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META-ANALYSIS

Body mass index, abdominal fatness and the risk of gallbladder disease

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Abstract Epidemiological studies have indicated a positive association between adiposity and gallbladder disease risk, however, the shape of the dose–response relationship and differences between overall and abdominal adiposity remains to be clarified. We conducted a systematic review and dose–response meta-analysis of cohort studies of body mass index (BMI), waist circumference and waist-to-hip ratio and risk of gallbladder disease. PubMed and Embase databases were searched up to January 9th 2015. Summary relative risks were calculated using a random effects model. Seventeen prospective studies of BMI and gallbladder disease risk with 55,670 cases among 1,921,103 participants were included. The summary relative risk (RR) for a 5 unit increment in BMI was 1.63 (95 % CI 1.49–1.78, $I^2 = 98$ %). There was evidence of a nonlinear association overall and among women, $p_{\text{nonlinearity}} < 0.0001$, but not among men, $p_{\text{nonlinearity}} = 0.99$, with a slight flattening of the curve at very high BMI levels (BMI 40–45), however, the risk of gallbladder disease increased almost twofold even within the "normal" BMI range. The summary RR for a 10 cm increase in waist circumference was 1.46 (95 % CI 1.24–1.72, $I^2 = 98$ %, n = 5) and for a 0.1 unit increment in waist-to-hip ratio was 1.44 (95 % CI 1.26–1.64, $I^2 = 92$ %, n = 4). Associations were attenuated, but still significant, when BMI and abdominal adiposity measures were mutually adjusted. Our results confirm a positive association between both general and abdominal fatness and the risk of gallbladder disease. There is an almost twofold increase in the risk even within the "normal" BMI range, suggesting that even moderate increases in BMI may increase risk.

Keywords Body mass index · Waist circumference · Waist-to-hip ratio · Gallbladder disease · Gallstones · Systematic review · Meta-analysis · Cohort studies

Introduction

Gallbladder disease, including gallstones and cholecystitis, is a major cause of morbidity in the US and in Europe and affects 10–30 % within these populations [1]. In the United Kingdom 49,000 cholecystectomies are conducted every year [2] and gallbladder disease is the most frequent and costly of digestive diseases that require hospitalization, while in the US approximately 700 000 cholecystectomies are conducted each year [3]. Gallstone disease is frequently complicated by acute cholecystitis, choledocholithiasis, cholangitis and several studies have also suggested increased gallbladder cancer risk in persons with gallstone disease [4, 5]. The economic costs of hospital treatment of gallstones is over 5 billion US dollar per year in the US [6]. However, there is substantial variation in the prevalence of gallstones worldwide, suggesting the possible importance of modifiable risk factors in its etiology [1].

A number of epidemiological studies have found increased risk of gallbladder disease with greater body

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mass index (BMI, weight in kg/height in m^2) [7–25], however, the strength of the association has varied between studies with some studies reporting twofold to threefold increases in the risk among obese persons [10, 12–15, 19, 21–23, 25, 26], while other studies using more refined and/or extreme categorisations of BMI have reported up to fivefold to sevenfold increases in the risk among persons with obesity [7, 9, 11, 17]. The optimal BMI for prevention of gallbladder disease is unknown. In addition, several studies have reported a positive association between measures of abdominal fatness, such as waist circumference and waist-to-hip ratio and gallbladder disease risk [14, 15, 17, 20, 27], but the strength of the associations reported has varied also for these measures. There is increasing evidence that insulin resistance plays a major role in the development of gallbladder disease [28] and abdominal obesity may be more strongly associated with insulin resistance than peripheral obesity, thus it would be of major importance to clarify whether abdominal obesity is an independent risk factor for gallbladder disease after taking into account BMI. To clarify the role of general and abdominal overweight and obesity in the role of gallbladder disease we conducted a systematic review and meta-analysis of published prospective studies. We particularly wanted to clarify the strength of the association, the shape of the dose–response relationship, potential confounding, and whether the associations with abdominal fatness and BMI are independent of each other.

Methods

Search strategy

We searched the PubMed and Embase databases up to January 9th 2015 for eligible studies. As part of a larger project on risk factors for gallbladder disease we used wide search terms in the PubMed search and a similar search was used in Embase: (body mass index OR BMI OR overweight OR obesity OR anthropometry OR fatness OR body fatness OR abdominal fatness OR abdominal obesity OR waist circumference OR waist-to-hip ratio OR physical activity OR exercise OR sports OR walking OR biking OR running OR fitness OR exercise test OR inactivity OR diabetes OR smoking OR tobacco OR risk factor OR risk factors) AND (gallstones OR gallbladder disease OR cholelithiasis OR cholecystectomy OR cholecystitis). We followed standard criteria for conducting and reporting meta-analyses [29]. In addition, we searched the reference lists of previous meta-analyses [30, 31] and the reference lists of the relevant publications for further studies.

