive.

Many studies have been conducted to establish a risk factor profile for bladder cancer. Age is considered the single most important non-modifi-

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able risk factor, with most patients diagnosed at a median age of 70 years [5]. Occupational exposure is associated with slightly increased incidence of the disease in miners, rubber and leather industry workers, bus drivers, mechanics, firefighters and hair dressers especially when working more than 10 years [6-8]. Tobacco smoking has been clearly linked to bladder cancer occurrence showing a dose-response relationship, with cigarette use leading to a 3 to 5 fold increase in risk, depending on intensity and duration of smoking [9]. Other environmental factors and dietary habits, such as high concentrations of arsenic in tap water [10] radiation exposure [11] diabetes mellitus [12] high intake of salt and red meat [13] and *Schistosoma hematobium* infection, seem to increase likelihood of bladder cancer.

Owing to the modern lifestyle and unhealthy eating habits, obesity consists a "pandemic" with prevalence ranging between 30-60% worldwide for total overweight and obese people [14]. Overweight and obese subjects are at greater risk for certain types of neoplasms [15]. Kanabrocki et al were the first who linked obesity to bladder carcinoma, back in 1965 [16] and since then a number of studieshave tried to quantify the risk, with conflicting results.At the level of meta-analyses, in 2011 Qin et al [17] synthesized 11 cohort studies and detected a strong relationship between bladder cancer and obesity, which increased the risk by 10%; in 2015, Sun et al [18] confirmed this association. In 2017, Zhao et al [19] performed a meta-analysis of 14prospective cohort studies and concluded that a non-linear association between body mass index (BMI) and bladder cancer exists.

Regarding other anthropometric characteristics, height has been associated with various cancers [20]; however, no meta-analysis has evaluated the association between height and bladder cancer risk. In addition, central obesity, reflected upon waist circumference has not been studied with respect to bladder cancer at the meta-analytical level.

The purpose of this systematic review and meta-analysis was to synthesize the existing evidence regarding the association between overweight, obesity, and other anthropometric characteristics,namely height and waist circumference, with bladder cancer risk in adults, based on longitudinal cohort studies.

Methods

Search algorithm, inclusion and exclusion criteria

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [21]. Two researchers (L.T., D.X.) performed an electronic review of the literature independently, to identify published articles in English language across several databases (MEDLINE, Cochrane Database of Systematic Reviews, EMBASE, Scopus, Google Scholar) until December 31, 2019. The algorithm used for search was : ("Urothelium" OR "urothelial" OR "UCC" OR "transitional cell" OR "TCC" OR "bladder") AND ("neoplasms" OR "neoplasm" OR "cancer" OR "cancers" OR "carcinoma" OR "carcinomas" OR "tumor" OR "tumour" OR "tumors" OR "tumours" OR "neoplasia") AND ("prospective" OR "prospectively" OR "follow-up" OR "followed up" OR "cohort" OR "cohorts" OR "longitudinal") AND ("overweighted" OR "overweight" OR "BMI" OR "obesity" OR "body mass index" OR "adiposity" OR "body size" OR "obese" OR "body weight" OR "height" OR "waist"). Studies were reviewed by title and/or abstract and the most relevant were full-text reviewed. Reference lists of included articles and previous reviews/meta-analyses were searched for relevant studies ("snowball procedure"). Only cohort studies focusing on the association of anthropometric characteristics with risk of bladder cancer in men or women were considered eligible, while comments, expert opinions, case-control and caseseries studies were excluded. Eligible articles examined the association between various anthropometric characteristics (BMI, height, waist to hip ratio, waist circumference) with incidence of urinary bladder carcinoma.

When studies' populations overlapped, only the study with the larger cohort and longer follow-up period was included. Disagreements were resolved upon consensus with a third, independent reviewer (T.N.S.).

Data abstraction

Two authors (L.T., D.X.) performed data abstraction independently based on a standard spreadsheet recording study information (year of publication, journal, first author, baseline characteristics of cohorts, sample size, age mean/ range, cases of bladder cancer, method of measurement of anthropometric characteristics, follow-up length, period and region where study was conducted and adjusting factors, as well as statistical measures used, namely relative risks (RR), hazard ratios (HR) and person-years).When more than one estimates per outcome was reported, the maximally adjusted effect estimate was extracted along with the relevant confidence interval (CI). In case of disagreements, consensus was reached after consensus with a third author (T.N.S.).

Statistical analysis: meta-analysis

In this study the term "study arms" refers to separate BMI categories, defined as overweight for BMI=25-30 kg/m^2 and obese for BMI>30 kg/m^2. Comparisons were made between overweight/obese with normal weight, separately for men and women. For the calculation of open-ended categories ≥a, the lower bound was multiplied by 1.2, as indicated by Berlin et al [22]. Subgroup analysis was performed by different geographical regions incorporating one study from Israel within Europe group, mean age (≥50 and <50 years), publication year (from 2011 onwards and before 2011), length of follow-up (≥10 and<10 years), sample size (≥ 300 000 and <300 000), method of

BMI estimation (measured; self-reported) and adjustment for smoking. Calculation of pooled effect estimate was performed using random effects model (DerSimonian-Laird, with the estimate of heterogeneity taken from the Mantel-Haenszel model). Assessment of heterogeneity between studies was done with Q-statistic (Cochran) and I^2 [23]. A synthesis of studies providing incremental estimations for height was performed; the effect estimates were transformed to reflect a 5 cm increase in height. Statistical analysis was performed with STATA/ SE version 13 (Stata Corp, College Station, TX, USA).

Assessment of risk of bias

Newcastle-Ottawa scale for observational cohort studies [24] a nine-item tool of study quality assessment, was used in order to evaluate each study regarding the selection of participants, comparability of groups and outcome assessment. Follow-up cut-off value in order to give a study a star was set a priori at 10 years, which is a long enough period to observe neoplasms incidence. Adequacy of follow-up in terms of loss-to-follow-up was set at 85% response rate. Two authors assessed the risk of bias independently (L.T., D.X.) and disagreements were resolved by consensus with a third reviewer (T.N.S.).

We evaluated existence of publication bias via Egger's statistical test and visual inspection of funnel plots.

Results

Overall, 801 abstracts and titles were identified and screened through literature search. 771 of them were excluded by title screening due to irrelevance, while the remaining 30 studies were assessed after full-text review. Six studies were excluded due to reporting reasons and one due to language restriction (Chinese language). In addition, six more studies were eligible for inclusion through reference screening from the included studies ("snowball procedure''). The male arm in the study by Jee et al [25] was excluded due to overlap with the study by Oh et al [26], which spanned a longer time period (1992-2001 vs 1992-1995). The male arm of Lee et al study [27] for waist circumference was also excluded due to overlap with the study by Choi JB et al [28]. Finally, after excluding two more studies due to overlapping populations, 27 studies were eligible for inclusion (88 593 bladder cancer cases in a total cohort of 49 647 098 subjects) [25-51]. The process of study selection is depicted graphically in Supplemental Figure 1.

