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META-ANALYSIS

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# Body Mass Index Can Increase the Risk of Gallbladder Cancer: A Meta-Analysis of 14 Cohort Studies

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Background:** This study sought to appraise the association between raised body mass index (BMI) and the risk of gallbladder cancer (GBC) by performing a meta-analysis of 14 cohort studies.

**Materials/Methods:** Eligible cohort studies were selected by searching PubMed and EMBASE from their inception to May 26, 2016, and the reference lists of retrieved articles were also consulted. The information was screened by two authors separately. We used a fixed-effects model to calculate the overall pooled risk estimates. A random-effects model was used to identify heterogeneity.

**Results:** The meta-analysis incorporated 14 cohort studies. Nine papers were deemed to be of high quality based on the Newcastle-Ottawa Scale (NOS). Compared with normal weight (BMI 18.5–24.9 kg/m$^2$), the overall pooled relative risks (RR) of GBC was 1.45 (95% CI 1.30–1.61) for excess body weight individuals (BMI ≥25 kg/m$^2$); 1.10 (95% CI 1.02–1.18) for overweight persons (BMI 25–29.9 kg/m$^2$) and 1.69(95% CI 1.54–1.86) for obese folks (BMI ≥30 kg/m$^2$). A higher risk of GBC was presented in obese women (women: RR 1.78, 95% CI 1.59–1.99; men: RR 1.50, 95% CI 1.25–1.79). And a positive relationship between overweight and GBC risk was also displayed in female (RR 1.25, 95% CI 1.11–1.40), but not in male (RR 1.01, 95% CI 0.93–1.11). The sensitivity analysis indicated stable results, and no publication bias was observed.

**Conclusions:** This meta-analysis of 14 cohort studies demonstrated that raised BMI has a dramatic association with risk of GBC, especially in women. But, no association between overweight and GBC in men was found.

**MeSH Keywords:** Body Mass Index • Cohort Studies • Gallbladder Neoplasms • Meta-Analysis

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## Background

The World Health Organization (WHO) Cancer Report [1] said that approximately 15 million new cancer cases could be further increased in the next decades. Gallbladder cancer (GBC) is a common disease which has poor prognosis and is highly aggressive [2]. The incidence and mortality rates are the highest cancer rates and the trend is increasing worldwide [3]. Many studies [4–12] have reported multiple factors closely related to GBC, such as gallstones, alcohol consumption, smoking, blood glucose and diabetes mellitus (DM), genetic susceptibility, and obesity. Thus, the etiologies of GBC in its acute stage are of interest.

Body mass index (BMI) is a simple index and an accepted measure used to distinguish excess body weight, including overweight and obesity [13]. A WHO report [14] indicated that global obesity, which is defined as abnormal or excessive fat accumulation, has more than doubled in the past thirty years. Another WHO report [15] indicated that obesity is a well-established risk factor of gallbladder disease. Furthermore, according to WHO, overweight (BMI ≥25 kg/m$^2$ and ≤29.9 kg/m$^2$) and obesity (BMI ≥30 kg/m$^2$) are recognized as important risk factors for multiple cancer types [16,17]. In our study, we defined excess body weight as BMI ≥25 kg/m$^2$.

Based on the complicated etiology of GBC, obesity plays an important role in biliary tract cancers [18] and the frequency of obesity was high among patients with GBC [19]. In order to further evaluate the relationship between obesity and GBC, we performed this meta-analysis. The study complied with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [20].

## Material and Methods

### Search strategy and data sources

We searched PubMed and EMBASE (from their inception to May 26, 2016) for cohort studies describing the association between BMI and GBC. To identify any additional studies, the bibliographies of relevant articles were also searched. The search used the following keywords: (1) "Cancer of Gallbladder", "Gallbladder Cancer", " Neoplasm, Gallbladder", "Gallbladder Neoplasm", "Gallbladder Cancers", "Gall Bladder Cancers", "Cancers, Gallbladder", "Cancers, Gall Bladder", "Cancer, Gallbladder", "Cancer, Gall Bladder", "Bladder Cancers, Gall", "Bladder Cancer, Gall", "Neoplasms, Gallbladder", "Gall Bladder Cancer", "Cancer of the Gallbladder" [Title/Abstract] OR "Gallbladder Neoplasms" [Mesh]; and (2) "Quetelets Index", "Index, Quetelet", "Quetelet Index", "Quetelet's Index", "Index, Body Mass", "overweight", "obesity", "excess body weight" OR "Body Mass Index"[Mesh]; and (3) "cohort study" OR "Cohort Studies"[Mesh].