Inclusion criteria and study selection

Published prospective studies (cohort studies and nested case-control studies within cohort studies) of the association between BMI, waist circumference, or waist-to-hip ratio and risk of gallbladder disease (defined as gallstones, gallstones and cholecystitis combined or cholecystectomies) were included. Retrospective case-control studies were excluded because of the greater potential for recall and selection bias and cross-sectional studies were excluded because of the difficulty in drawing causal inferences from such studies. Studies of gallstones in pregnancy or childhood or in specific populations such as cirrhosis or diabetes patients were excluded. Adjusted relative risk estimates (hazard ratio, risk ratio) had to be available with the 95 % confidence intervals in the publication, but for one study which only reported crude estimates [12], but stated that adjustment for age did not alter the results an exception was made. For the dose–response analysis, a quantitative measure of the exposure and the total number of cases and person-years or non-cases had to be available in the publication. We identified 29 publications that were potentially relevant for this meta-analysis [7–27, 32–39]. Five duplicate publications were excluded [26, 32–35], three publications which only had two categories of exposure were excluded [36–38], two publications which did not quantify the increment of BMI used in the analysis were excluded [24, 39], and one study with unadjusted risk estimates was excluded [25]. For the Nurses' Health Study 1 and the Health Professionals Follow-up Study we selected the publications which used the most refined and extreme categorisation of BMI to have the largest number of data points in the extreme ranges and these publications also adjusted for more confounding factors [9, 15] than the most recent publication [32].

Data extraction

The following data were extracted from each study: The first author's last name, publication year, country where the study was conducted, study period, sample size, number of cases/controls, exposure variable, exposure level, relative risks and 95 % confidence intervals and variables adjusted for in the analysis.

Statistical analysis

We calculated summary RRs and 95 % CIs for a 5 unit increment in BMI, 10 cm increment in waist circumference and for a 0.1 unit increment in waist-to-hip ratio using a random effects model [40]. For the primary analysis we used the model from each study that had the greatest degree of control for potential confounding, with the exception of studies that also adjusted mutually between BMI and waist

circumference and waist-to-hip ratio, for which we used the multivariate model without mutual adjustment between these variables. The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted using random effects weighting. A two-tailed $p < 0.05$ was considered statistically significant. If studies reported results separately for men and women we combined the sex-specific estimates using a fixed-effects model to generate an estimate for both genders combined so that each study was only represented once in the analyses.

The method described by Greenland and Longnecker [41] was used for the dose–response analysis and study-specific slopes (linear trends) and 95 % CIs were computed from the natural logs of the reported RRs and CIs across categories of anthropometric measures. The method requires that the distribution of cases and person-years or non-cases and the RRs with the variance estimates for at least three quantitative exposure categories are known. The mean BMI, waist circumference or waist-to-hip ratio level in each category was assigned to the corresponding relative risk for each study and for studies that reported the exposures in ranges we calculated the average of the upper and the lower cut-off point which was used as a midpoint. A potential nonlinear dose–response relationship between BMI, waist circumference and waist-to-hip ratio and gallbladder disease was examined by using fractional polynomial models [42]. We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity [42].

Subgroup and meta-regression analyses were conducted to investigate potential sources of heterogeneity and heterogeneity between studies was quantitatively assessed by the Q test and I^2 [43]. Small study effects, such as publication bias, were assessed by inspecting the funnel plots for asymmetry and with Egger's test [44] and Begg's test [45], with the results considered to indicate small study effects when $p < 0.10$. Sensitivity analyses excluding one study at a time were conducted to clarify whether the results were simply due to one large study or a study with an extreme result. We also conducted further subgroup analyses to explore the independent contribution of abdominal and general obesity by analyzing studies that provided results that were mutually adjusted for these measures. We contacted the authors of two studies [20, 24] asking for additional data so the studies could be included in the dose–response meta-analysis, and received additional data from one of these studies [20]. Study quality was assessed using the Newcastle-Ottawa scale which rates the studies from 0 to 9 stars by assessing the selection, comparability and outcome of each study [46].

Results

We identified seventeen prospective studies [7–23] (one of the studies was a nested case–control study [16]) that were included in the analyses of BMI and gallbladder disease risk (Supplementary Table 1, Fig. 1). Five studies were included in the analysis of waist circumference [15, 17, 19, 20, 27] and four studies [14, 15, 20, 27] were included in the analysis of waist-to-hip ratio. Characteristics of the included studies are provided in Supplementary Table 1. Nine studies were from the US and seven were from Europe and one was from Asia (Supplementary Table 1).

