

Central obesity and nonalcoholic fatty liver disease risk after adjusting for body mass index

Qing Pang, Jing-Yao Zhang, Si-Dong Song, Kai Qu, Xin-Sen Xu, Su-Shun Liu, Chang Liu

Qing Pang, Jing-Yao Zhang, Si-Dong Song, Kai Qu, Xin-Sen Xu, Su-Shun Liu, Chang Liu, Department of Hepatobiliary Surgery, the First Affiliated Hospital of Medical College, Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China

Author contributions: Pang Q and Zhang JY contributed equally to this work; Pang Q participated in the research design, writing of the paper, and literature searches; Zhang JY participated in writing of the paper, literature searches, and data analysis; Song SD and Qu K participated in critical revision of the paper, and extraction and analysis of data; Xu XS and Liu SS participated in revision of the paper, and final approval; Liu C participated in the research conception and design.

Supported by National Natural Science Foundation of China, No. 30872482 and No. 81072051.

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Correspondence to: Chang Liu, MD, PhD, Professor, Department of Hepatobiliary Surgery, the First Affiliated Hospital of Medical College, Xi'an Jiaotong University, No. 277 West Yan-ta Road, Xi'an 710061, Shaanxi Province, China. liuchangdoctor@163.com
Telephone: +86-29-82653900
Fax: +86-29-82653905

Received: May 10, 2014

Peer-review started: May 10, 2014

First decision: May 29, 2014

Revised: June 11, 2014

Accepted: August 28, 2014

Article in press: August 28, 2014

Published online: February 7, 2015

METHODS: The online databases PubMed, EMBASE, and ISI Web of Science were searched for studies estimating the influence of central obesity on NAFLD occurrence published through April 2014. Studies that did not adjust for body mass index (BMI) were excluded. In addition, the independent effect of BMI was also assessed with the included studies. The pooled effect sizes and 95% confidence intervals (CIs) were calculated using random- or fixed-effects models based on the degree of heterogeneity. Furthermore, subgroup analyses, meta-regression, sensitivity analyses, and publication bias were performed.

RESULTS: Twenty eligible studies were identified. The summary odds ratio (OR) values per-unit increase in waist circumference (WC) and BMI for NAFLD formation were 1.07 (95%CI: 1.03-1.10, $I^2 = 73.9\%$, $n = 11$ studies) and 1.25 (95%CI: 1.13-1.38, $I^2 = 88.7\%$, $n = 11$ studies), respectively. When the indices were expressed as binary variables (with the non-obesity group as reference), the pooled OR in WC, waist-to-hip ratio, and BMI were 2.34 (95%CI: 1.83-3.00, $I^2 = 41.8\%$, $n = 7$ studies), 4.06 (95%CI: 1.53-10.79, $I^2 = 65.7\%$, $n = 3$ studies), and 2.85 (95%CI: 1.60-5.08, $I^2 = 57.8\%$, $n = 5$ studies), respectively. Using the same studies as the latter ($n = 5$), pooled OR in WC was 3.14 (95%CI: 2.07-4.77), which is greater than that in BMI.

CONCLUSION: Central obesity may pose a greater threat to national health than general obesity, although both are independently associated with increased risk of NAFLD.

Key words: Central obesity; General obesity; Nonalcoholic fatty liver disease; Body mass index; Waist circumference

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Abstract

AIM: To investigate whether central obesity is associated with nonalcoholic fatty liver disease (NAFLD) formation after adjusting for general obesity.

Core tip: Central and general obesity are independently associated with increased risk of nonalcoholic fatty liver disease (NAFLD). Per-unit increase in waist circumference

and body mass index increased the incidence risk of NAFLD by 0.07- and 0.25-fold, respectively. The risk for disease is increased in individuals with a higher waist circumference, waist-to-hip ratio, and body mass index by 1.34-, 3.06-, and 1.85-fold, respectively. The results of this analysis suggest that central obesity poses a greater threat to national health than general obesity. Therefore, future studies should place a greater emphasis on central obesity.

Pang Q, Zhang JY, Song SD, Qu K, Xu XS, Liu SS, Liu C. Central obesity and nonalcoholic fatty liver disease risk after adjusting for body mass index. *World J Gastroenterol* 2015; 21(5): 1650-1662 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i5/1650.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i5.1650>

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of non-cancerous liver diseases ranging from simple steatosis to nonalcoholic steatohepatitis (NASH). Considering that NAFLD has been increasingly recognized as a major cause of liver-related mortality, the disease has become a global problem^[1,2]. NAFLD may progress to liver fibrosis, liver cirrhosis, or even hepatocellular carcinoma (HCC), the fifth most common cancer and the third most common cause of death from cancer worldwide^[3]. Moreover, due to the high prevalence of NAFLD worldwide, especially in developed countries, the incidence of NAFLD-related HCC has gradually increased^[4].

As a hepatic manifestation of metabolic syndrome (MS), NAFLD is closely associated with metabolic disorders such as diabetes and obesity^[5,6]. The incidences of general/central obesity have greatly increased over the past few decades due to unhealthy dietary patterns, decreased physical activity, and sedentary lifestyles. Along with the rapid increase of obese patients, the morbidity and impact of NAFLD have increased in recent years^[6,7]. However, the majority of hepatologists are exclusively focused on the association between general obesity and NAFLD risk, thus neglecting the effect of central obesity. Moreover, several meta-analyses and epidemiological studies demonstrated that central obesity might be a better predictor of metabolic disorders and tumors than general obesity^[8-10]. Nevertheless, these studies failed to show the independent risk of central obesity as odds ratio (OR) values were calculated without adjustments for general obesity.

In various definitions of MS^[11], central obesity, rather than general obesity, is generally considered to be an indispensable component of MS. This suggests that central obesity should not be neglected as a risk factor for NAFLD. In fact, some individuals with no general obesity could potentially develop NAFLD^[12].