Overweight/obesity and risk of urinary bladder cancer: overall analysis and subgroup analyses by geographical region

Results of meta-analysis regarding association between overweight, obesity and risk of bladder cancer is shown in Table 1 for overweight and obese men and women. Pooled analysis of 17 study arms examining the risk of bladder cancer in overweight men resulted in a significant association (pooled RR=1.12, 95% CI: 1.04-1.21, Figure 1A); a similar finding was noted in the synthesis of19 study arms in obese men (pooled RR=1.14, 95% CI: 1.06-1.22, Figure 1B). In overweight women pooled analysis of 16 study arms did not show an increased risk (pooled RR=1.06, 95% CI: 0.96-1.17, Figure 1C);in contrast, the synthesis of 15 arms regarding obese women resulted in a significantly increased risk (pooled RR=1.19, 95% CI: 1.02-1.38, Figure 1D).

Table 1. Results of the meta-analyses examining the association between BMI and risk of bladder cancer

	Overweight			*Obese*		
	*n**	*RR (95%CI)*	*Heterogeneity I^2, p*	*n**	*RR (95%CI)*	*Heterogeneity I^2, p*
Men						
Overall	17	1.12 (1.04, 1.21)	64.8%, <0.001	19	1.14 (1.06, 1.22)	40.9%, 0.033
Geographical region						
Australia	1	1.51 (1.15, 1.98)	%	1	1.70 (1.23, 1.34)	%
East Asia	3	1.19 (1.15, 1.23)	0%, 0.869	2	1.17 (1.05, 1.29)	0%, 0.383
Europe	9	1.06 (0.95, 1.18)	60.8%, 0.009	10	1.11 (0.97, 1.26)	41.6%, 0.080
US/Canada	4	1.19 (1.07, 1.32)	0%, 0.955	6	1.12 (1.01, 1.24)	34.5%, 0.177
Women						
Overall	16	1.06 (0.96, 1.17)	18.0%, 0.248	15	1.19 (1.02, 1.38)	40.6%, 0.051
Geographical region						
Australia	1	1.30 (0.92, 1.83)	%	1	2.03 (1.42, 2.90)	%
East Asia	1	1.10 (0.75, 1.62)	%	1	0.74 (0.27, 2.04)	%
Europe	7	1.08 (0.91, 1.29)	41.0%, 0.118	7	1.08 (0.94, 1.23)	4.8%, 0.390
US/Canada	7	0.98 (0.84, 1.15)	0%, 0.473	6	1.23 (1.00, 1.51)	6.9%, 0.373

*number of study arms

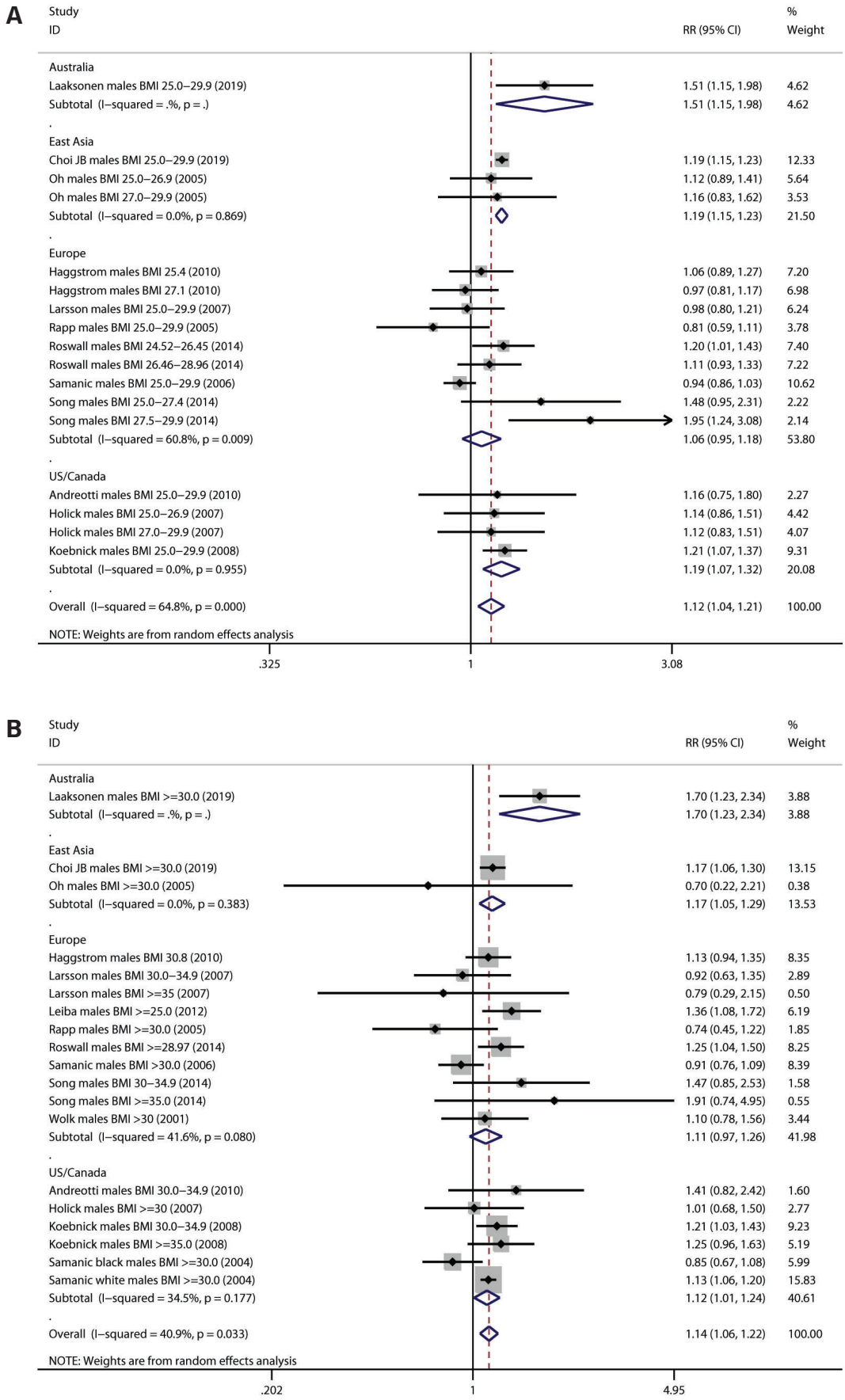

Figure 1. A: Forest plot presenting the association between overweight and bladder cancer risk in males. Studies are subgrouped by geographical region. **B:** Forest plot presenting the association between obesity and bladder cancer risk in males. Studies are subgrouped by geographical region.