Body mass index

Seventeen prospective studies [7–23] were included in the dose–response analysis of BMI and gallbladder disease risk and included a total of 55,670 cases among 1,921,103 participants. The summary RR for a 5 unit increment in BMI was 1.63 (95 % CI 1.49–1.78), with extreme heterogeneity, $I^2 = 98.0$ %, $p < 0.0001$ (Fig. 2a). All studies found increased risk, but the strength of the association differed between studies. In sensitivity analyses excluding

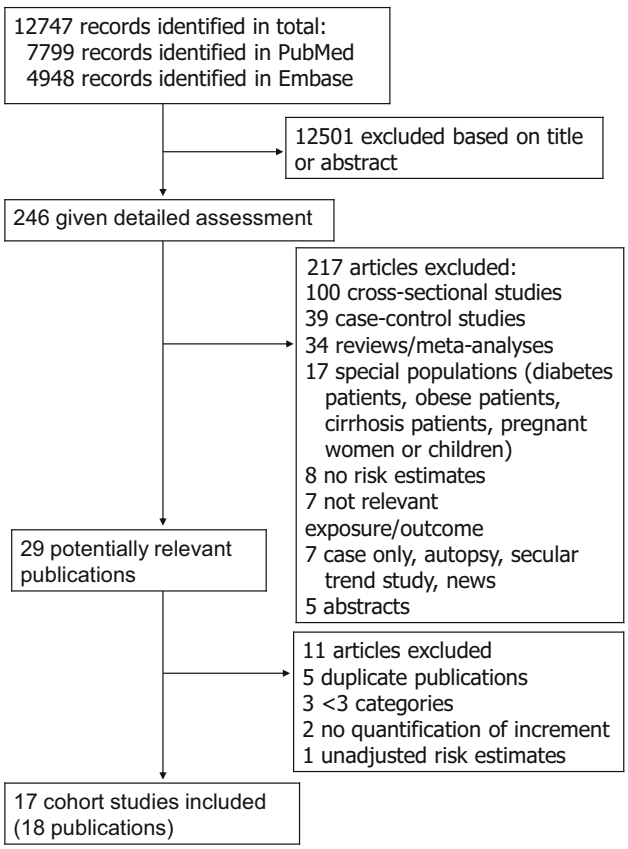

Fig. 1 Flow-chart of study selection

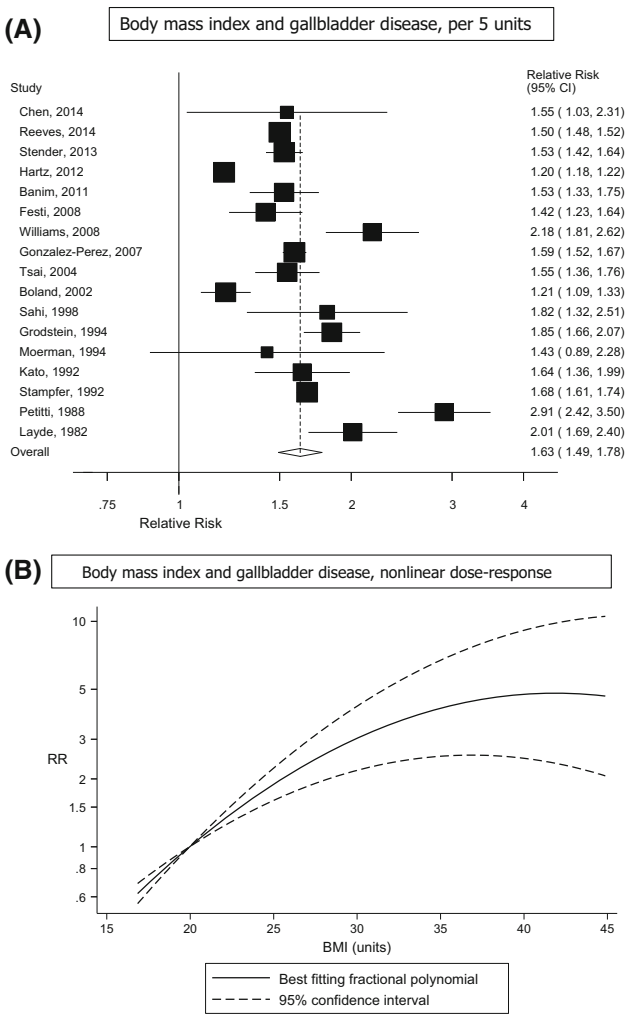

Fig. 2 Body mass index and gallbladder disease

the most influential studies, the summary RR ranged from 1.57 (95 % CI 1.44–1.71) when excluding the Walnut Creek Contraceptive Drug Study [8] to 1.66 (95 % CI 1.52–1.82) when excluding the ARIC study [14]. By visual inspection of the forest plot, six studies [8, 11, 14, 17, 20, 23] appeared to explain a large part of the heterogeneity and when excluded the heterogeneity was reduced, $I^2 = 40$ %, but the results remained similar, summary RR = 1.60 (95 % CI 1.53–1.67). Although the test for publication bias was not significant with Egger's test, $p = 0.13$ or with Begg's test, $p = 0.13$, there was suggestion asymmetry in the funnel plot (Supplementary Fig. 1), but this appeared to be driven by two very large studies [20, 23] and when excluded there was little indication of asymmetry (Supplementary Fig. 2). The summary RR was 1.46 (95 % CI 1.29–1.65) and 1.73 (95 % CI 1.57–1.91) per 5 BMI units in men and women, respectively (Fig. 3a, c). There was evidence of a nonlinear association between BMI and gallbladder disease risk, $p_{\text{nonlinearity}} < 0.0001$ overall and among women (Figs. 2b, 3d, Supplementary Table 2), with a steep increase in risk with increasing BMI even within the normal BMI range, and a flattening of the curve at around a BMI of 40–45, but there was no evidence of nonlinearity in the analysis of men, $p_{\text{nonlinearity}} = 0.99$ (Fig. 3b, Supplementary Table 2).