Previous studies have demonstrated that patients with NAFLD have significantly higher visceral fat areas and waist circumferences (WCs) compared with body mass indices (BMIs) of matched control individuals^[13,14]. In addition, central obesity is an important predictor for NAFLD, even in individuals with normal weight^[15,16]. A recent study emphasized that no other anthropomorphic parameters are independently associated with NAFLD after adjusting for waistline^[17]. Furthermore, as a metabolic factor, WC is strongly associated with insulin resistance and increased alanine aminotransferase activity in patients with NAFLD^[18,19]. According to the above findings, we hypothesized that central obesity is closely associated with the incidence of NAFLD, and the association may be independent of general obesity. However, several epidemiological studies have suggested no statistically significant association between central obesity and NAFLD after adjusting for BMI^[20-23]. Thus, the principal aim of this review was to assess whether central obesity independently conveys increased NAFLD risk after excluding BMI as a confounder. All of the relevant studies were summed with the meta-analysis method. Furthermore, the independent effect of BMI in NAFLD was investigated in the included studies.

MATERIALS AND METHODS

Search strategy and selection criteria

Two independent investigators (Pang Q and Zang JY) performed a systematic search with no language restrictions using the PubMed, EMBASE, and ISI Web of Science databases up until April 2014. The core search consisted of terms "central obesity" or "abdominal obesity" or "abdominal adiposity" or "central adiposity" or "waist circumference" or "waist-to-hip ratio" or "waist" or "WC" or "WHR", combined with terms "nonalcoholic fatty liver" or "nonalcoholic steatohepatitis" or "hepatic steatosis" or "NAFLD" or "NASH". In addition, the reference lists of included studies and review articles were searched by hand.

Included studies had to meet the following criteria: (1) published as an original article; (2) used a cohort, case-control, cross-sectional, or nested case-control design; (3) estimated the association between WC or waist-to-hip ratio (WHR) and the incidence of NAFLD in adults, and reported OR value with 95% confidence interval (CI) adjusting for BMI; and (4) diagnosed NAFLD by imaging or biopsy, and excluded patients with alcoholic liver disease (ALD). If a study was published more than once, the publication with the most adjusted OR value was used. Studies were excluded if they recruited all fatty liver patients without distinguishing NAFLD from ALD. A study was excluded if it met one of the following criteria: (1) evaluated the influence of WC in the progress of NAFLD; (2) recruited non-adult individuals; (3) recruited special individuals with pre-existing diseases

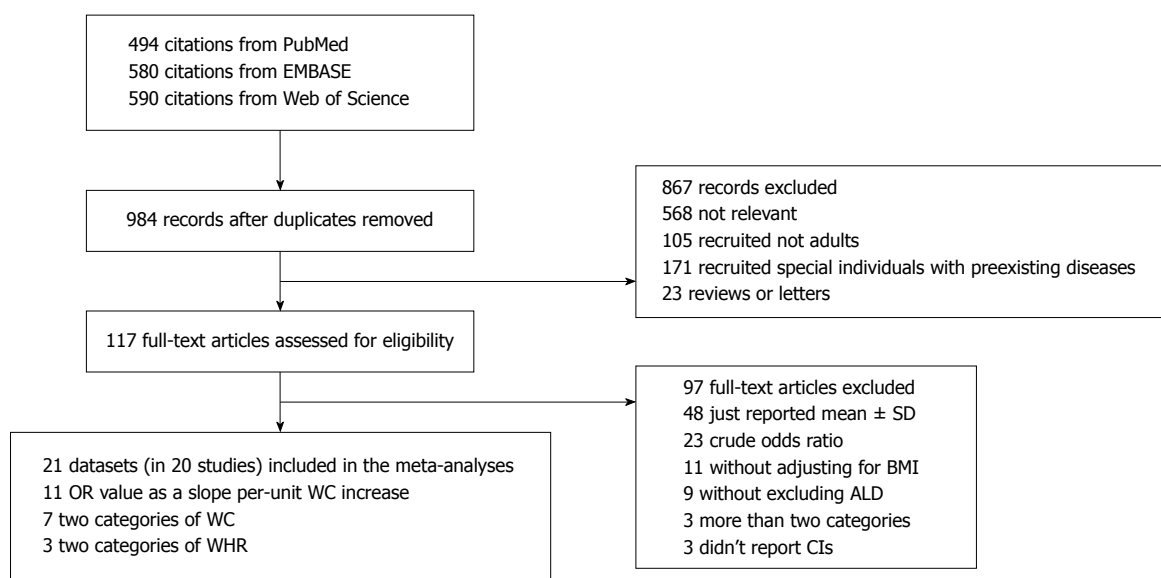


Figure 1 Flow diagram of search strategy and study selection. ALD: Alcoholic liver disease; OR: Odds ratio; WC: Waist circumference; WHR: Waist-to-hip ratio.

(diabetes, obese); (4) not published as full reports (conference abstracts and letters to editors); and (5) reported only the relation between central obesity and NAFLD-related fibrosis, cirrhosis, or cancer.

Data extraction

Three investigators (Pang Q, Qu K, Xu XS) independently evaluated and retrieved studies for inclusion according to the selection criteria. Discrepancies among investigators were solved through discussion. For each included study, the following information was extracted using a standardized protocol for collecting data: (1) the first author's last name; (2) publication year; (3) region in which the study population dwelled; (4) number of recruited patients; (5) cohort characteristics (age, sex, and WC); (6) study design; (7) diagnostic basis for NAFLD; (8) the cut-off values for WC, WHR, and BMI (if reported); (9) OR value and 95%CI; and (10) controlled confounders. The MOOSE guidelines^[24] were followed for the current meta-analysis, and the quality of each study was assessed using the Newcastle-Ottawa Scale. All data were double-checked by a single investigator (PQ).

Statistical methods

WC/WHR ratio was expressed as a binary variable in most of the included studies. This did not meet the specific requirement in at least three categories of dose-response meta-analysis^[25,26]. In other words, binary variables (with a lower level as a reference) could not be converted to continuous variables (expressed OR value as a slope per-unit increase in variables) by using generalized least-squares trend estimation. Thus, the two types of variables were analyzed separately to estimate the association between central obesity and the risk of NAFLD occurrence. Variables that entered multiple factor

analyses in the corresponding study were considered as adjusted confounders.