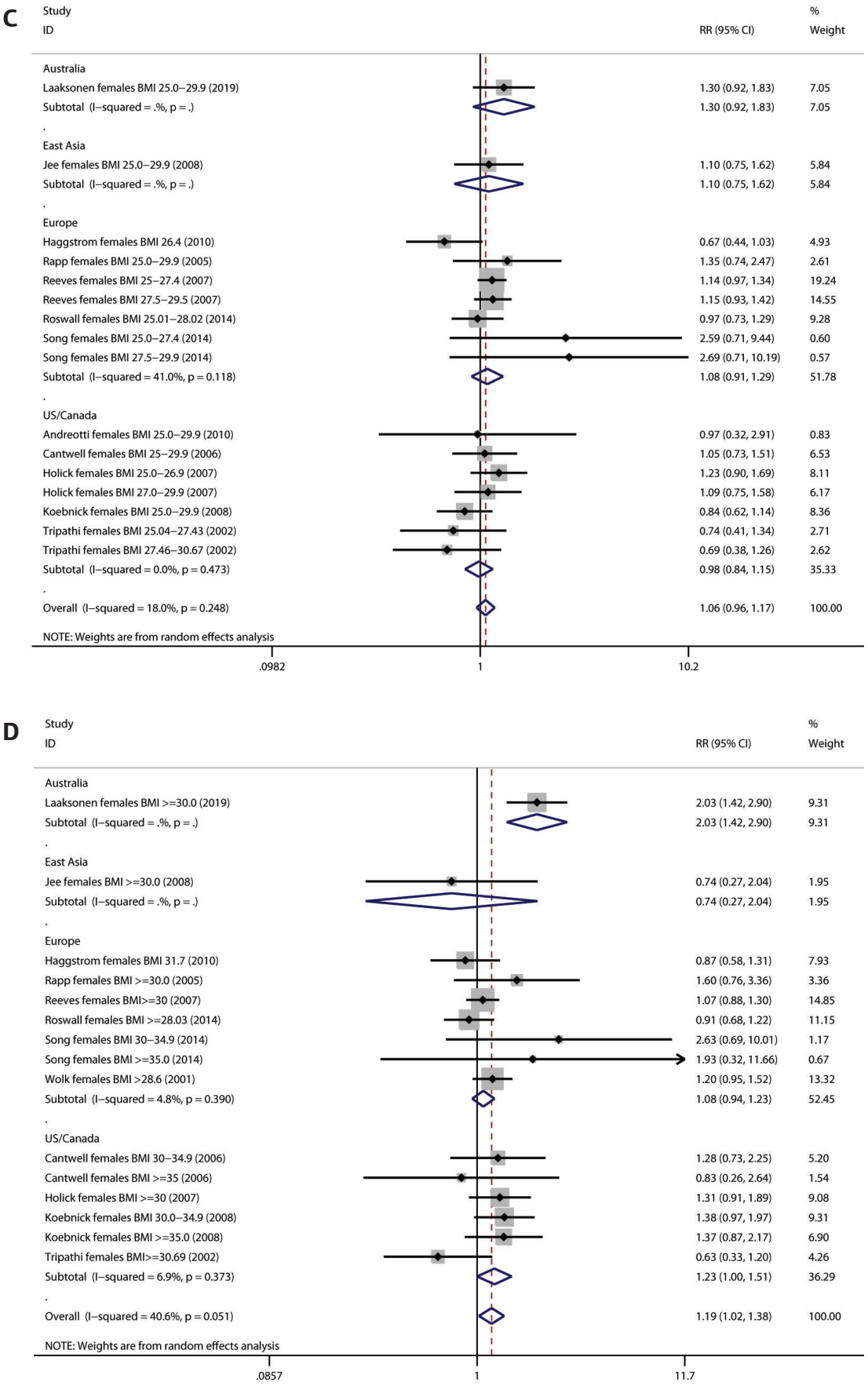

Figure 1. C: Forest plot presenting the association between overweight and bladder cancer risk in females. Studies are subgrouped by geographical region. **D:** Forest plot presenting the association between obesity and bladder cancer risk in females. Studies are subgrouped by geographical region.

Subgroup analyses were performed to examine the association of overweight/obese status in men and women with bladder cancer across geographical regions. Pooled analysis of studies for overweight men, revealed a persistent significant increased risk in Australia (pooled RR=1.51, 95% CI: 1.15-1.98) with 1 study arm, in East Asia (pooled RR=1.19, 95% CI: 1.15-1.23) with 3 study arms and in US/ Canada (pooled RR=1.19, 95% CI: 1.07-1.32) with 4 study arms, while in Europe the association in risk didn't persist (pooled RR=1.06, 95% CI: 0.95-1.18) (Figure 1A). In a similar fashion, pooled analysis of studies for obese men revealed a persistent significant increased risk in Australia (pooled RR=1.70, 95% CI: 1.23-1.34) with 1 study arm, in East Asia (pooled RR=1.17, 95% CI: 1.05-1.29) with 2 study arms and in US/ Canada (pooled RR=1.12, 95% CI: 1.01-1.24) with 6 study arms, while in Europe significant risk was not detected (pooled RR=1.11, 95% CI: 0.97-1.26) (Figure 1B). Regarding overweight women, pooled analysis did not reveal any significant increased risk in any geographical region (Figure 1C), while for obese women a significantly increased risk persisted for Australia (pooled RR=2.02, 95% CI: 1.42-2.90) with 1 study arm, while in the remaining regions no significant difference was detected (Figure 1D).

Subgroup analyses by mean age

Pooled analysis of 7 study arms revealed that overweight men ≥50 years old showed a significant increased risk (pooled RR=1.17, 95% CI: 1.08-1.27), while overweight men <50 years old and overweight women of any age did not show any difference from normal weight individuals (Supplemental Figures 2A, 2B). Similarly, only obese men aged ≥50 years old showed a significant increased risk (pooled RR=1.18, 95% CI: 1.08-1.29) in a pooled analysis of 8 study arms, while obese men <50 years old and obese women of any age did not show any increased risk (Supplemental Figures 2C, 2D).

Subgroup analyses by publication year

Pooled analysis of 6 study arms published from 2011 onwards showed a significant increased risk for overweight men (pooled RR=1.25, 95% CI: 1.13-1.38), while overweight men in studies published up to 2010 and all overweight women regardless of publication year did not show significant differences with normal weighted individuals (Supplemental Figures 3A, 3B). Similarly, obese males after pooled analysis of 6 study arms published after 2011 showed a significant increased risk (pooled RR=1.29, 95% CI: 1.15-1.44) in contrast with studies published up to 2010. Obese women also showed a significantly increased risk in a pooled analysis of 11 study arms up to 2010 (pooled RR=1.14, 95% CI: 1.02-1.27), while analysis of 4 studies published after 2011 did not reveal significant difference.

Subgroup analyses, by length of follow-up

Pooled analysis of 8 study arms in overweight men with a median follow-up of <10 years showed a significantly increased risk (pooled RR=1.15, 95% CI: 1.06-1.26), while 9 study arm analysis of overweight men and all analyses of overweight women did not show significant differences. Pooled analysis of 10 study arms for obese males with median follow-up <10 years showed a significantly increased risk (pooled RR=1.18, 95% CI: 1.06-1.31). Similarly, pooled analysis of 6 study arms for obese females with a median follow-up <10 years showed a significantly increased risk (pooled RR=1.34, 95% CI: 1.06-1.71). Analysis of studies with median follow-up ≥10 years for obese men and women did not reveal significant differences.

Subgroup analyses by sample size

Pooled analysis of 13 study arms regarding overweight men with sample size <300000 showed a significantly increased risk (pooled RR=1.14, 95% CI: 1.04-1.24). Similarly, analysis of 3 study arms for overweight women and sample size ≥300000 showed a significant increased risk (pooled RR=1.14, 95% CI: 1.01-1.29). Analysis of 13 study arms for obese men and sample size <300000 showed a significantly increased risk (pooled RR=1.19, 95% CI: 1.09-1.31). Analysis of 13 study arms for obese women and sample size <300000 showed a significantly increased risk (pooled RR=1.22, 95% CI: 1.02-1.46).