### Study selection

Studies were considered eligible if they met all of the following criteria: (1) a cohort study not a case-control study; (2) it evaluated the association of raised BMI with GBC incidence;(3) the interesting outcome was GBC incidence; (4) the interesting exposure was overweight or obesity defined by BMI; and (5) it provided HRs or RRs and the corresponding 95% CIs or data to calculate them. Extra studies were identified by a hand search of all the references of the retrieved articles.

### Data extraction and quality assessment

The two authors (HL and ZWT) independently computed all the retrieved studies based on the aforementioned selection criteria. We also performed a cross-reference search of eligible articles to identify studies which we did not find in the computerized search. The following information from cohort studies were extracted: the name of the first author; publication year; regions of study; study period; sample size; cases size; gender; mean age or age range; follow-up year; BMI categories; assessment of BMI; RR or HR and the 95% CI; and the confounding factors. Together with the co-corresponding authors (LL and YSW), we resolved any disagreements by discussion or consultation. The Newcastle-Ottawa Scale (NOS) [21] was used for methodological quality assessment. The three parameters for quality of a cohort study were consisted with the NOS, namely selection, comparability, and outcome. The maximum NOS score was 9. NOS score <7.0 was defined as low quality and NOS score ≥7.0 was high quality.

### Statistical analyses

The association between raised BMI and GBC was estimated by computing the pooled RR and its 95% CI, which was calculated from the adjusted RR or HR and 95% CI offered in the studies. In this meta-analysis, HRs was deemed equivalent to relative risks (RRs) [22]. The Q test and the $I^2$ test [23] were used to assess the studies heterogeneity. The D-L random effects model [24] was used as the pooling method when significant heterogeneity existed and the M-H fixed effect model [25] was used when no heterogeneity was observed. Subgroup analyses by gender, geographic location, and follow-up time (≥10 years and <10 years) were performed in order to further explore the origin of heterogeneity. Additionally, Begg funnel plots and Egger regression test [26] were done to test potential publication bias. The data analyses were performed using Stata version 13.1 (StataCorp LP, College Station, TX, USA).





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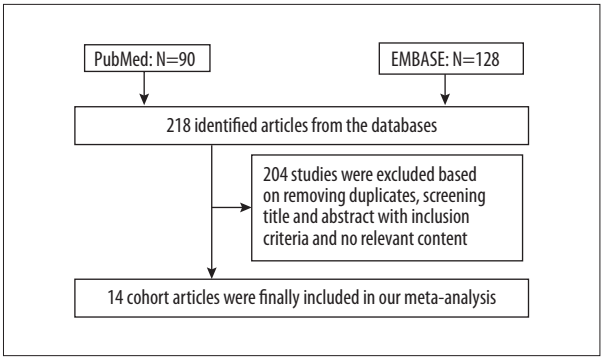


**Figure 1.** Flow chart illustrating the literature search for cohort studies on BMI in relation to GBC. BMI – means body mass index; GBC – means gallbladder cancer.

## Results

### Literature search and study characteristics

As shown in Figure 1, a total of 218 articles (90 from PubMed and 128 from EMBASE) were retrieved. Among these articles, 204 articles were excluded after screening the titles and abstracts, eliminating repetitions, and reviewing the full paper. Finally, we retained 14 cohort studies in our analysis. Six [10,27–31] of the 14 cohort studies were from Europe, five [32–36] were from Asia and three [37–39] were from America. The main information and NOS scores of the 14 studies are summarized in Table 1. Nine of the 14 articles were high-quality studies (scores ≥7.0).

### Main analysis

The meta-analysis, which included 10,530,142 individuals, found a positive association between excess body weight and GBC risk (RR 1.45, 95% CI 1.30–1.61) compared with normal weight (Figure 2). After combining the data, we also found a promising association between overweight and GBC risk (RR 1.10, 95% CI 1.02–1.18) compared with normal weight (Figure 3). In addition, we found a dramatic association between obesity and GBC risk (RR 1.69, 95% CI 1.54–1.86) compared with normal weight (Figure 4). No heterogeneities were observed.