The heterogeneity among studies was assessed with Q and I^2 statistic values (25%, 50%, and 75% correspond to cut-off points for low, moderate, and high degrees of heterogeneity, respectively). A fixed-effects model was used when significant heterogeneity was observed [$P < 0.1$ (Q), or $I^2 > 50\%$]; otherwise, a random-effects model was used. To identify those factors that could significantly alter the pooled OR value, as well as to explore the source of heterogeneity among studies, subgroup and meta-regression analyses were performed for the covariates in at least two studies in each group. Sensitivity analyses were performed to investigate whether any single study markedly affected the results, and the effects model was used to observe changes in the results. Publication bias was examined in funnel plots using Begg's and Egger's tests. The STATA software, version 12.0 (StataCorp LP, College Station, TX, United States) was used to analyze the data.

RESULTS

Identification and selection of studies

A flow diagram of the literature search and selection process is shown in Figure 1. Of the total 1664 citations, 21 datasets were identified in 20 studies (published 2005–2013)^[20–23,27–42]. The consensus among the three observers concerning which studies to include was good ($\kappa = 0.925$ – 0.974). No additional articles were included from review of the references. Thus, a total of 21 datasets were used in this meta-analysis; 11 of which expressed OR values as a slope per-unit increase in WC. Seven studies reported OR values for WC, and three studies reported ORs for WHR with the lower category (a subgroup with a lower level) as a

Table 1 Baseline characteristics for studies included in meta-analysis

First author and year	Country	Case, <i>n</i> (M/W)	Control, <i>n</i> (M/W)	Design	Excluding ¹	Cut-off	Adjusted factors	NOS
High vs low category in waist circumference								
Zelber-Sagi <i>et al</i> ^[27]	Israel	66/32	108/120	c-s	Hep B, C, DILI	102/88	5	8
Park <i>et al</i> ^[28]	Korea	62/84	118/86	c-s	Hep B, C	90/80	11	6
Choi <i>et al</i> ^[29]	Korea	246/68	216/129	c-s	Hep B, C	90/80	7	6
Tsai <i>et al</i> ^[30]	Taiwan	253/120	275/228	c-s	None	90/80	7	7
Kogiso <i>et al</i> ^[31]	Japan	33/24	60/113	c-s	Hep B, C	85/90	10	7
Das <i>et al</i> ^[32]	India	89/75	926/821	n-c-c	Hep B, C, DILI	90/80	6	8
Pinidiyapathirage <i>et al</i> ^[33]	Sri Lanka	45/27	144/185	c-s	Hep B, C	90/80	4	8
High vs low category in waist-to-hip ratio								
Kogiso <i>et al</i> ^[31]	Japan	33/24	60/113	c-s	Hep B, C	0.845/0.845	10	7
Zheng <i>et al</i> ^[34]	China	189/61	192/48	c-c	Hep B, C	0.900/0.850	8	7
Wengert <i>et al</i> ^[35]	Germany	58/22	138/125	c-s	Hep B, C	NR	8	9
Per-unit increase in waist circumference								
Yoon <i>et al</i> ^[36]	Korea	11/27	15/38	c-s	Other liver diseases	/	3	7
Church <i>et al</i> ^[22]	USA	24/0	218/0	n-c-c	Other liver diseases	/	3	7
Sung <i>et al</i> ^[37]	Korea	7155/1867	10461/11757	c-s	Hep B, C, DILI	/	2	6
Seo <i>et al</i> ^[20]	Korea	45/28	50/36	c-c	Hep B, C, DILI	/	12	8
Xu <i>et al</i> ^[38]	China	139/88	416/235	c-s	Other liver diseases	/	7	7
Sathiaraj <i>et al</i> ^[39]	India	77/21	75/27	c-c	Hep B, C, DILI	/	2	6
Zhou <i>et al</i> ^[40]	China	211	513	Cohort	Other liver diseases	/	11	8
Eshraghian <i>et al</i> ^[21]	Iran	127	705	c-s	DILI, other liver diseases	/	12	7
Cheah <i>et al</i> ^[41]	Malaysia	17/17	19/24	c-s	None	/	9	8
Foster <i>et al</i> ^[42]	USA	227/294	1144/1391	c-s	DILI, other liver diseases	/	9	7
Li <i>et al</i> ^[23]	China	28/51	130/233	Cohort	Other fatty liver	/	17	8

¹In addition to exclusion of alcoholic liver disease. c-c: Case-control; c-s: Cross-sectional; DILI: Drug-induced liver injury; Hep: Hepatitis; M: Men; n-c-c: Nested case-control; NOS: Newcastle-Ottawa scale; NR: Not reported; W: Women.

reference. One cohort study estimated the association between WC and NAFLD without distinguishing the NAFLD incidence rate (185 patients) from the NAFLD prognosis (26 patients)^[40]. The qualities of the studies were moderate to high (mean Newcastle-Ottawa Scale score 7.24, range: 6-9). With exception of two Korean studies, all articles were published in English.

Characteristics of included studies

The baselines of the included studies are summarized in Table 1. The meta-analysis involved 12065 cases (9135 men and 2930 women) and 33692 controls (15983 men and 15709 women). Two studies used a prospective cohort design; five studies used case-control or nested case-control designs, whereas the remaining studies used a cross-sectional design. All studies recruited both men and women except one study that exclusively recruited men^[22]. Three studies were performed in western countries (Europe and the United States), and others were from Asia. The mean patient age ranged from 35.5 to 71.9 years. NAFLD was assessed by imaging (computed tomography or ultrasound) in all the included studies.