Subgroup analyses by method of BMI estimation

Pooled analysis of 5 study arms regarding overweight men, where BMI was self-reported showed a significant increased risk (pooled RR=1.14, 95% CI: 1.04-1.25), while analysis of 11 studies where BMI was measured did not reveal significant difference. Pooled analysis of studies regarding overweight women did not reveal any significant differences neither with measured nor with self-reported BMI. Regarding obese males, pooled analysis of 12 studies with measured BMI revealed a significant increased risk (pooled RR=1.11, 95% CI: 1.02-1.20) as well as analysis of 6 studies with self-reported BMI (pooled RR=1.17, 95% CI: 1.04-1.32). Analyses on obese females did not show differences in either subgroups.

Subgroup analyses by adjustment for smoking

Pooled analysis of 16 study arms for overweight men, which adjusted models for smok-

ing habits revealed a significantly increased risk (pooled RR=1.11, 95% CI: 1.03-1.21), while for overweight women no significantly increased risk was found, regardless of adjustment for smoking or not. Pooled analysis of 13 study arms for obese men, which adjusted models for smoking habits, revealed a significantly increased risk (pooled RR=1.13, 95% CI: 1.01-1.27). Analysis of 6 study arms for obese men which did not adjust for smoking, also revealed a significant increased risk (pooled RR=1.14, 95% CI: 1.03-1.27). Analysis of 3 study arms on obese women, which did not adjust for smoking revealed a significantly increased risk (pooled RR=1.27, 95% CI: 1.06-1.52), while analysis of 12 studies that adjusted for smoking did not reveal significant differences.

Height and risk of urinary bladder cancer

Dose-response meta-analysis of 8 studies regarding risk of bladder cancer of every 5 cm increase of height in men revealed no significant association (pooled RR=1.03, 95% CI: 0.99- 1.06, Supplemental Figure 3A). Similarly, a pooled analysis of 5 studies revealed no significant correlation in women per 5 cm increase of height (pooled RR=1.02, 95% CI: 0.97-1.06, Supplemental Figure 3B). Albanes et al [50] and Larsson et al [32] also reported RRs for height and bladder cancer risk without providing

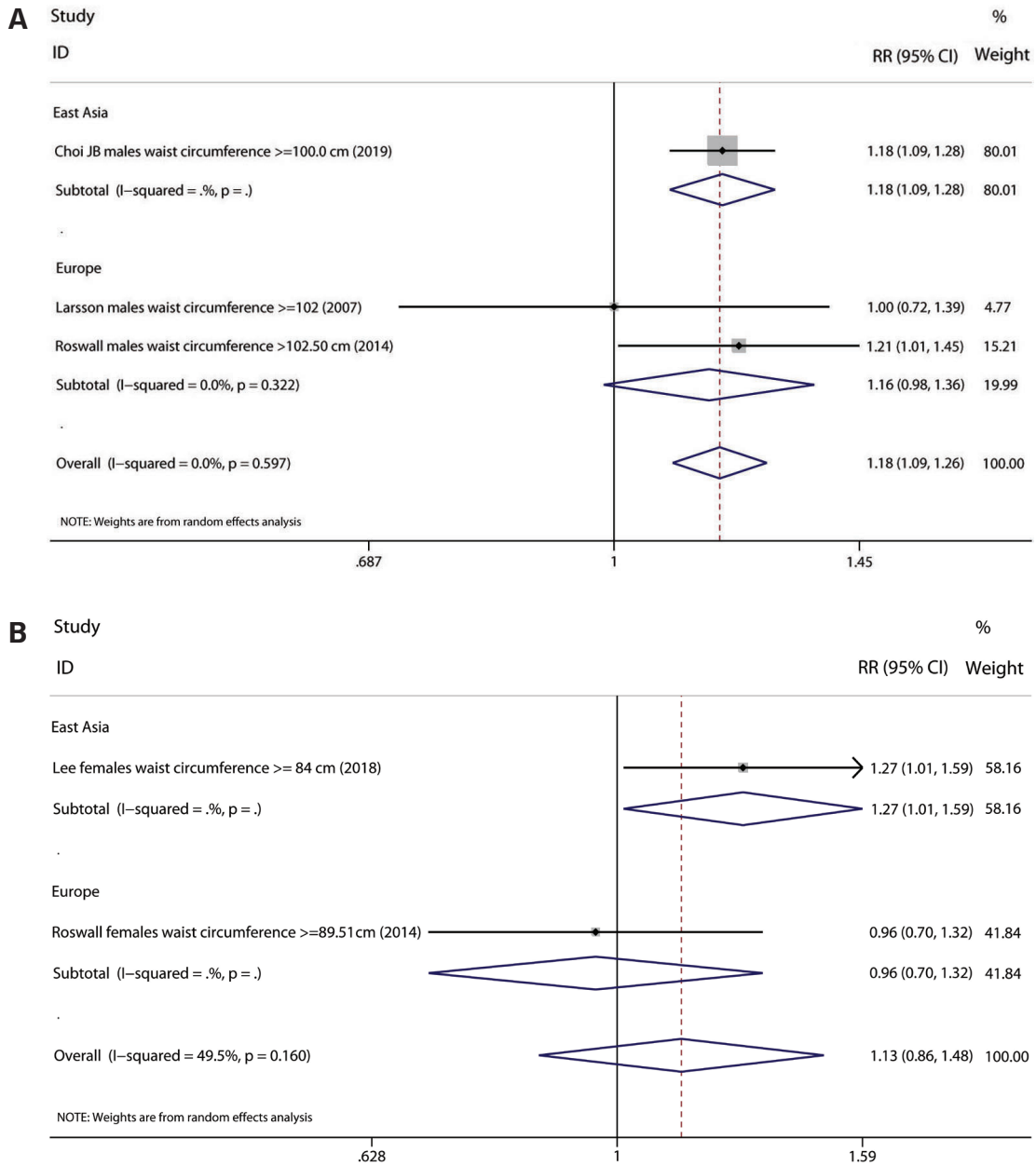

Figure 2. A: Forest plot presenting the association between waist circumference and bladder cancer risk in males. **B:** Forest plot presenting the association between waist circumference and bladder cancer risk in females.

data about incremental estimates; nevertheless, both of these studies found no significant effect of increased height in incidence of bladder cancer in men.

Waist circumference and risk of bladder cancer

Pooled analysis of 3 study arms regarding risk of bladder cancer with increased waist circumference in men, resulted in significant increased risk in a highest vs. lowest (pooled RR=1.18, 95% CI: 1.09-1.26, Figure 2A). On the other hand, pooled analysis of 2 study arms showed no significant risk in women with increased waist circumference (pooled RR=1.13, 95% CI: 0.86-1.48, Figure 2B).

Sensitivity analyses

We performed sensitivity analysis after removing the study by Wolk et al [46] due to potential overlapping population with the study by Larsson et al [32]; the results were similar and remained significant for obese men (pooled RR=1.14, 95% CI: 1.06-1.23). We also performed sensitivity analysis for obese men after removing the study by Leiba et al [41] since it presented overall urothelial cancer, among which 94.4% was located in the bladder; the results also persisted, showing a significantly increased risk (pooled RR=1.12, 95% CI: 1.04-1.21).

Risk of bias and publication bias

Newcastle-Ottawa rating per domain and study are presented in Supplemental Table 1. No evidence of publication bias was detected by visual inspection of funnel plots and after performing Egger's test for outcomes with ≥ 10 study arms (Supplemental Table 2).

Discussion

This systematic review and meta-analysis highlight an association between increased bladder cancer risk in overweight and obese men, as well as in obese women. Central obesity also correlated with bladder cancer risk in men, but not women. No associations were noted with height were noted in either sex.