### Subgroup meta-analysis

Depending on the subgroup analysis of gender, a promising connection between BMI and GBC risk was observed, especially in women. Higher risks for GBC were present in women compared to men who had BMI of excess body weight and obesity. No relationship was found in overweight men (RR 1.01, 95% CI 0.93–1.11). When BMI ≥25 kg/m$^2$, statistical heterogeneity was observed in women ($p$=0.002; $I^2$=59.3). A positive relationship between excess body weight and obesity and GBC risk were revealed in the subgroup analysis of study region. No statistical heterogeneity was observed in the European group. Moreover, among each stratum of BMI, the risk of GBC in the Asia group was lower than the other three groups. Additionally, we also observed statistical heterogeneity in American overweight and excess body weight groups. Furthermore, no association was observed between overweight and GBC risk in the follow-up ≥10 year group (RR 1.05, 95% CI 0.97–1.15) (Table 2).

### Sensitivity analysis

To appraise the study's robustness, a sensitivity analysis was performed by excluding one study per iteration and recounting the pooled results of the primary analysis. The overall combined result was stable (Figure 5).

### Publication bias

Among the studies, no evidence of publication bias was appeared by the Begg test and Egger linear regression test [Begg, $p$>|z|=0.125; Egger, $p$=0.051, 95% CI: –0.065–2.519] (Figures 6, 7).

## Discussion

The primary results of this study demonstrated that excess body weight, overweight, or obesity were associated with an increase in GBC risk. In this meta-analysis, we found that the risk of GBC were 1.45 times, 1.10 times, and 1.69 times that of normal weight people in excess body weight (BMI ≥25 kg/m$^2$), overweight (BMI 25–29.9 kg/m$^2$) and obesity (BMI ≥30 kg/m$^2$) groups, respectively. Among each stratum of BMI, the risk of GBC in men was lower than women, a finding that was consistent with previous studies. Our sensitivity analysis suggested that the combined results were stable and robust. No publication bias was observed in our study.

The etiology of gallbladder carcinoma involves an intricate interaction of metabolic alterations [40]. Numerous of studies [4,5,41] have confirmed that gallstone are the main cause of GBC. We found that obesity was not only strongly associated with gallstones [42] but also had an increased frequency of gallstones [43]. Another study [44] found that obese people had supersaturated gallbladder bile accounting for the inclination to cholesterol cholelithiasis. In addition, diabetes has been shown to be a risk factor for gallstones [45] in general, and in people with abdominal obesity [46]. A Danish study [47] found a positive association between elevated glucose levels and gallbladder carcinoma. When individuals with gallstone diseases or unknown status were excluded in an analyses on GBC, one study [46] found that the risk of GBC was 1.50 times (1.01–2.22) than the risk of GBC for an increment of 5 kg/m$^2$ in





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**Table 1.** Characteristics of 14 cohort studies.