Pooled OR value for WC and WHR

Figure 2A-C shows the results of meta-analyses for WC and WHR. Eleven studies involving 10 454 individuals estimated OR values as a slope unit increase in WC. A high degree of heterogeneity was observed ($I^2 = 73.9\%$; $P = 0.000$), and thus, the summary OR value was calculated using a random-

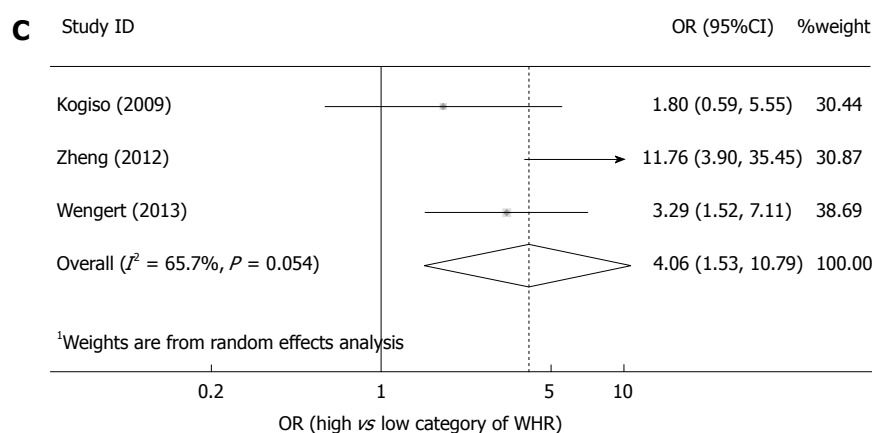
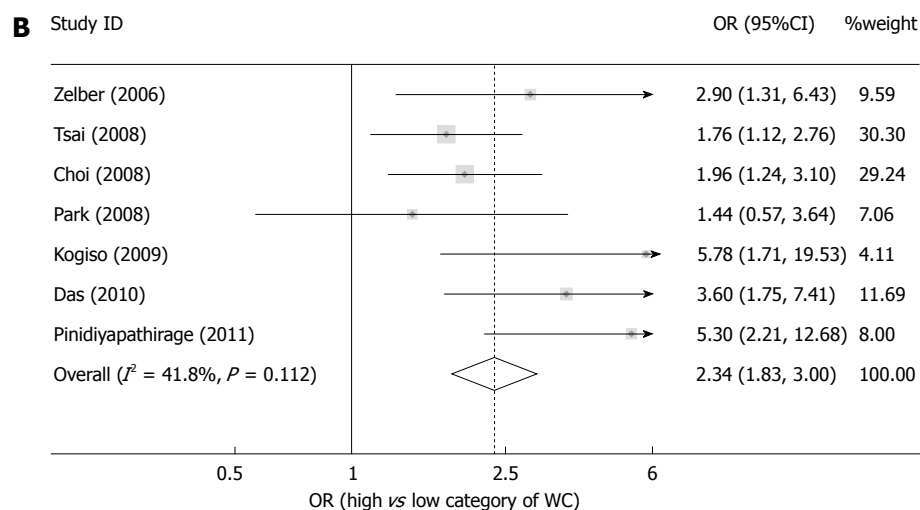
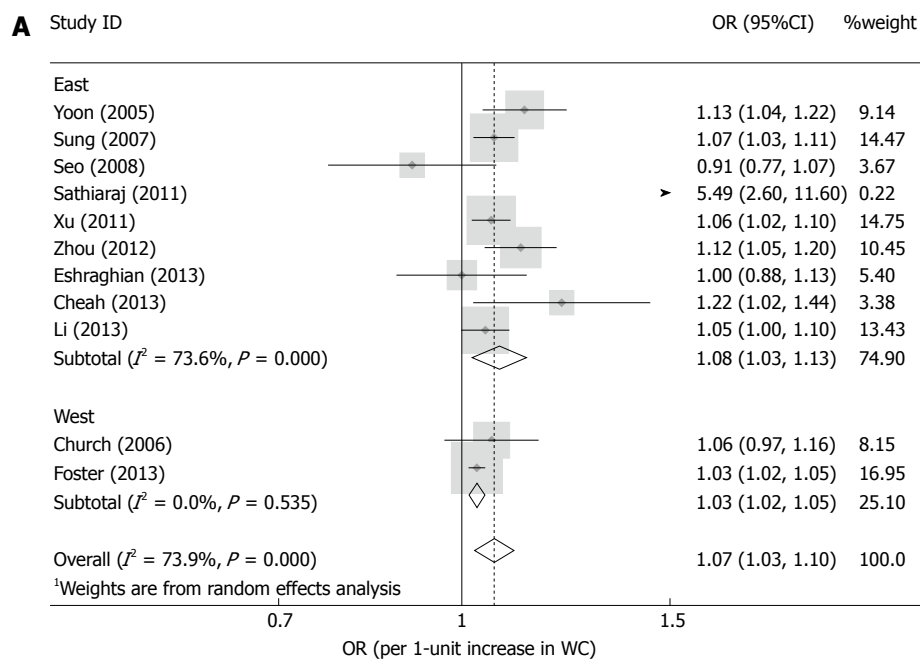
effects model. WC was independently associated with NAFLD, and the pooled OR value was 1.065 (95%CI: 1.029-1.103). When stratified by region, the OR values were 1.076 and 1.031 in the Asian (nine studies) and American (two studies) populations, respectively.

A meta-analysis was performed from six cross-sectional, and one nested case-control studies that expressed WC as a binary variable. WC cut-off values were all in accordance with the definition of central obesity of the national or international scientific associations/federations. A fixed-effects model was used when a low heterogeneity was present ($I^2 = 41.8\%$; $P = 0.112$). The pooled effect size was 2.344 (95%CI: 1.831-3.0), and the result suggested that central obesity was independently associated with NAFLD.

WHR is another accepted anthropometric measure for defining central obesity. Three studies estimated the influence of elevated WHR level in the occurrence of NAFLD. The summary OR value was 4.061 (95%CI: 1.529-10.790), with moderate heterogeneity among studies ($I^2 = 65.7\%$; $P = 0.054$).