Waist circumference

Five cohort studies [15, 17, 19, 20, 27] were included in the analysis of waist circumference and gallbladder disease risk and included 15,523 cases among 284,095 participants. Four studies were from the US and one was from Europe (Supplementary Table 1). The summary RR for a 10 cm increase in waist circumference was 1.46 (95 % CI 1.24–1.72) with very high heterogeneity, $I^2 = 98$ %, $p < 0.0001$ (Fig. 4a). The summary RR ranged from 1.43 (95 % CI 1.20–1.71) when the Nurses' Health Study was excluded to 1.55 (95 % CI 1.50–1.61) when the Women's Health Initiative was excluded, and the latter study also explained all the heterogeneity, and when excluded $I^2 = 0$ %, $p_{\text{heterogeneity}} = 0.94$. The summary RR per 10 cm increase in waist circumference was 1.53 (95 % CI 1.41–1.66, $I^2 = 0$ %, $p = 0.49$) for men and 1.43 (95 % CI 1.17–1.73, $I^2 = 98$ %, $p < 0.0001$) for women (Supplementary Fig. 3), with no heterogeneity between genders, $p = 0.48$. Because of few studies and differences in the reference categories we were not able to fit an interpretable nonlinear curve for women, but the association for men appeared to be linear, $p_{\text{nonlinearity}} = 0.79$ (Fig. 4b, Supplementary Table 3).

Waist-to-hip ratio

Four cohort studies [14, 15, 20, 27] were included in the analysis of waist-to-hip ratio and gallbladder disease risk and included 14,458 cases among 230,166 participants. All four studies were from the US (Supplementary Table 1). The summary RR for a 0.1 unit increment in waist-to-hip ratio was 1.44 (95 % CI 1.26–1.64) with high heterogeneity $I^2 = 92$ %, $p < 0.0001$ (Fig. 5a). The summary RR ranged from 1.37 (95 % CI 1.20–1.55) when the Health Professional's Follow-up Study was excluded to 1.52 (95 % CI 1.37–1.69) when the Women's Health Initiative was excluded, and exclusion of the latter study also explained much of the heterogeneity, $I^2 = 50$ %, $p = 0.13$. The summary RR per 0.1 unit increase in waist-to-hip ratio was 1.55 (95 % CI 1.12–2.16, $I^2 = 46$ %, $p = 0.18$) for men and 1.37 (95 % CI 1.21–1.57, $I^2 = 91$ %, $p < 0.0001$) for women (Supplementary Fig. 4), with no heterogeneity between genders, $p = 0.29$. There was no evidence of a nonlinear association between waist-to-hip ratio and gallbladder disease risk, $p_{\text{nonlinearity}} = 0.29$ (Fig. 5b, Supplementary Table 4).