| Author, year, country (study period) | Sample | Age: Mean or range | Follow-up years | BMI ascerta-inment | BMI categories (kg/m²) | RR and 95% CI | | | Adjustments | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Total | Men | Women | | |
| Ikuko Kato, 1992, Hawaii (1965–1968) | 7,831 m | Born from 1900 to 1919 | ≥22 | Measured | <21.65<br>21.65–23.19<br>23.80–25.80<br>>25.80 | NA | 1.0<br>1.1 (0.9–1.5)<br>1.4 (1.1–1.9)<br>1.8 (1.4–2.3) | NA | Occupation, education, smoking, dietary, alcohol, age, physical activity | 6 |
| Moller, 1994, Denmark (1977–1987) | 43,965 | 50 m<br>60 f | 5 | Discharge diagnosis | Non-obese<br>Obese | 1.30 (0.8–1.8) | 0.50 (0.1–1.8) | 1.40 (0.9–2.1) | Age | 6 |
| Wolk, 2001, Sweden (1965–1993) | 28,129 | 46.1 | 10.3 | Discharge diagnosis | Non-obese<br>Obese | 1.60 (1.1–2.3) | 0.90 (0.1–3.4) | 1.70 (1.1–2.5) | Age, calendar year | 7 |
| Calle, 2003, USA (1982–1998) | 900,053 | 57 | 16 | Self-reported | 18.5–24.9<br>25.0–29.9<br>30.0–34.9<br>≥35 | NA | 1.00 (reference)<br>1.34 (0.97–1.84)<br>1.76 (1.06–2.94)<br>NA | 1.00 (reference)<br>1.12 (0.86–1.47)<br>2.13 (1.56–2.90)<br>NA | Age, race, marital status, smoking, aspirin, alcohol, estrogen therapy | 8 |
| Samanic, 2004, USA (1969–1996) | 4,500,700 m<br>B: 832,214<br>W: 3,668,486 | 52.18 W<br>47.63 B | 1–27 | Discharge diagnosis | Non-obese<br>Obese | 1.62 (1.09–2.41) | 0.93 (0.23–3.86)<br>W 1.70 (1.13–2.57)B | NA | Age, calendar year | 6 |
| Anders England, 2005, Norway (1963–2001) | 2,001,511 | 44(20–74) | 23 | Measured | <18.5<br>18.5–24.9<br>25.0–29.9<br>≥30.0 | NA | 0.31 (0.04–2.24)<br>1.00 (referent)<br>1.00 (0.84–1.17)<br>1.38 (1.01–1.89) | 1.02 (0.54–1.91)<br>1.00 (referent)<br>1.27 (1.10–1.47)<br>1.88 (1.60–2.21) | Age, birth | 7 |
| Kuriyama, 2005 Japan (1984–1992) | 27,539 | ≥40 | 9 | Self-reported | <18.5<br>18.5–24.9<br>25.0–29.9<br>≥30.0 | NA | 1.00 (reference)<br>0.46 (0.05–3.93)<br>NA<br>NA | 1.00 (reference)<br>0.83 (0.23–2.98)<br>3.43 (1.19–9.94)<br>4.45 (1.39–14.23) | Age, smoking, health insurance, alcohol | 7 |
| Sang Woo Oh, 2005, Korea (1992–2001) | 781,283 m | ≥20 | 10 | Measured | <18.5<br>18.5–22.9<br>23.0–24.9<br>25.0–26.9<br>27.0–29.9<br>≥30.0 | NA | 2.44 (1.12–5.34)<br>1.00 (reference)<br>1.5 (1.10–2.20)<br>1.1 (0.74–1.80)<br>1.2 (0.70–2.24)<br>NA | NA | Age, smoking, alcohol, exercise, region | 7 |
| Samanic, 2006, Sweden (1971–1999) | 362,552 m | 18-67 | 28 | Measured | 25.0–29.9<br>≥30.0 | NA | 0.93 (0.62–1.39)<br>1.40 (0.73–2.70) | NA | Age, smoking | 8 |





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**Table 1 continued.** Characteristics of 14 cohort studies.

| Author, year, country (study period) | Sample | Age: Mean or range | Follow-up years | BMI ascerta-inment | BMI categories (kg/m²) | RR and 95% CI | | | Adjustments | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Total | Men | Women | | |
| Ishiguro, 2008, Japan (1994–2004) | 101,868 | 40–69 | 10.9 | Self-reported | ≤22.9<br>23.0–24.9<br>25.0–26.9<br>≥27.0 | NA | 1.00 (reference)<br>0.74 (0.28–1.92)<br>1.26 (0.48–3.33)<br>1.39 (0.45–4.34) | 1.00 (reference)<br>0.47 (0.22–0.98)<br>0.62 (0.29–1.34)<br>0.94 (0.48–1.88) | Age, gender, study area, diabetes, smoking, alcohol | 6 |
| Sun Ha Jee, 2008, Korea (1992–2006) | 1,213,829 | 45.0 m<br>49.4 f | 10.8 | Measured | 25.0–29.9<br>≥30 | 1.00 (0.89–1.12)<br>1.54 (1.17–2.03) | 0.97 (0.86–1.10)<br>1.65 (1.11–2.44) | 1.27 (1.02–2.12)<br>1.44 (0.98–2.12) | Age, smoking, alcohol, physical activity | 8 |
| Yun-Mi Song, 2008, Korea (1994–2003) | 170,481 f | 40–64 (55.9) | 8.75 | Measured | <18.5<br>18.5–20.9<br>21.0–22.9<br>23.0–24.9<br>25.0–26.9<br>27.0–29.9<br>≥30 | NA | NA | 1.91 (0.78–4.68)<br>1.35 (0.74–2.47)<br>1.00 (reference)<br>1.06 (0.62–1.80)<br>1.30 (0.76–2.22)<br>1.86 (1.09–3.18)<br>2.10 (0.97–4.51) | Age, height, smoking, alcohol, exercise, pay level | 7 |
| Kari Hemminki, 2011, Sweden (1964–2006) | 30,020 | NA | 11.2 | Discharge diagnosis | Non-obese obese | 1.73 (1.16–2.57) | NA | 1.55 (0.93–2.43) | Age, sex, region, economic status | 7 |
| Schlesinger, 2013, Europe (1992-2000) | 363,426 | 25–70 | 8.5 | Discharge diagnosis | Non-obese obese | 2.71 (1.17–6.31) | NA | NA | Weight, height, waist circumference, alcohol, smoking, education, diet, lifestyle, medical history, Blood samples | 6 |

BMI – means body mass index(kg/m²); RR – represents the relative risk; CI – represents the confidence interva; m – means men; f – means female; B – means black; W – means white; NA – represents data not applicable; NOS – means the Newcastle-Ottawa Scale.