Pooled OR value for BMI

To utilize the included studies fully, the association between BMI and NAFLD risk was estimated after adjusting for WC. The results summarizing 16 studies are shown in Figure 2D and E. A per-unit increase in BMI was independently associated with the risk of NAFLD, with significant heterogeneity among studies



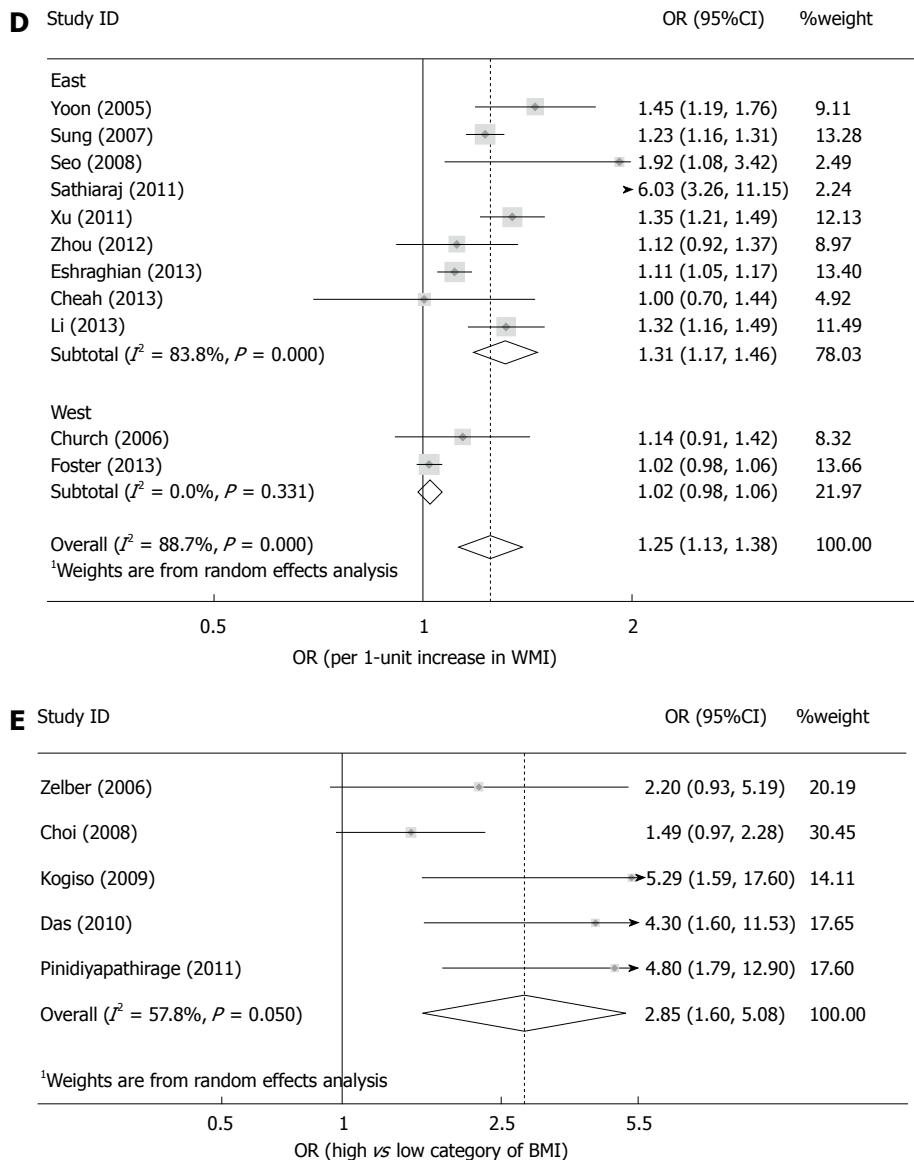


Figure 2 Meta-analyses of the included studies. Forest plots of studies for the associations of various obesity parameters with nonalcoholic fatty liver disease generated using random-effects model analyses (exception: fixed-effects model for plot in B). A: Per-unit increase in waist circumference (WC); B: High vs low category of WC; C: High vs low category of WHR; D: Per-unit increase in BMI; E: High vs low category of BMI.

(OR = 1.250, 95%CI: 1.131-1.382, $I^2 = 88.7\%$; $P = 0.000$). Stratified by region, the pooled OR values in the eastern (Asia) and western (Europe and the US) populations were 1.307 and 1.023, respectively. There was no significant heterogeneity among the studies performed in western regions ($I^2 = 0.0\%$; $P = 0.331$).

Five Asian studies expressed BMI as a binary variable. Four of them evaluated NAFLD risk in overweight individuals (in comparison to the lower BMI level), and one estimated risk in obese patients. Given moderate heterogeneity among studies ($I^2 = 57.8\%$; $P = 0.050$), a random-effects model was implemented indicating an overall adjusted OR of 2.854 (95%CI: 1.604-5.080).

Exploration of heterogeneity

With 11 studies estimating the influence of per-unit WC increase in NAFLD, subgroup and meta-regression analyses were performed for the covariates region, design method, number of adjusted confounders, and the number of involved patients. The covariate regions and number of individuals were analyzed for seven studies estimating the association between central obesity and NAFLD (Table 2). When WC was expressed as a continuous variable, the number of individuals and adjusted confounders affected the summary effect size. The OR value was found to be statistically significant (lower CI > 1) only in studies with > 700 individuals, and more than three adjusted confounders. There were significantly higher

Table 2 Subgroup and meta-regression analyses of waist circumference and the risk of nonalcoholic fatty liver disease

Covariates	Subgroup	Studies, <i>n</i>	OR (95%CI)	<i>P</i> of <i>Q</i>	<i>I</i> ²	Inter-group <i>P</i> value	Univariate <i>P</i> value	Multivariate <i>P</i> value
Per-unit increase in waist circumference								
Region	East	9	1.076 (1.025-1.129)	0.000	73.6	0.006	0.171	0.214
	West	2	1.031 (1.016-1.046)	0.535	0.0			
Design	c-s	8	1.063 (1.014-1.114)	0.000	79.1	0.157	0.764	0.984
	Others	3	1.071 (1.026-1.119)	0.254	26.9			
Adjusted (> 3 confounders)	Yes	7	1.051 (1.019-1.084)	0.035	55.8	0.031	0.489	0.770
	No	4	1.126 (1.000-1.269)	0.000	85.0			
Individuals (> 700)	Yes	6	1.054 (1.025-1.083)	0.055	56.7	0.163	0.728	0.975
	No	5	1.100 (0.991-1.22)	0.000	81.5			
High <i>vs</i> low category of waist circumference								
Design	c-s	5	2.113 (1.615-2.765)	0.180	36.2	0.057	0.642	0.947
	Others	2	4.072 (2.189-7.575)	0.512	0.0			
Individuals (> 600)	Yes	3	2.070 (1.546-2.774)	0.245	28.9	0.122	0.635	0.942
	No	4	3.185 (2.010-5.046)	0.164	41.2			