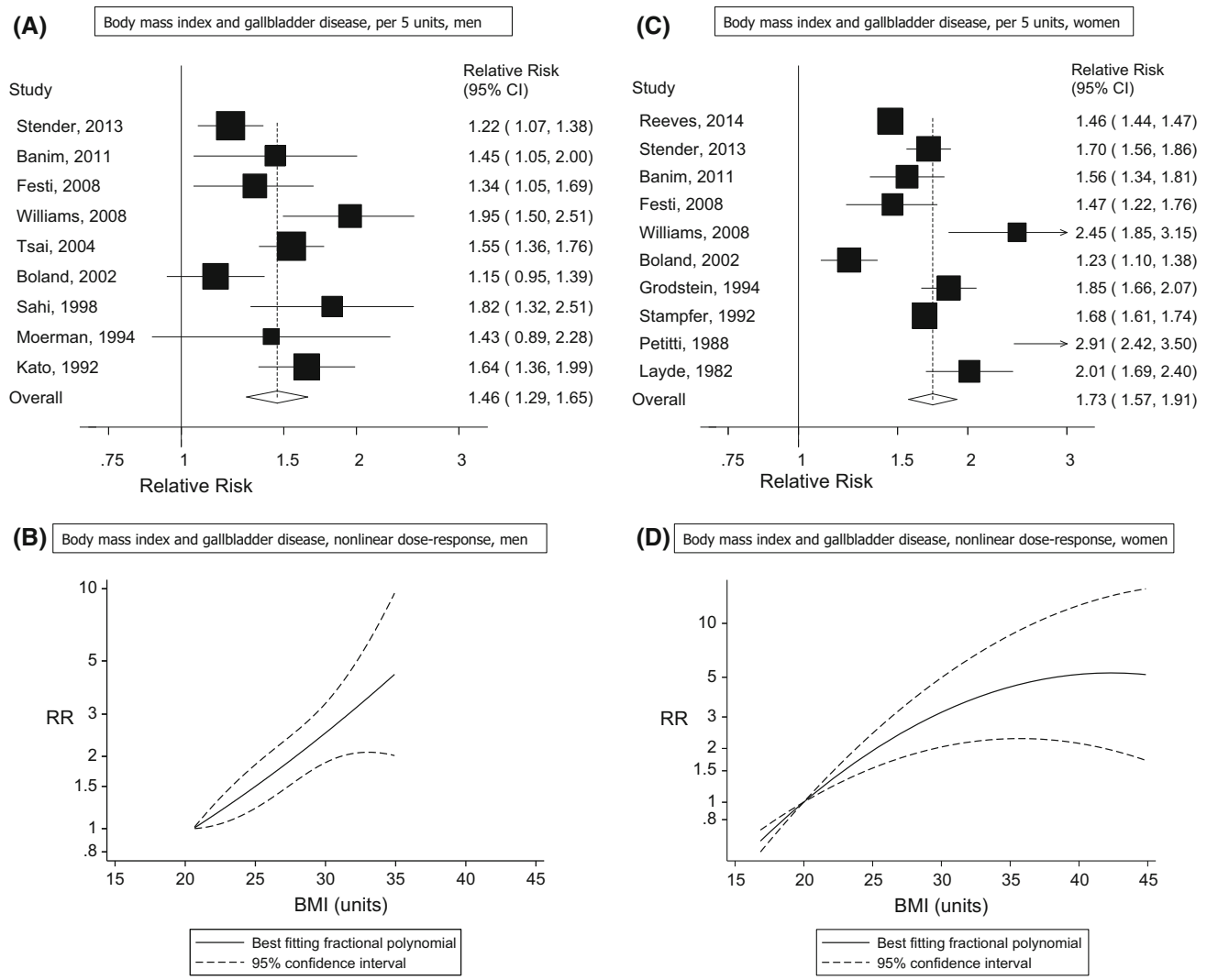

Fig. 3 Body mass index and gallbladder disease by gender

Subgroup and sensitivity analyses

The positive association between BMI and gallbladder disease persisted in all subgroup analyses defined by gender, assessment of anthropometric measures, outcome type, duration of follow-up, geographic location, number of cases, study quality and adjustment for confounding and potential intermediate factors. Only in the analysis of study quality was there evidence of heterogeneity between subgroups with meta-regression analyses and there was a stronger association among the studies which had medium study quality scores compared to studies which had a high study quality score (Table 1). In general, heterogeneity was very high in many of the subgroup analyses, but moderate heterogeneity was observed in the subgroups of studies of men, among the studies with gallstones as the outcome, among the European studies, and among the studies that adjusted for oral contraceptive use in women and energy intake (Table 1).

To assess whether BMI, waist circumference and waist-to-hip ratio were associated with gallbladder disease risk independent of each other we conducted further analyses among studies that provided results with mutual adjustment between BMI and waist circumference or waist-to-hip ratio. Only two studies of BMI and gallbladder disease risk conducted additional analyses adjusting for either waist circumference or waist-to-hip ratio [14, 15], and the summary RR per 5 unit increase in BMI was 1.12 (95 % CI 1.03–1.23, $I^2 = 0$ %, $p_{\text{heterogeneity}} = 0.36$). Four studies conducted further analyses of waist measures adjusted for BMI, and the summary RR per 10 cm increase in waist circumference was 1.24 (95 % CI 1.13–1.35, $I^2 = 77$ %, $p_{\text{heterogeneity}} = 0.005$) (15, 17, 20, 27] and per 0.1 unit