BMI. Another analysis [17] found that the risk of GBC in individuals with gallstones was 1.31 times (1.12–1.52). Rapp et al. [12] reported that elevated BMI was positively correlated with blood glucose. Thus, we can affirm that obesity could increase the prevalence of GBC by promoting formation of gallstones and elevating blood glucose level. Some studies [48–50] have shown that retinol binding protein 4 (RBP4) is closely associated with insulin resistance and obesity. Elevated RBP4 has been shown to increase the incidence rate of gallstone disease [51]. Wang et al. [52] reported that bile RBP4 was correlated with BMI positively. Hence, we can suppose that increased BMI may play a role in the course of gallstone formation so as to influence the morbidity of GBC by elevating RBP4. These aforementioned interconnected pathways may suggest pathophysiological mechanism of the obesity-cancer link.

However, one study [53] showed that estrogen was the main factor for the difference between males and females in terms of gallbladder stone formation. Another study [54] revealed that exogenous estrogens affected physiological markers facilitating gallstones formation. In addition, estrogens play a role in cholesterol secretion increasing and bile salt secretion diminishing [2]. Female sex hormones influence hepatic bile secretion and gallbladder function adversely [55] and oral hormonal replacement therapy could increase the risk of GBC [2], which have been shown to play an important role in the carcinogenesis process of this organ. These findings may partially explain the reason why the connection between raised BMI and GBC was stronger in women than in men.





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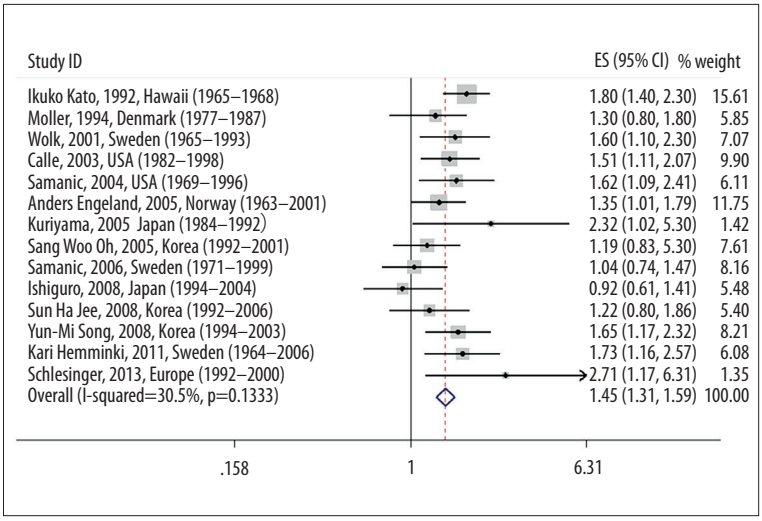