Table 3 Further analyses after adding several studies

Covariates	Subgroup	<i>n</i> of studies	OR (95%CI)	<i>P</i> of <i>Q</i>	<i>I</i> ²	Inter-study <i>P</i> value	Univariate <i>P</i> value	Multivariate <i>P</i> value
Per-unit increase in waist circumference								
Region	East	15	1.089 (1.057-1.122)	0.000	94.1	0.001	0.180	0.145
	West	5	1.040 (1.028-1.052)	0.149	40.8			
Design	c-s	14	1.067 (1.042-1.193)	0.000	94.6	0.010	0.734	0.968
	Others	6	1.076 (1.049-1.103)	0.140	39.8			
Adjusted (> 3 factors)	Yes	11	1.059 (1.038-1.081)	0.000	82.9	0.806	0.393	/
	No	9	1.101 (1.055-1.149)	0.000	95.9			
Adjusting for BMI	Yes	14	1.064 (1.040-1.089)	0.000	84.8	0.000	0.649	0.918
	No	6	1.086 (1.046-1.127)	0.000	95.3			
Excluding ALD	Yes	16	1.079 (1.051-1.107)	0.000	90.0	0.000	0.603	0.869
	No	4	1.056 (1.022-1.093)	0.000	93.8			
High vs low category of waist circumference								
Region	East	11	2.687 (2.018-3.579)	0.000	74.4	0.000	0.545	0.934
	West	5	3.098 (2.005-4.785)	0.000	83.3			
Design	c-s	12	2.471 (1.958-3.119)	0.000	72.3	0.000	0.015	0.078
	Other	4	5.212 (2.121-12.807)	0.858	0.0			
Adjusted (> 3 factors)	Yes	10	3.002 (2.268-3.973)	0.000	73.1	0.000	0.459	/
	No	6	2.840 (2.184-3.691)	0.000	75.2			
Adjusting for BMI	Yes	10	2.492 (1.898-3.271)	0.002	65.8	0.000	0.221	0.591
	No	6	3.281 (2.308-4.664)	0.000	79.5			
Excluding ALD	Yes	12	2.856 (2.115-3.855)	0.000	74.9	0.000	0.910	1.000
	No	4	2.794 (1.716-4.549)	0.000	89.5			

heterogeneities and wider CIs in the subgroups of: eastern population, cross-sectional study, fewer adjusted potential confounders, and fewer individuals. For all the covariates, no significant between-group differences were found in univariate or multivariate meta-regression analyses.

Further analysis with several additional studies

Nine additional studies were identified for further exploration. Although all the studies provided OR values that estimated the influence of per-unit WC in NAFLD incidence, six studies calculated ORs without adjusting for BMI^[17,43-47] and four studies recruited patients without excluding ALD^[47-50] (Table 3). Likewise, when stratified by geographic region, the association was stronger in the eastern populations (OR = 1.089, *I*² = 94.1%; *P* = 0.000) in comparison with

the western populations (OR = 1.040, *I*² = 40.8%; *P* = 0.149). Moreover, the association between WC and risk of NAFLD was stronger in case-control/cohort studies than in cross-sectional studies (*P* = 0.010). There were higher heterogeneities and wider CIs in the subgroups of an eastern population, cross-sectional study, without adjusting for BMI, and without excluding ALD; all of which could be a source of heterogeneity (*P* < 0.05). For all the covariates, no significant between-group differences were found by univariate and multivariate meta-regression analyses.

Similarly, further analysis was performed after the addition of nine studies estimating NAFLD risk in individuals with central obesity. Of these nine studies, five OR values were not adjusted for BMI^[22,51-54], and four studies did not distinguish ALD from NAFLD^[55-58]. The result was inconsistent with the previous

Table 4 Summary estimates by fixed- vs random-effects methods

	OR (95%CI)	
	Fixed-effects	Random-effects
Categorical variable		
WC	2.344 (1.831-3.000)	2.550 (1.799-3.615)
WHR	3.910 (2.255-6.780)	4.061 (1.529-10.790)
BMI	2.183 (1.582-3.013)	2.854 (1.604-5.080)
WC ¹	2.844 (2.082-3.885)	3.139 (2.067-4.767)
Per-unit increase		
WC	1.043 (1.031-1.055)	1.065 (1.029-1.103)
BMI	1.121 (1.093-1.150)	1.250 (1.131-1.382)

¹Pooled same studies from above body mass index (BMI) category.

results after being stratified by region, as the OR value in the western population (3.098) was higher than in the eastern population (2.687). Univariate meta-regression analyses demonstrated that the association was significantly stronger in studies with a case-control or cohort design than in cross-sectional studies ($P = 0.015$). However, the statistical significance disappeared in multivariable meta-regression ($P = 0.078$). There were no significant between-group differences for other covariates in univariate and multivariate meta-regression analyses.

Sensitivity analysis and test of publication bias

To compare the degree of influence of central and general obesity in the NAFLD incidence rate, the five studies that provided adjusted OR estimations of both higher vs lower WC and higher vs lower BMI, were analyzed separately. The results showed a greater risk of NAFLD in individuals with central obesity in comparison with individuals with higher BMI levels. All the results were consistent, with no significant differences between fixed-effects or random-effects models were found (Table 4). WHR, which had the greatest effect in both effects models, might be the best parameter in predicting NAFLD. In addition, the influence analyses found that no single study affected the summary estimates (not shown).

There was no statistical evidence of publication bias among studies expressing WC as a continuous variable ($P = 0.436$ using Begg's test; $P = 0.222$ using Egger's test), as well as among studies expressing WC as a binary variable ($P = 0.230$ using Begg's test; $P = 0.092$ using Egger's test) (Figure 3).

DISCUSSION

This is believed to be the first meta-analysis investigating the independent relationship between two types of obesity and NAFLD risk. The results indicate that high WC, WHR and BMI levels are all independently associated with NAFLD. WC and BMI per-unit increases led to 0.07- and 0.25-fold increases in the risk of developing NAFLD, respectively. Individuals with

higher levels of WC, WHR or BMI (with a lower level as a reference) faced an increase in the NAFLD incidence rate by 1.34-, 3.06- and 1.85-fold, respectively. When these factors are expressed as continuous variables, comparing the strength of association among the three anthropomorphic parameters is meaningless due to enormous differences in their values and ranges. In contrast, it is more meaningful to compare the strength between higher WC (or WHR) level and higher BMI level within the same studies. This approach showed that patients with central obesity had a higher risk of NAFLD than individuals with general obesity.