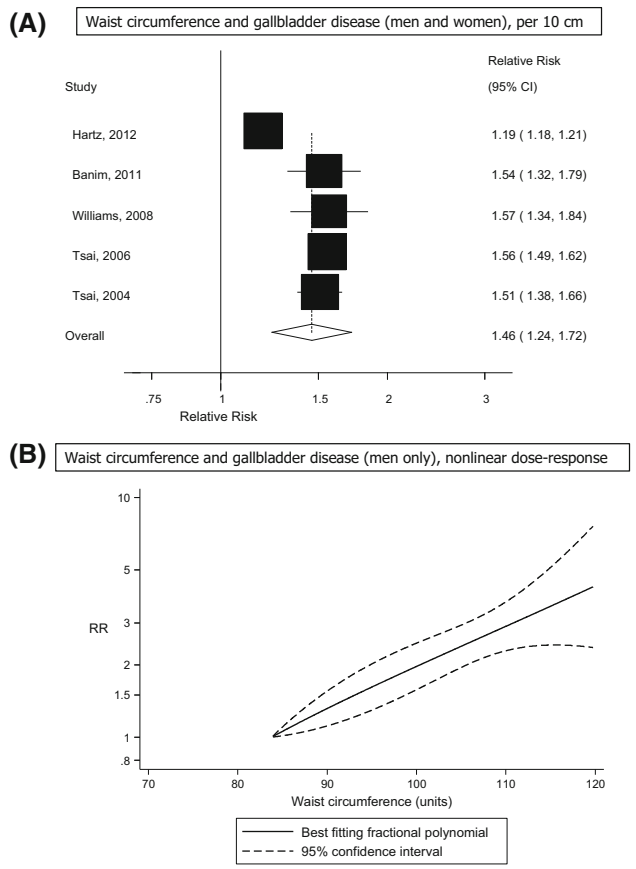

Fig. 4 Waist circumference and gallbladder disease

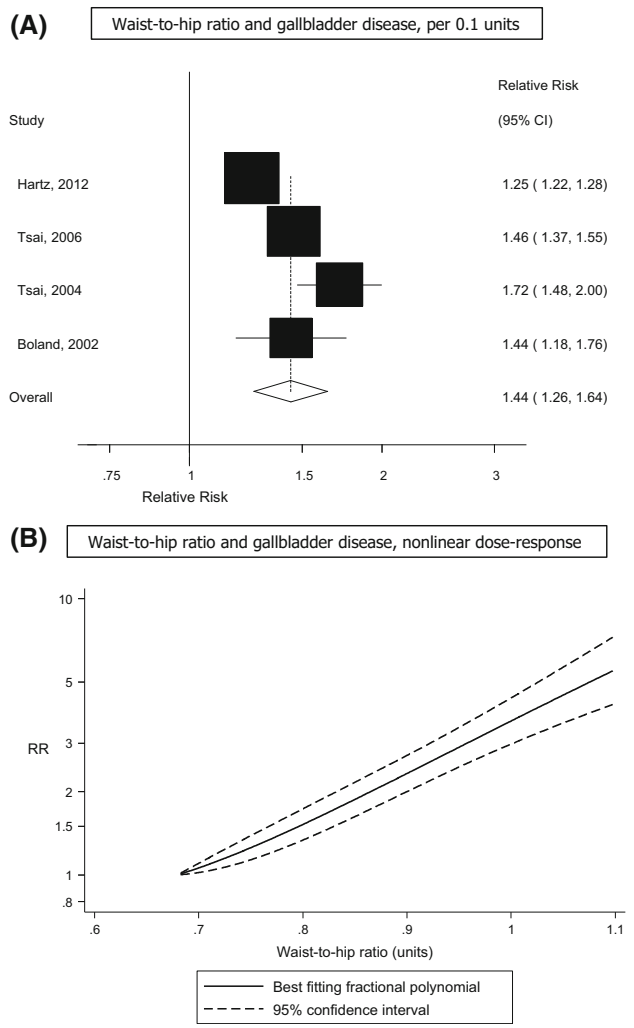

Fig. 5 Waist-to-hip ratio and gallbladder disease

increase in waist-to-hip ratio was 1.25 (95 % CI 1.15–1.37, $I^2 = 79$ %, $p_{\text{heterogeneity}} = 0.005$) (14, 15, 20, 27] with adjustment for BMI.

Discussion

This is to our knowledge the first nonlinear dose–response meta-analysis of both overall and abdominal fat measures and gallbladder disease risk. In the linear dose-response analysis we found a 63 % increase in the relative risk of gallbladder disease per 5 units increase in BMI, 46 % increase in relative risk per 10 cm increase in waist circumference and 44 % increase in the relative risk per 0.1 unit increase in waist-to-hip ratio. The associations were attenuated when adjusted mutually for BMI and waist measures, however, they remained statistically significant suggesting that overall and abdominal fatness independently predict gallbladder disease risk. Although the test for heterogeneity by gender was not significant the association between BMI and gallbladder disease appeared to be slightly stronger among women than among men in the linear dose–response analysis (RR of 1.73 vs. 1.46 per 5 BMI units, respectively). In the nonlinear analysis the association reached a plateau at BMI 40–45 in the overall analysis and among women, but appeared to be linear in men. However, the range of BMI values was lower among men than women, thus further studies are needed of BMI values in the morbidly obese range among men. The associations between waist circumference and waist-to-hip ratio and gallbladder disease risk did not differ by gender and appeared to be linear.