Pooled analysis of twenty prospective cohort studies suggested that an increased risk of bladder cancer by 12% (RR=1.12) in overweight men, while for overweight women the respective difference was not significant. In accordance with our findings, Zhao et al supported that this association becomes significant only at a particular range of BMI, especially for obese people, while for overweight subjects there were no important findings [19]. On the other hand, Sun et al observed a 7% increased risk in preobese patients [18]. The difference noted between the two sexes is worth commenting. Several studies have proposed the protective role of estrogens in women regarding occurrence of bladder cancer, which is more common in post-menopausal women [52,53]. On the other hand, when considering the same embryologic origin of urinary bladder with prostate and seminal vesicles, such sex-specific differences can be partially explained by the role of androgens on development and growth of bladder tumor cells [54]. At any case, our results indicated that the effect of obesity spanned both sexes, conferring increased risk by 14% in obese men and by 19% in obese women.

After performing subgroup analyses to identify potential sources of heterogeneity, results were similar across several geographical regions except Europe, where different dietary habits among Mediterranean and non- Mediterranean countries could be a source of diversity. Men older than 50 years were those affected the most, probably because of longer duration of increased BMI biological effect, compared to younger patients. Another possible explanation could be the higher incidence of bladder carcinoma at ages ≥ 50 y/o. Interestingly, studies where BMI was self-reported showed significant results in contrast to studies with measured BMI. The fact that self-reported anthropometric characteristics can correlate up to a certain degree to realistic measurements according to various cross-sectional studies [55] partly ameliorates the implications of this observation in terms of information bias, as overweight and obese individuals tend to underestimate their weight and overestimate their height, which leads to BMI underestimation [56]. In subgroup analyses, studies with a mean follow-up duration of<10 years showed significant results in contrast with studies with longer follow-up.

Various pathogenic mechanisms that link obesity with bladder cancer have been suggested. A well established link between obesity and insulin resistance along with excess insulin production has been supported; insulin stimulates mitosis and supports carcinogenesis and tumor growth through increased production of insulin-like growth factor I (IGF-I), which further promotes cell proliferation and inhibits programmed cell death [57]. Excess adipose tissue is associated with high levels of cholesterol, which is a prodrome molecule of testosterone [58]. The link between adiposity, mitochondrial dysfunction, increased oxidative stress [59] and leptin secretion, which promotes angiogenesis [60] may also explain this association. Finally, chronic inflammation, as expressed by the increased levels of C-reactive protein and interleukins in the serum of patients with cancer, may also play a role in

the interplay between obesity and bladder cancer [61,62].

Choi et al [39] studied the association between bladder cancer and increased height and found that per 5 cm increased height, risk rose by 8%; however, our systematic review and meta-analysis did not confirm this association. It has been postulated that, similarly with obesity effect, increased organ size translates in more active cell proliferation and potential for DNA mutations [63]. Data from other centers [29,32,33,47-51] support our observation, since no significant difference was detected. Holick et al [33]. interestingly reported an inverse relation and protective role of height regarding urothelial carcinoma; since height depends both on genetic and environmental effects, authors implied that this observation would be explained by poor nutrition during early life, which potentially elevates bladder cancer incidence [33]. Due to conflicting results, further studies are indicated to clarify this aspect.

To the best of our knowledge this is the first meta-analysis studying waist circumference effect on bladder cancer risk. There was an increased risk by 18% for males with increased waist circumference, especially when > 100 cm. The mechanisms proposed pertain to enhanced insulin and IGF-1 action and adipokine pathophysiology [64]. For women, after analysis of 2 arms, no significant difference was noted. Once again, additional studies are needed to investigate this association.

One of the key strengths of this meta-analysis is the inclusion of prospective cohort studies, with large sample sizes and long-term follow-up in most cases. In conjunction with analyzing the largest number of studies, it can provide an accurate estimate of the association between various anthropometric characteristics with bladder cancer incidence. Heterogeneity was assessed via a large number of subgroup analyses, which showed in general consistent results. The low probability of publication bias is another strength of this systematic review.

Our study however suffers from some limitations. Including studies only in English is a limitation, but since we included the large number of studies when compared to previous reviews, the potential is attenuated. Of course, even though most studies adjusted their model for a number of confounders, the risk of residual confounding is never eliminated, especially in non-randomized studies. Various assessments of obesity and possibility of BMI fluctuation through time is also a matter of concern. Finally, we have chosen not to perform a dose response analysis of BMI and we adhered to the standard classifications of overweight and obese status, to avoid effects of approximation and stay as close to the published data as possible.

In conclusion, our meta-analysis detected an increased risk of bladder cancer in overweight males, obese males and females and males with central obesity. The effect was more pronounced in men older than 50 years, while height did not seem to be a risk factor. Taking into consideration the low number of studies regarding waist circumference, this could be an area of future research.

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Conflict of interests

The authors declare no conflict of interests.

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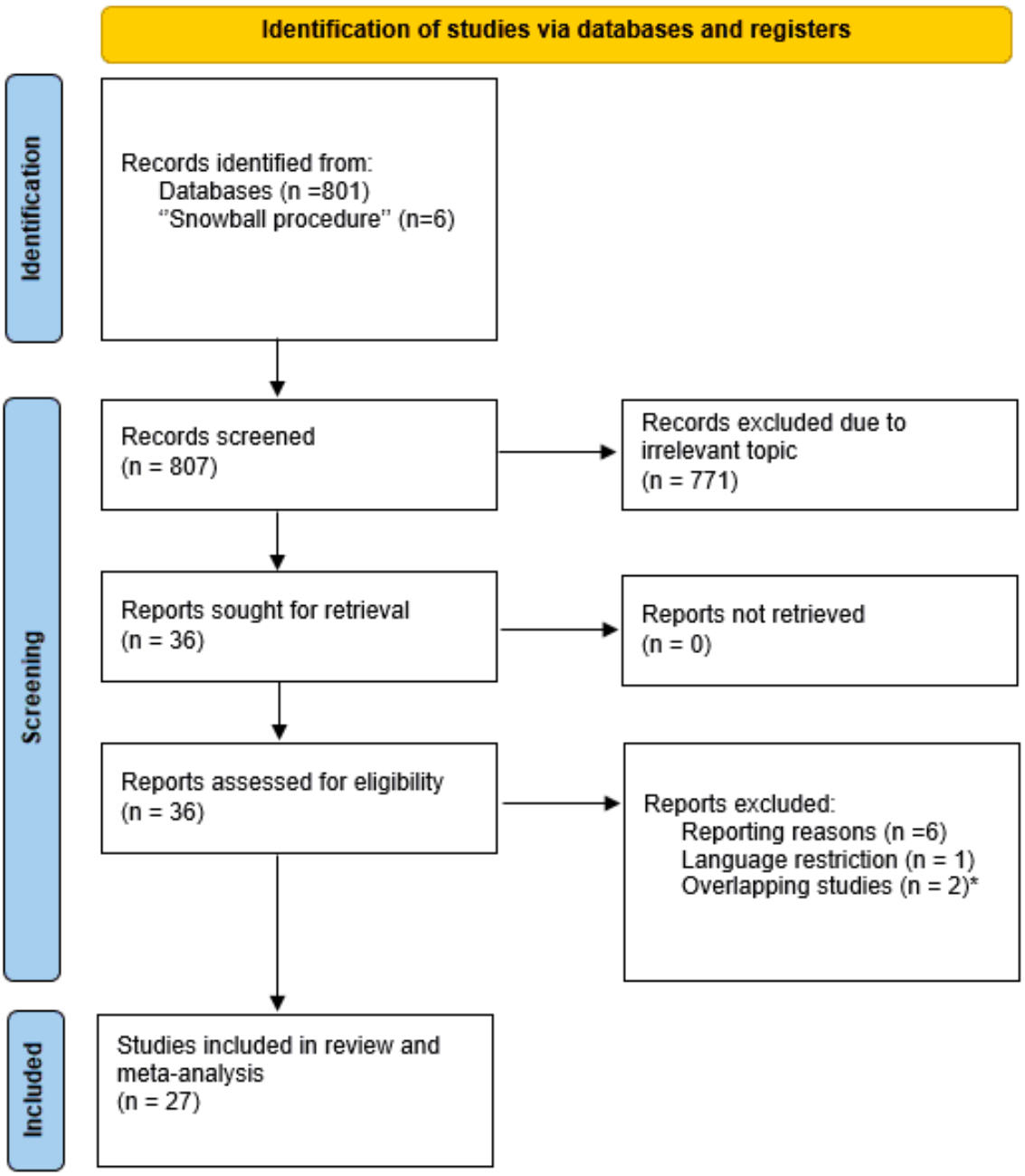
Supplemental Table 1. Evaluation of the eligible studies with Newcastle-Ottawa scale