**Figure 2.** Forest plot of risk of GBC associated with excess body weight (BMI ≥25 Kg/m$^2$) in general population.

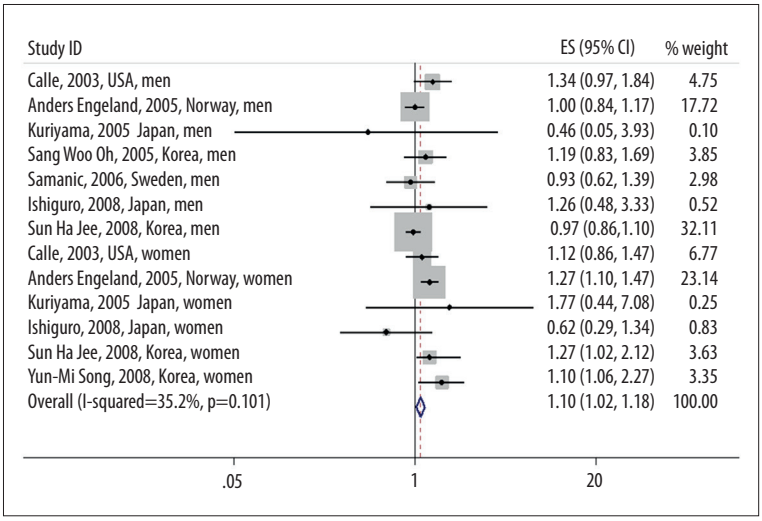


**Figure 3.** Forest plot of risk of GBC associated with overweight (25–29.9 Kg/m$^2$) in general population.

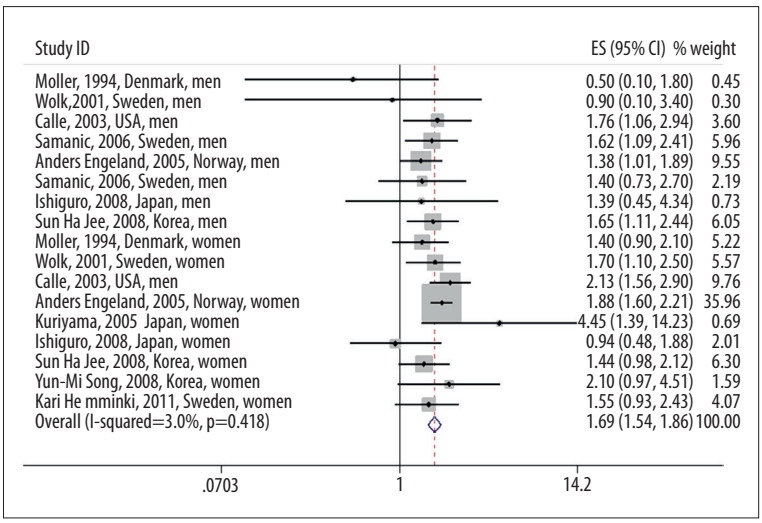


**Figure 4.** Forest plot of risk of GBC associated with obesity (≥30 Kg/m$^2$) in general population.





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**Table 2.** Subgroup analyses of the association between BMI and GBC risk.

| | Overweight (25–29.9 Kg/m²) | | | Obesity (≥30 Kg/m²) | | | Excess body weight (≥25 Kg/m²) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Studies | RR (95%CI) | P (I²%) | Studies | RR (95%CI) | P (I²%) | Studies | RR (95%CI) | P (I²%) |
| Sex | | | | | | | | | |
| Men | 6 | 1.01 (0.93, 1.11) | 0.532 (0.0) | 9 | 1.50 (1.25, 1.79) | 0.822 (0.0) | 11 | 1.09 (1.01, 1.18) | 0.058 (39.5) |
| Women | 6 | 1.25 (1.11, 1.40) | 0.362 (8.5) | 9 | 1.78 (1.59, 1.99) | 0.237 (23.2) | 9 | 1.48 (1.27, 1.72) | 0.002 (59.3) |
| Region | | | | | | | | | |
| Asia | 5 | 1.04 (0.94, 1.16) | 0.193 (34.3) | 4 | 1.55 (1.23, 1.96) | 0.136 (45.9) | 5 | 1.29 (1.02, 1.62) | 0.007 (62.0) |
| Europe | 2 | 1.07 (0.88, 1.32) | 0.415 (0.0) | 5 | 1.56 (1.31, 1.87) | 0.861 (0.0) | 6 | 1.36 (1.19, 1.55) | 0.100 (41.8) |
| America | 2 | 1.47 (0.99, 2.16) | 0.016 (82.8) | 2 | 1.89 (1.51, 2.35) | 0.365 (0.0) | 3 | 1.62 (1.26, 2.09) | 0.013 (72.1) |
| Non-Asia | 4 | 1.14 (0.96, 1.37) | 0.157 (50.1) | 7 | 1.68 (1.46, 1.93) | 0.185 (43.0) | 9 | 1.41 (1.26, 1.59) | 0.230 (30.7) |
| Follow-up time | | | | | | | | | |
| <10 | 2 | 1.52 (1.06, 2.19) | 0.677 (0.0) | 3 | 1.59 (1.13, 2.24) | 0.106 (55.1) | 4 | 1.63 (1.28, 2.07) | 0.288 (19.2) |
| ≥10 | 6 | 1.05 (0.97, 1.15) | 0.490 (0.0) | 7 | 1.70 (1.49, 1.93) | 0.449 (0.0) | 10 | 1.37 (1.17, 1.60) | 0.000 (76.5) |

BMI – represents the body mass index; GBC – represents the gallbladder cancer; RR – represents the relative risk; CI – represents the confidence interval; the values of P and I² represent the heterogeneity.