This study demonstrates a stronger association between obesity and NAFLD risk in the eastern population compared with the western population when WC and BMI were reported as measurement data. Therefore, region may have been a potential source of heterogeneity in these studies. However, when WC was expressed as a categorical variable, individuals in the west had a greater NAFLD risk. This contradiction is easily explained by the fact that the WC cut-off-value was higher in westerners (102 cm) than easterners (90 cm). Further analysis with 18 additional datasets found that the region, design, adjusting for BMI, and excluding ALD were all potential causes of heterogeneity. However, none of the covariates were statistically different by multivariate meta-regression. The lack of significant changes after excluding any single study or using the other effects model demonstrates the reliability of the results from this meta-analysis.

Obesity has been shown to be an important risk factor for many liver diseases^[59]. Most hepatologists stress only the role of general obesity on the etiologies of these disorders while ignoring the special role of central obesity. Central obesity can also lead to some hepatic pathological changes. It is still not clear whether the effect of central obesity on NAFLD is independent of general obesity. Our findings have clarified this controversy, and can easily explain why some patients with NAFLD have a normal BMI level but an expanded waistline. We also verified that the impact of central obesity was more serious than the impact of general obesity. Furthermore, the independent effects of the two obesity modes suggested that they might be synergistic risk factors for NAFLD. This supposition is consistent with an Asian study that indicated that patients with both general and central obesity showed more than twofold risk of developing fatty liver compared to obese individuals with no central obesity^[16]. General obesity is mainly caused by overeating, whereas central obesity is a result of a sedentary lifestyle. Thus, our results emphasize the importance of considering the pathophysiological factor when treating NAFLD. The individuals with an elevated BMI, as well as a wider waistline, should follow moderate diets and increase physical activity as a preventive measure against

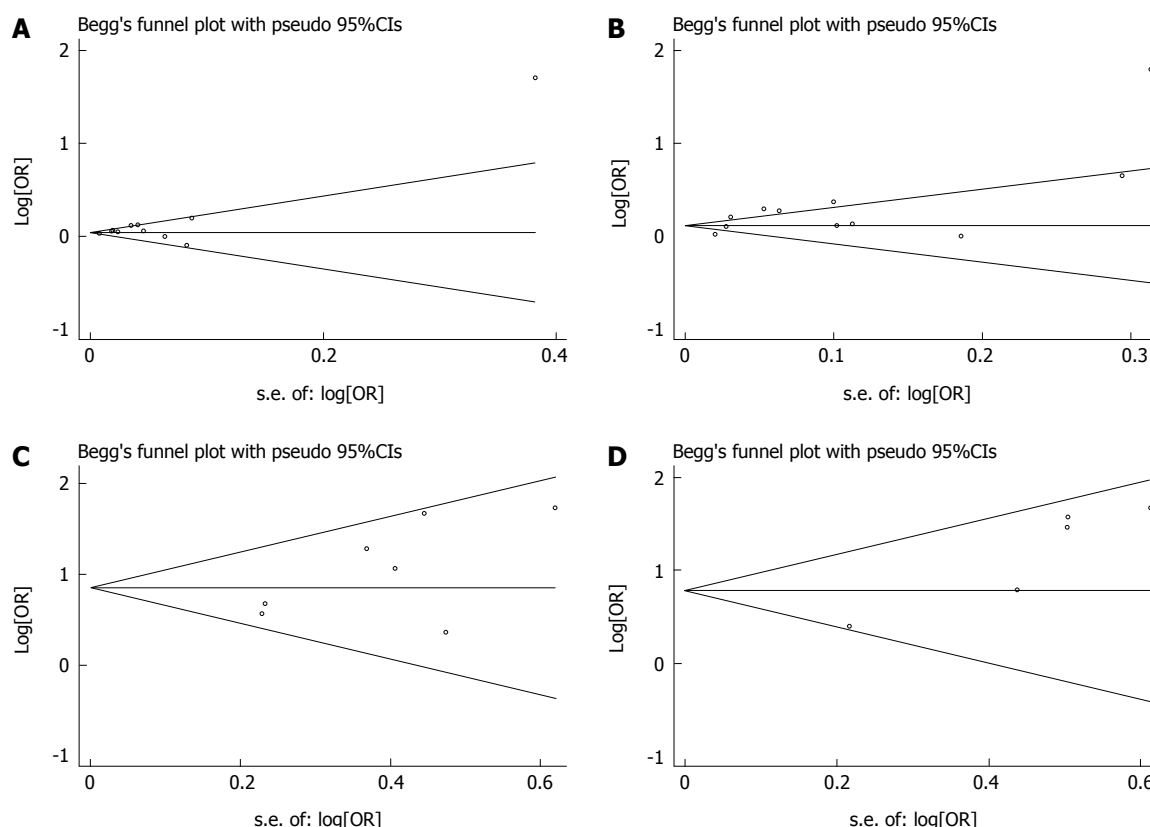


Figure 3 Funnel plots for publication bias. A: Per-unit increase in waist circumference (WC) ($P = 0.436$); B: High vs low category of WC ($P = 0.230$); C: Per-unit increase in body mass index (BMI) ($P = 0.533$); D: High vs low category of BMI ($P = 0.086$). s.e.: Standard error.

NAFLD. While only few studies reported an association between central obesity and HCC, several meta-analyses have demonstrated a significant increase in cancer risk in patients with central obesity^[10,60,61]. The significant effects of WC and WHR on NAFLD, a pivotal cause of HCC, may partly suggest that central obesity could independently increase HCC risk.