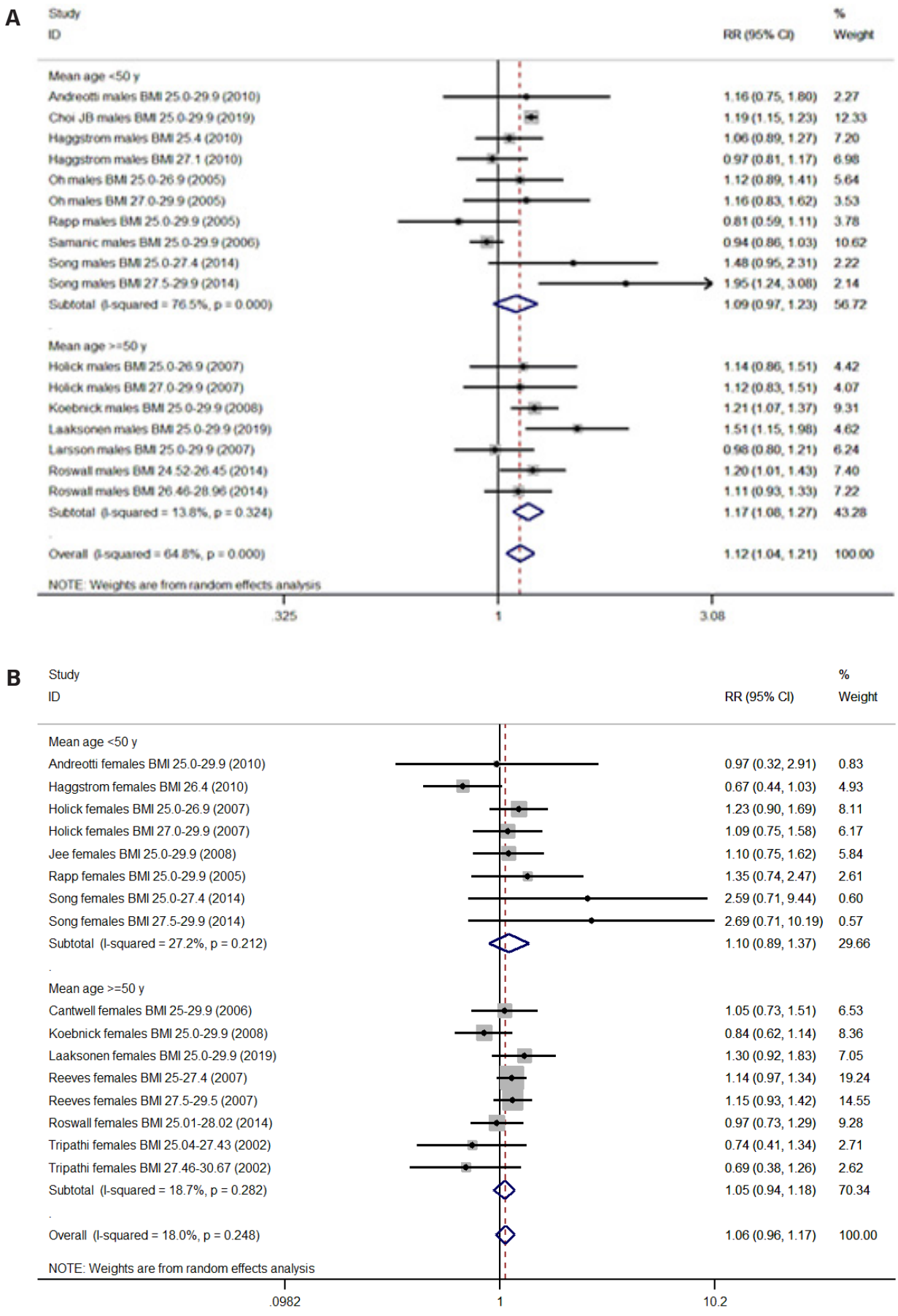
Study ID	*Selection*				*Comparability*		*Outcome*		
	Representativeness	*Selection of non-exposed*	*Ascertainment of exposure*	*Outcome not present at start*	*Comparability on age*	*Comparability on other risk factors*	*Assessment of outcome*	*Long enough follow-up (median ≥10 years)*	*Adequacy (completeness) of follow-up (≥85% response rate)*
Albanes (1988)	-	*	*	*	*	*	*	*	-
Andreotti (2019)	*	*	-	*	*	*	-	-	*
Cantwell (2006)	*	*	*	*	*	*	*	-	*
Choi JB (2019)	*	*	*	*	*	*	*	-	*
Choi YJ (2019)	*	*	*	*	*	*	-	-	-
Green (2011)	*	*	-	*	*	*	*	-	*
Haggstrom (2010)	*	*	*	*	*	*	*	*	*
Holick (2007)	*	*	-	*	*	*	*	*	*
Jee (2008)	*	*	*	*	*	*	*	*	*
Kabat (2012)	*	*	*	*	*	-	*	*	*
Kabat (2013)	*	*	*	*	*	*	-	*	-
Kabat (2014)	*	*	-	*	*	*	*	*	*
Koebnick (2008)	*	*	-	*	*	-	*	-	*
Laaksonen (2019)	*	*	-	*	*	*	*	-	*
Larsson (2007)	-	*	-	*	*	*	*	-	*
Leiba (2012)	-	*	*	*	*	-	*	*	*
Oh (2005)	*	*	*	*	*	*	*	-	*
Rapp (2005)	*	*	*	*	*	*	*	- (males) * (females)	*
Reeves (2007)	*	*	-	*	*	*	*	-	*
Roswall (2014)	*	*	*	*	*	*	*	*	*
Samanic (2006)	*	*	*	-	*	*	*	*	*
Samanic (2004)	*	*	*	*	*	-	*	*	*
Song (2014)	*	*	*	*	*	*	*	*	*
Teleka (2018)	*	*	*	*	*	*	*	*	*
Tripathi (2002)	*	*	-	*	*	*	*	-	*
Wiren (2013)	*	*	*	*	*	-	*	*	*
Wolk (2001)	*	*	*	*	*	-	*	- (males) * (females)	*