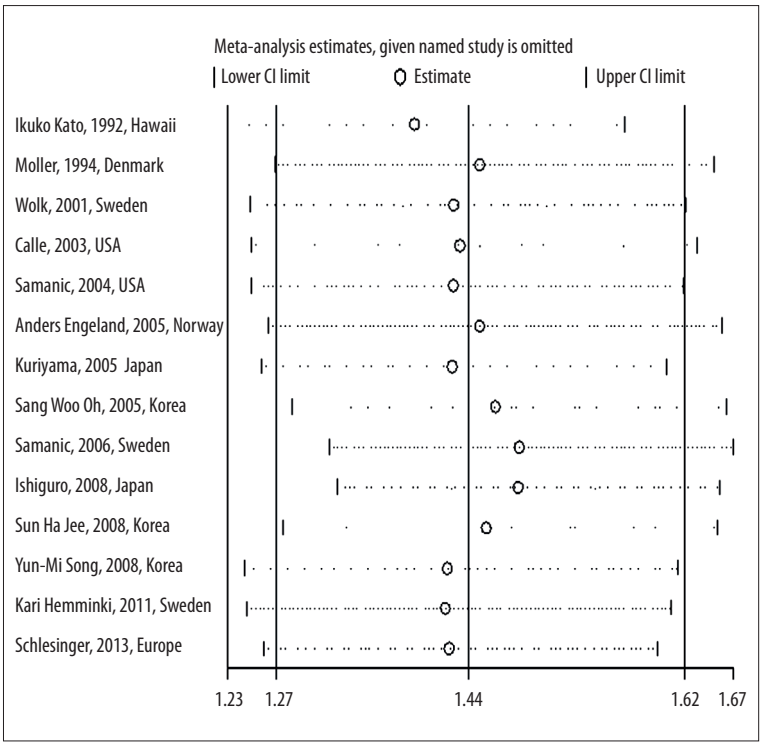


**Figure 5.** Sensitivity analysis of the association between BMI (≥25 Kg/m²) and GBC.





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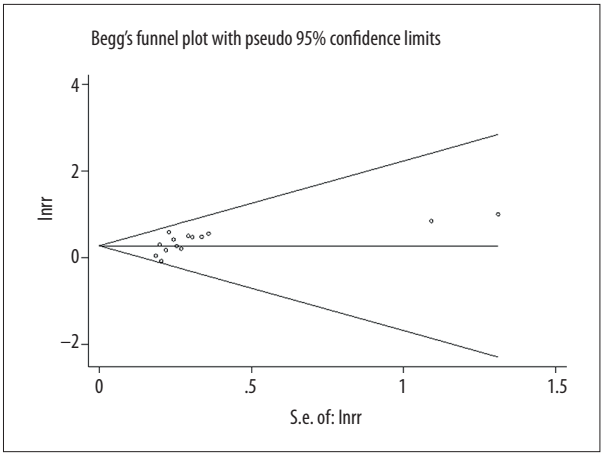


**Figure 6.** Begg's funnel plot of the 14 cohort studies.

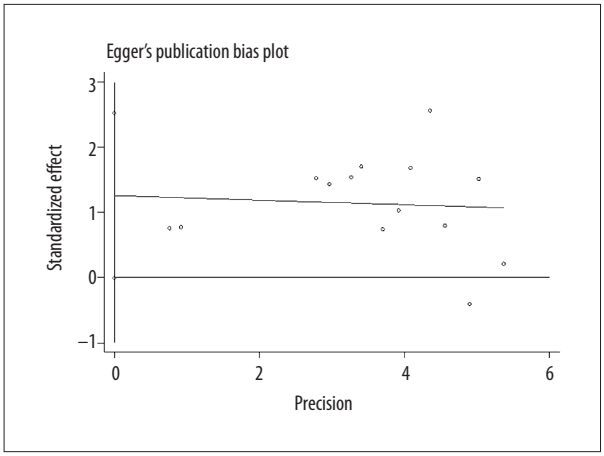


**Figure 7.** Egger's publication bias plot.

A meta-analysis [56] found that BMI for persons from East Asian countries was 1.9–3.2 kg/m$^2$ lower than for Caucasians, when they were at the same percentage of body fat. Another study [57] found that compared with Asian populations, Western white populations have a lower percentage of body fat at a particular BMI level. For the aforementioned evidence, Asian populations may have a higher risk of GBC than Caucasians. But in our study, the subgroup meta-analysis found that the risk of GBC in the Asia group was lower than the other three groups within each stratum of BMI. It is possible that race or lifestyle is a principal factor. One research study [58] concluded that a Western diet elevates body adiposity without changing body weight. BMI associating with cancer risk was defined by a Western cut-off point [35]. Hence, what we need is the establishment of different cut-off points for Asian populations or identical cut-off points for the globe population.