Our meta-analysis has some limitations that need to be mentioned. The main limitation is the low number of cohort studies available reporting on waist circumference and waist-to-hip ratio which limited our possibility to conduct subgroup, sensitivity analyses, and test for publication bias for these measures. Residual confounding might have affected the findings, however, the association persisted in several subgroup analyses with adjustment for a number of important confounding factors. Considering the strength of the association between BMI and abdominal fatness and gallbladder disease we consider it unlikely that

Table 1 Subgroup analyses of BMI and gallbladder disease

	BMI					
		n	RR (95 % CI)	I^2 (%)	P_h^a	P_h^b
All studies		17	1.63 (1.49–1.78)	98.0	<0.0001	
Sex						
Men		9	1.46 (1.29–1.65)	64.7	0.004	0.26/0.11[c]
Women		10	1.73 (1.57–1.91)	94.2	<0.0001	
Men and women		2	1.59 (1.52–1.66)	0	0.89	
Assessment of weight/height						
Measured		8	1.58 (1.34–1.87)	95.4	<0.0001	0.40
Self-reported		6	1.73 (1.58–1.90)	91.9	<0.0001	
Outcome						
Gallstones		8	1.59 (1.50–1.70)	47.9	0.06	0.44
Gallbladder disease		7	1.64 (1.49–1.81)	91.8	<0.0001	
Cholecystectomy		3	1.78 (1.30–2.42)	99.5	<0.0001	
Duration of follow-up						
< 10 yrs follow-up		10	1.58 (1.42–1.76)	98.8	<0.0001	0.52
≥ 10 yrs follow-up		7	1.71 (1.42–2.07)	86.2	<0.0001	
Geographic location						
Europe		7	1.55 (1.48–1.63)	65.2	0.008	0.62
America		9	1.70 (1.43–2.02)	98.1	<0.0001	
Asia		1	1.55 (1.03–2.31)			
Number of cases						
Cases <500		11	1.74 (1.47–2.05)	89.9	<0.0001	0.18
Cases 500–<1000		0				
Cases ≥1000		6	1.50 (1.32–1.70)	99.2	<0.0001	
Study quality						
0–3 stars		0				0.04
4–6 stars		4	1.99 (1.43–2.77)	93.7	<0.0001	
7–9 stars		13	1.54 (1.40–1.69)	98.2	<0.0001	
Adjustment for confounders						
Age	Yes	16	1.63 (1.50–1.78)	98.1	<0.0001	0.67
	No	1	1.43 (0.89–2.28)			
Alcohol	Yes	10	1.59 (1.44–1.76)	98.7	<0.0001	0.57
	No	7	1.70 (1.30–2.24)	92.5	<0.0001	
Smoking	Yes	9	1.64 (1.47–1.84)	98.9	<0.0001	0.83
	No	8	1.61 (1.35–1.93)	90.1	<0.0001	
Physical activity	Yes	5	1.45 (1.26–1.67)	99.2	<0.0001	0.11
	No	12	1.73 (1.56–1.91)	89.0	<0.0001	
OC use	Yes	2	1.90 (1.72–2.08)	0	0.43	0.33
	No	11	1.58 (1.43–1.76)	98.7	<0.0001	
HRT	Yes	3	1.57 (1.45–1.70)	92.3	<0.0001	0.69
	No	10	1.67 (1.43–1.95)	97.4	<0.0001	
Parity	Yes	4	1.75 (1.56–1.96)	94.0	<0.0001	0.37
	No	9	1.57 (1.36–1.82)	97.4	<0.0001	
Energy intake	Yes	3	1.66 (1.60–1.73)	0	0.50	0.94
	No	14	1.63 (1.48–1.80)	98.2	<0.0001	
Adjustment for potential intermediates						
Diabetes	Yes	2	1.54 (1.38–1.71)	54.9	0.14	0.57
	No	15	1.65 (1.50–1.81)	98.2	<0.0001	

Table 1 continued

	BMI					
		n	RR (95 % CI)	I^2 (%)	P_h^a	P_h^b
Triglycerides	Yes	2	1.51 (1.31–1.74)	31.4	0.23	0.64
	Yes	15	1.64 (1.50–1.80)	98.2	<0.0001	

n denotes the number of studies. The number of studies is not always equal to the total because the subgroup analyses were not applicable to some studies or information was not provided in the publication. For example only studies of women were included in subgroup analyses by parity, HRT and OC use and in addition, information regarding how anthropometric measures were assessed was not clear in three studies

[a] P for heterogeneity within each subgroup

[b] P for heterogeneity between subgroups

[c] P for heterogeneity between men and women (excluding men/women combined)

the observed findings could be entirely due to confounding. Measurement errors could have influenced the findings, however, when we stratified the analysis by whether the anthropometric factors were measured or self-reported the results were not significantly different. As a meta-analysis of published literature publication bias may have affected our findings. Although the tests for publication bias were not significant the funnel plot appeared to be asymmetric, and if this really is due to publication bias it is possible that the strength of the association between adiposity and gallbladder disease may have been overestimated. However, the association persisted in the subgroup of the largest studies (relative risk of 1.53 vs. 1.63 in the overall analysis), which would be centered at the top of the funnel plot and less likely to be affected by this asymmetry. There was high heterogeneity in the main analyses for BMI, waist circumference, and waist-to-hip ratio, however, this appeared to be explained by differences in the effect size more than the presence or lack of an association, as all the studies included found positive associations. In subgroup and meta-regression analyses the positive associations persisted across all subgroups defined by gender, exposure assessment, outcome type, publication year, duration of follow-up, geographic location, number of cases, study quality and adjustment for important confounding and mediating factors. In the analyses of waist circumference and waist-to-hip ratio we found that one study [20] explained all the heterogeneity, while in the BMI analysis heterogeneity was reduced in analyses of men and with gallstones as the outcome, and among the European studies. In addition, heterogeneity was also reduced when excluding six studies [8, 11, 14, 17, 20, 26] that had more extreme risk estimates in either direction, without substantially altering the summary estimate.