Supplemental Table 2. Publication bias assessment by Egger's test

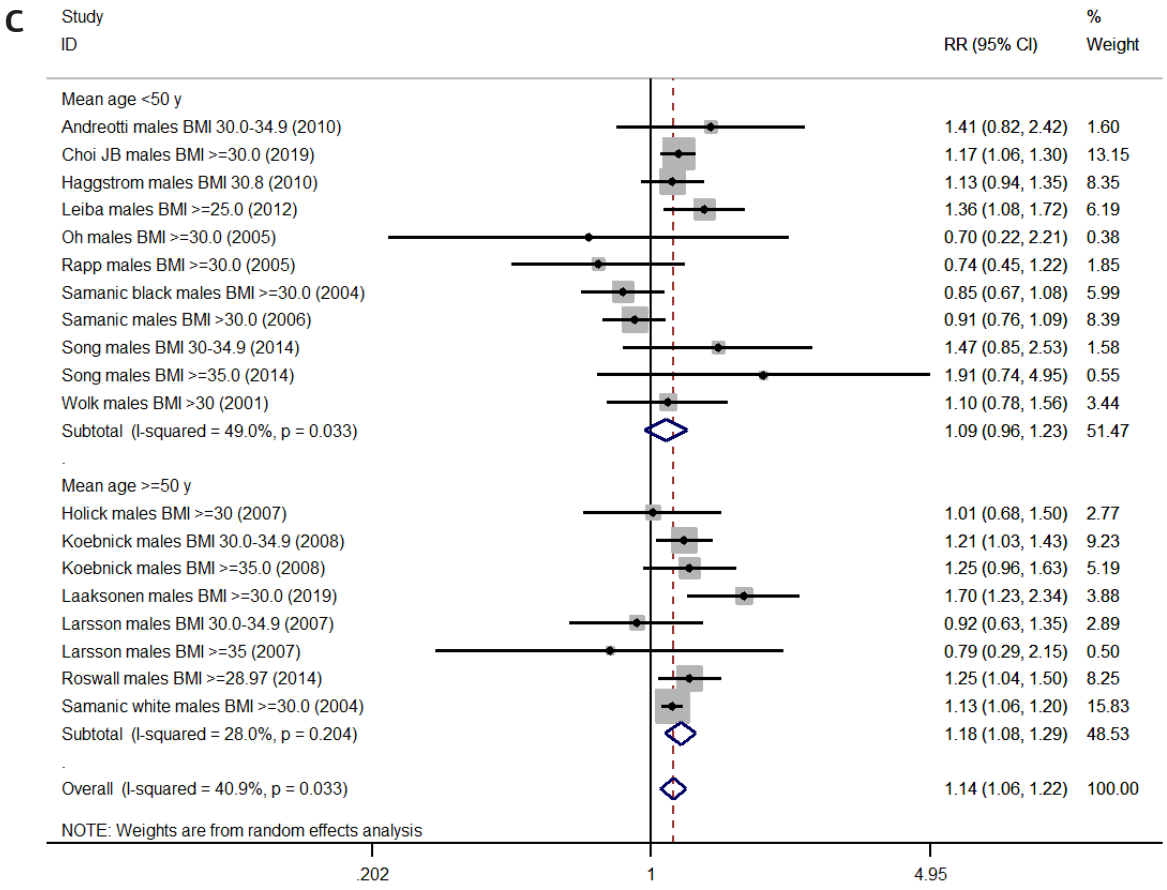
Outcome	*Egger's test p value*
Men overweight	0.557
Men obese	0.917
Women overweight	0.864
Women obese	0.708

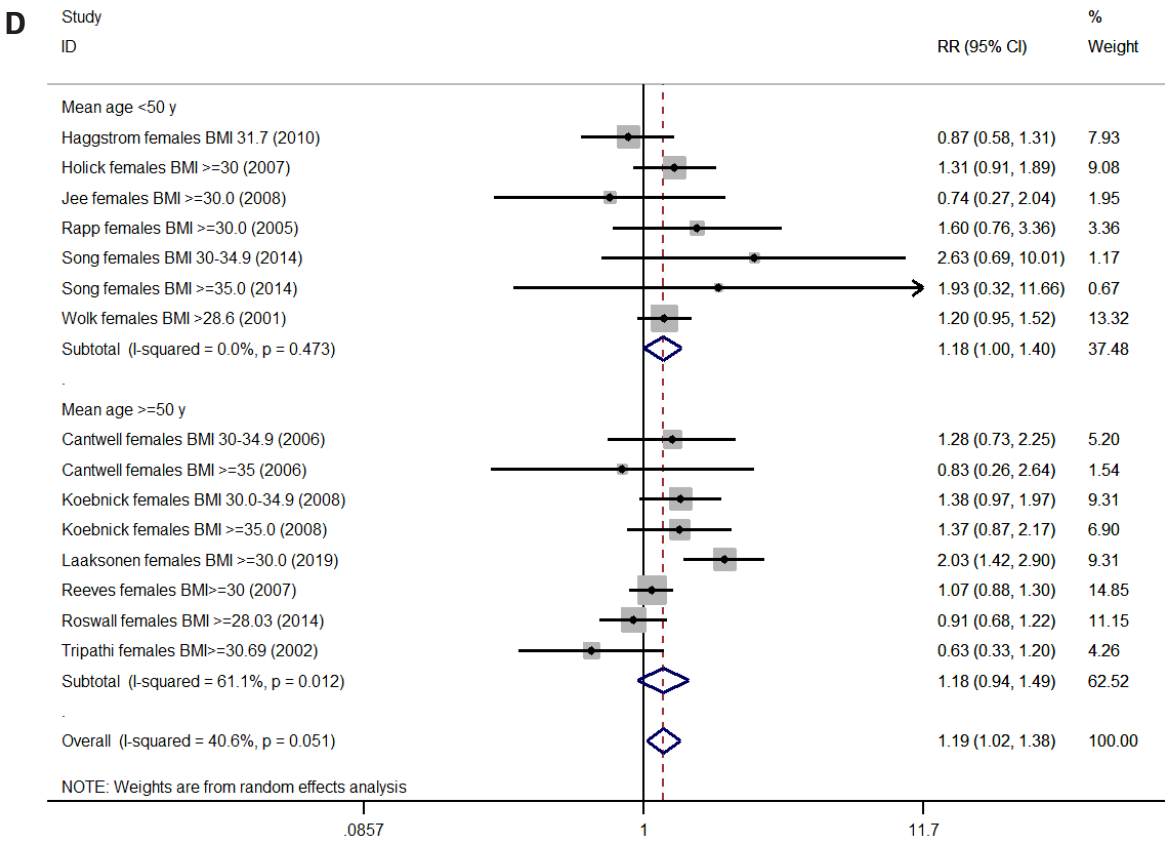


Supplemental Figure 1. Flow diagram for study selection. *The male arm in the study by Jee (2008) et al. was excluded due to overlap with the study by Oh et al. that spanned a longer time period (1992-2001 *vs.* 1992-1995) *The male arm in the study by Lee et al (2018) was excluded due to overlap with the study by Choi J.B. et al that spanned the same time period (2009-2015).