There were several strengths in our meta-analysis. Observational studies cannot prove causality [59]. All of the included studies were cohort design with no epidemiological observational studies, which are considered a higher level of study design. A majority of the cohorts comprised at least one RR and 95% CI, allowing for subgroup analysis. Fourteen studies followed the participants for a long time (e.g., 10 years). All the included studies estimated multiple confounders. Of the studies that had large sample sizes, nine studies were judged to be high quality. Additionally, though several studies with high $I^2$ values (Table 2) were presented in certain subgroup analyses, we did not find heterogeneity in the three main analyses presented. However, in the subgroup analysis of study regions, studies conducted in America made principal contributions to heterogeneity. The number of articles (only three) may be an important reason for the heterogeneity. Yet, no heterogeneity was observed after we put the European group and American group into one group called non-Asian group. In addition, gender and follow-up year also introduced heterogeneity to some extent in the subgroup analysis. When more data is available, we will evaluate these factors again, in a future study.

Regardless of the advantages of this study, the meta-analysis also had limitations. First, notwithstanding that we searched all cohort studies for the association between BMI and GBC risk; all eligible studies were restricted to English language publications. This linguistic barrier excluded some non-English language studies. We also missed some studies published in a book or a journal that was not available through the internet databases. Additionally, journals may reject studies with non-significant results, or studies showing an absence of effect may not be submitted by investigators. Fortunately, no publication bias was found in our study, although we could not rule out publication bias completely. Second, a few studies did not present clear or entire data, making data analysis difficult. For this reason, in the sub-analysis, the sum of some of the groups' data were not equal to the total numbers included in the literature. When we could not get original data from the authors by email or other means, we combined data. Moreover, some studies only described the relationship between BMI and men or women and did not describe the relationship among the general population. In these cases, we dealt with the data only in subgroup analysis depending on gender. In the gender sub-group analysis, significant heterogeneity was found in data for women whose BMI ≥25 kg/m$^2$, unfortunately, we did not find the reason for this heterogeneity by searching the databases. Furthermore, the class of BMI of other studies did not always follow the WHO criterion. In order to resolve this problem, we chose the class of BMI closest to the WHO criterion. For example in one study [37], the authors divided BMI (kg/m$^2$) into <21.65, 21.65–23.19, 23.80–25.80, and >25.80, and we then classified BMI >25.80 kg/m$^2$ as excess body weight group. Another study [33] divided BMI (kg/m$^2$) classes into 25.0–6.9, 27.0–29.9, and ≥30.0. Similarly, we combined 25.0–26.9 and 27.0–29.9 into one group. No heterogeneity was observed. Third, although nine of the fourteen studies were considered high quality, the NOS score of five articles were less than 7. In other word, nearly one third of the study reports supplied vague data, which would overestimate the





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pooled effect. Fourth, we did not appraise all the adjustments for confounders. The subgroup analysis only used gender, region, and follow-up year without other confounding factors. One meta-analysis [60] noted that smoking and alcohol consumption were also strongly associated with GBC risk in overweight people. Considering the difference and uncontrollability of lifestyles among people, we assumed that all confounders were equal, and our results were consistent with this assumption. Fifth, although BMI is the authoritative measure for normal weight assessment, there are still other tools for weight assessment used in judging abdominal adiposity that may be more sensitive in forecasting the risk of cancer, namely waist-to-hip ratio and waist circumference. Adipose tissue is known to play a positive role in tumor microenvironment [61]. However, BMI cannot make the distinction between fat mass and muscle mass. Finally, because of the small number of eligible articles, our study was not the most comprehensive. Thus, more comprehensive and higher quality analyses are still required in the future when more practicable data are published.

## Conclusions

In summary, the cohort studies meta-analysis indicated that raised BMI played an important role in the risk of GBC. Further studies that meet strict criteria on this subject are needed in order to provide more convincing evidence and to reinforce the association between BMI and GBC risk.

### Conflicts of interest

All authors declared no conflicts of interest.

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