Some investigations have previously reported an association between increased abdominal obesity and hepatic steatosis. There were some shortcomings in these studies. On one hand, many of the studies assessed NAFLD by abnormal liver biochemistry levels^[62,63]. Although most patients with this disorder demonstrate abnormal liver function, Sorrentino *et al.*^[64] indicated that liver enzyme levels could not be used as surrogate markers of NAFLD. On the other hand, some of the studies involved all fatty liver patients, but failed to distinguish NAFLD from ALD. Despite NAFLD and ALD having similar pathology performance and pathogenesis, the nutritional status and adiposity condition of the two diseases are different. Central obesity is not a significant determinant for ALD-induced liver dysfunction^[65,66]. Moreover, there is a synergistic effect between risky alcohol consumption and obesity in relation to liver diseases^[67]. Thus, to improve the accuracy of diagnosis and reduce heterogeneity among studies, only studies that assessed NAFLD by imaging/biopsy were included and those involving ALD were excluded.

The influence of ALD on heterogeneity was tested in our further analyses. In addition, as the diagnostic criteria for children's central obesity are significantly different from those for adults, we excluded studies that did not recruit adults. To assess the validity and reliability of our results, subgroup analyses, meta-regression, and sensitivity analyses were performed.

The rigorous selection criteria of our study may have led to some potential limitations. First, NAFLD is highly prevalent in obese children^[68], and our restriction to adults meant that we were unable to extrapolate the risk of obesity to children. Second, liver biopsy is universally considered the best tool for identifying NAFLD. However, none of our included studies diagnosed fatty liver by biopsy. Third, the effect of obesity may be different between men and women. Previous studies suggested that the hypoandrogenism in men and hyperandrogenism in women can potentially lead to NAFLD *via* obesity^[69]. In addition, there is a correlation between liver fat deposition and WC in men with NAFLD, but not in women^[70]. Thus, our results may produce gender distinction, and gender may be a potential source of heterogeneity. Few studies separately reported OR values for both genders, thus, we could not stratify by gender. Finally, the causal exploration designs, such as cohort, case-control, and cross-sectional design, have lower reliability^[71]. Involving more cohort design studies would strengthen the argument, something

that our study did not do.

There are a variety of reasons why central obesity induces fatty liver. Central obesity is an essential component of MS; a disorder strongly associated with many metabolic factors. As an indispensable metabolic organ, the liver is inseparable from metabolism. These universally accepted facts disclose the intrinsic links between central obesity and liver diseases. Additionally, NAFLD is often accompanied by diabetes, dyslipidemia, and hypertension^[72,73], and these metabolic disorders could coexist in non-general obese individuals^[74]. A case-control study showed that central obesity without insulin resistance can play a limited role in fatty liver^[75], indicating that metabolic factors were significant in the role of central obesity. These results suggest that central obesity-induced metabolic disorders may be a major cause for NAFLD. Furthermore, central obesity could disturb the secretion of adipose tissue-derived adipokines, subsequently leading to an increase in harmful (tumor necrosis factor- α , interleukin-6, and resistin) and a decrease in protective (adiponectin) adipocytokines^[76,77]. Increased serum levels of detrimental cytokines in obese subjects accelerate the occurrence of NAFLD^[78,79].

As no therapies have been widely accepted, the treatment of NAFLD is another puzzling problem. Dietary modification (total calorie, fat, and carbohydrate restriction), exercise, weight loss, pharmacotherapy, and surgical intervention are potential options^[80-82]. It is worth noting that bariatric surgery could improve hepatic histology in most of the obese NAFLD patients, however, a small number of patients, especially those who lose weight too rapidly, might become worse^[83]. There are some animal data, as well as preliminary human data, showing that metformin may offer some benefits for NAFLD^[84]. Liver transplantation is still the best choice for patients with decompensated nonalcoholic cirrhosis^[85].

NAFLD is considered as a cause of many other liver diseases. Thus, our results suggest that central obesity poses a bigger threat to national health than general obesity. However, further investigation is still needed to determine whether central obesity is independently associated with NAFLD-related disorders, and whether it can induce NAFLD that progresses into NASH, cirrhosis, or HCC.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Ming-Hui Tai from the University of Kansas for polishing the manuscript.

COMMENTS

Background

Nonalcoholic fatty liver disease (NAFLD) can progress to liver fibrosis, liver cirrhosis, or hepatocellular carcinoma (HCC). HCC is the fifth most common cancer and the third most common cause of death from cancer worldwide. Due to the high prevalence of NAFLD worldwide, especially in developed countries,

the incidence of HCC in NAFLD has increased. Moreover, there has been an increase in the obesity rate and the morbidity and impact of NAFLD.

Research frontiers

The majority of hepatologists focus exclusively on the association between general obesity and NAFLD risk, while neglecting the influence of central obesity. Several meta-analyses and epidemiological studies have indicated that central obesity is a better predictor of metabolic disorders and tumors than general obesity. Nevertheless, these studies failed to show an independent risk of central obesity as they reported odds ratio values without adjusting for general obesity.

Innovations and breakthroughs

This is the first meta-analysis to investigate the independent relationship between general/central obesity and NAFLD risk. A total of 12065 cases and 33692 controls in 20 studies were included. The results indicate that higher waist circumference (WC), waist-to-hip ratio (WHR), and body mass index (BMI) are all independently associated with NAFLD. Therefore, patients with central obesity are at a higher risk of developing NAFLD than individuals with general obesity.

Applications

General obesity is caused mainly by overeating while central obesity results from a sedentary lifestyle. Thus, our results emphasize the importance of considering the pathophysiological factor in the treatment of NAFLD. Individuals with an elevated BMI and a wider waistline should follow moderate diets and increase exercise levels to prevent NAFLD. The significant effects of WC and WHR on NAFLD, a pivotal cause of HCC, suggest that central obesity could independently increase HCC risk.

Terminology

WC, a common anthropometric measure for defining central obesity, is related to many diseases, especially metabolic diseases. WHR is another index for defining central obesity. Abnormal BMIs, the most important index for defining general obesity, could increase the morbidity and mortality rates of many diseases, as well as a variety of tumors.

Peer-review

This meta-analysis is the result of an extensive and rigorous selection of articles. The statistical analysis is comprehensive and rigorously presented. The discussions are logical. The authors observed that both central and general obesity, particularly increases in WC and BMI, are independently associated with increased risk of NAFLD.

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ISSN 1007-9327