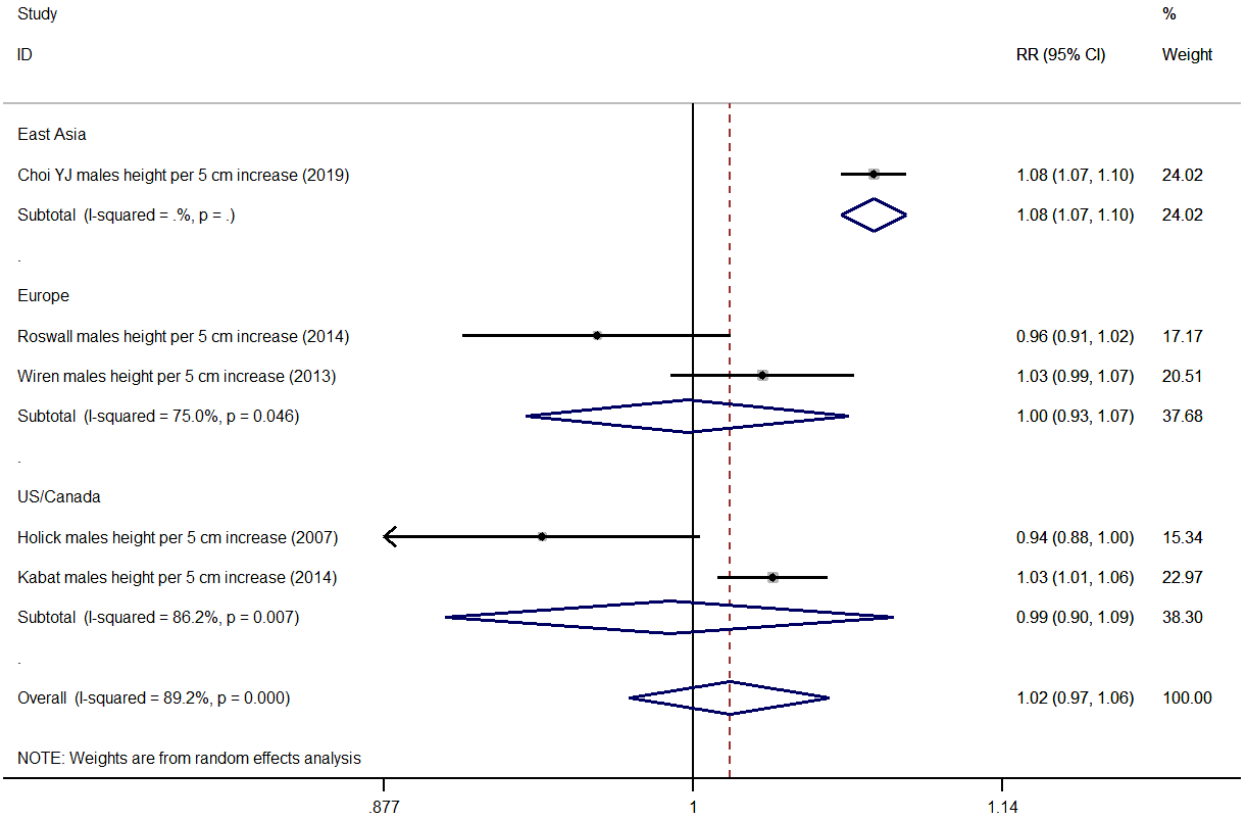
Supplemental Figure 2. A: Forest plot of subgroup analysis, by age in overweight males. **B:** Forest plot of subgroup analysis, by age in overweight females.



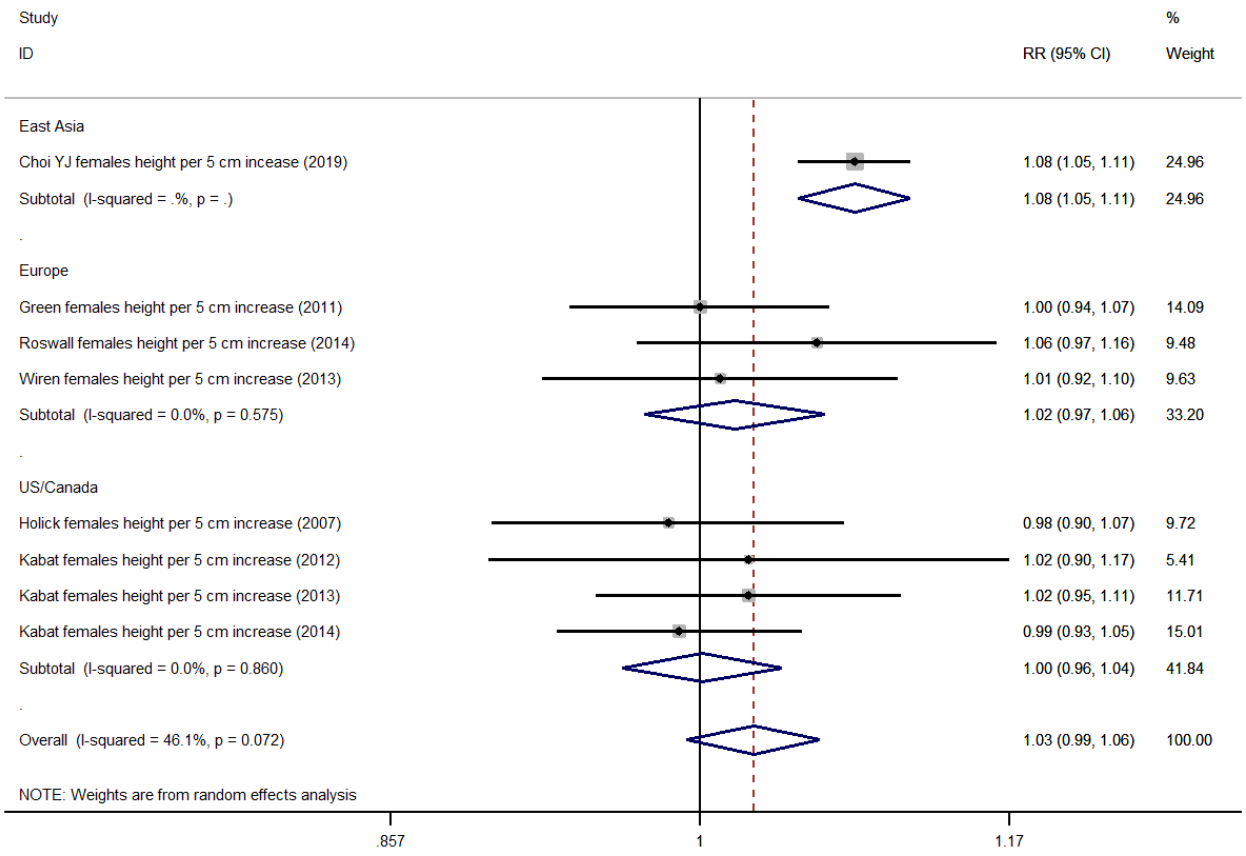


Supplemental Figure 2. C: Forest plot of subgroup analysis, by age in obese males. **D:** Forest plot of subgroup analysis, by age in obese females

A



B



Supplemental Figure 3. A: Forest plot for height increase per 5 cm in males. **B:** Forest plot for height increase per 5 cm in females.