Our meta-analysis also has several strengths. Because we based our analysis on prospective studies, recall bias is not likely to explain our results and the possibility for selection bias is reduced. In addition, the possibility of reverse causation biases, e.g. changes in weight due to loss of appetite or diet-induced weight loss, which may affect cross-sectional studies is avoided. The meta-analysis included a large number of cohort studies with more than 55,000 cases among almost 2 million participants in the BMI analysis, providing sufficient statistical power to detect even modest associations. To increase comparability between studies we conducted linear and nonlinear dose–response analyses. The results persisted in a number of subgroup and sensitivity analyses, suggesting that the findings are not likely to be due to confounding, and they were robust to the influence of single studies. Although the dose–response analyses suggest that the risk of gallbladder disease is further reduced in underweight persons compared with persons with a normal weight, overall health and mortality have to be taken into account when interpreting these findings in terms of public health recommendations, thus being as lean as possible within the normal BMI range is probably the best advice that can be given in terms of body weight and overall health [47]. The current findings are consistent with two previous meta-analyses which found increased risk with greater BMI in relation to gallbladder disease [30, 31], but the present results indicate a slightly stronger dose–response relationship 1.63 (95 % CI 1.49–1.78) versus 1.40 (95 % CI 1.15–1.65) per 5 unit increase in BMI [31]. The stronger association observed in the current meta-analysis may be because we included additional studies that have since been published and because the previous meta-analysis also included non-general population studies (studies in diabetics, pregnant women, or only among obese subjects) which may have had a higher baseline risk than subjects from the general population. The current results suggest that both BMI and abdominal fat measures are independently associated with increased gallbladder disease risk.

Several potential mechanisms could explain an association between body fatness and gallbladder disease risk. In Western populations 80 % of gallstones are cholesterol stones. Obesity has been associated with more lithogenic bile, i.e. bile that contains more cholesterol than can be

solubilised by the bile acid or phospholipid content [48, 49]. Studies have suggested that cholesterol is hypersecreted from the liver into the bile of obese persons due to upregulation of HMG-CoA reductase activity [50, 51], and in addition, reduced output of bile acids and phospholipids may contribute to more lithogenic bile [50, 52]. Because the rate of cholesterol secretion into the bile exceeds that of the other lipids, cholesterol is supersaturated in the bile leading to increased flux into the muscle cells of the gallbladder which disrupts normal gallbladder function [53]. In addition, gallbladder volumes and residual volumes are higher and gallbladder motility is lower in obese women [54, 55]. In this meta-analysis, both overall and abdominal adiposity were strongly associated with increased risk of gallbladder disease, but with mutual adjustment between BMI and abdominal adiposity measures the association with BMI was attenuated to a larger degree than the waist measures (RR attenuated from 1.62 to 1.12 for BMI, compared with from 1.46 to 1.24 for waist circumference and 1.44 to 1.25 for waist-to-hip ratio, respectively), although results for all three measures remained statistically significant. This might suggest that abdominal adiposity is particularly important in the etiology of gallbladder disease. It has been shown that abdominal adiposity may be more strongly associated with insulin resistance and hyperinsulinemia than overall obesity [56] and persons with diabetes are at an increased risk of developing gallstones [57, 58]. Abdominal fat is more metabolically active and increases hepatic exposure to unesterified fatty acids which decreases insulin sensitivity [59]. Hyperinsulinemia and insulin resistance may increase gallstone risk through similar pathways as obesity, with supersaturation of bile, and effects on gallbladder motility and volume [28]. Further support for a causal interpretation of the association between adiposity and gallstones comes from a Mendelian randomisation study which reported an increased risk of gallstones with three common genetic variants that are known to be associated with BMI [21].

Our findings provides further evidence that body fatness is an important risk factor for gallbladder disease and suggest that the risk is increased almost twofold even within the "normal" BMI range, suggesting that even moderate increases in BMI may increase risk. Further studies on abdominal fatness are warranted, and any further studies on BMI might benefit from using more refined BMI categories in addition to the WHO classification of overweight and obesity.

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Contribution DA, TN, LJV conceived of and designed the study. DA conducted the literature search and analyses and wrote the first draft of the paper. All authors interpreted the data, contributed to the draft of the paper, revised the subsequent drafts for important intellectual content, read and approved the final manuscript. D. Aune takes primary responsibility for the integrity of the data and the accuracy of the data analysis.

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