Association between obesity and the risk of uterine fibroids: a systematic review and meta-analysis

Hao Qin,[1,2] Zhijuan Lin,[3] Elizabeth Vásquez,[4] Xiao Luan,[2] Feifei Guo,[2] Luo Xu [2]

► Supplemental material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jech-2019-213364).

For numbered affiliations see end of article.

Correspondence to
Zhijuan Lin, School of Basic Medicine, Weifang Medical University, 7166 Baotongxi Street, Weifang 261053, China; eva1949@163.com and Luo Xu, School of Basic Medicine, Qingdao University, 308 Ningxia Road, Qingdao, Shandong 266071, China; xu.luo@163.com

Received 10 October 2019
Revised 25 June 2020
Accepted 1 October 2020

To cite: Qin H, Lin Z, Vásquez E, *et al. J Epidemiol Community Health* Epub ahead of print: [*please include* Day Month Year]. doi: 10.1136/jech-2019-213364

ABSTRACT

Background Uterine fibroids (UFs) are the most common form of sex steroid hormone-dependent benign tumours that grow in the walls of the uterus. Several observational studies have examined the association between obesity and the risk of UFs, but findings are inconsistent. The objective of this systematic review and meta-analysis is to further examine the association of obesity with the risk/prevalence of UFs.

Methods A literature search was performed in three databases (PubMed, EMBASE and Web of Science) from 1 January 1992 to 30 May 2020. We used random-effect models to calculate the pooled ORs with corresponding 95% CIs. Additionally, we performed a dose–response meta-analysis to analyse the effect of body mass index (BMI), weight change since age 18, waist-to-hip ratio and waist circumference on the risk/prevalence of UFs.

Results A total of 22 articles, covering 24 studies including 325 899 participants and 19 593 cases, were selected based on our inclusion criteria. We found a positive association between obesity and the risk/prevalence of UFs (OR, 1.19; 95% CI, 1.09 to 1.29). Among participants with the highest BMI, the pooled OR was 1.19 (1.09 to 1.31) when compared to participants with normal BMI. For weight change since age 18, the pooled OR (95% CI) of UFs was 1.26 (1.12 to 1.42) among the highest change group when compared with no change. Additionally, our meta-analysis indicated the relationship of BMI with risk of UFs to be an inverse J-shaped pattern.

Conclusions The results of this meta-analysis suggest that obesity may increase the risk/prevalence of UFs, and the association is non-linear.

INTRODUCTION

Uterine fibroids (UFs) are the most common benign smooth muscle neoplasms of uterus in women of reproductive age. The overall prevalence of UFs has been reported to be 9.6%. The prevalence is known to increase with age, especially among women aged 50–54 years (15.9%).[1] UFs usually result in a series of chronic symptoms, such as heavy menstrual bleeding, pelvic pain and bladder dysfunction. In addition, UFs may cause reproductive problems including infertility and pregnancy complications. Due to its high incidence and severe symptoms, UFs result in 40% to 60% of hysterectomies and almost US$4.1–9.4 billion of direct costs annually in the USA.[2 3] However, the pathogenesis of UFs remains unclear except for its sex steroid hormone-dependent characteristics.[4 5]

As living standards rise, excess nutrients and calories in the diet lead to changes in disease spectrum. Obesity (a global syndemic) has affected most people in every country and region worldwide.[6] It is also well known that obesity leads to a dramatic increase in the prevalence of serious health problems such as diabetes, cardiovascular diseases, sleep apnoea, osteoarthritis and neoplasms.[7 8] Among these diseases, the contribution of obesity to the risk/prevalence of UFs has stimulated interest among researchers. Further elucidation of the role of obesity on the risk of UFs will be helpful for both prevention and diagnosis of UFs.

There is biological evidence to support the role of obesity on female reproductive health.[9] Several mechanisms are reported to impact the association of obesity with the reproductive system among women. One mechanism describes the endocrine response that obesity produces excess adipose tissue and increases the conversion of circulating androgens to oestrogens.[10] Another mechanism suggests that obesity is more likely to decrease the hepatic production of sex hormone binding globulin (SHBG), leading to increased levels of peripheral unbound oestrogens.[11] It is possible that through any of these biological mechanisms, obesity may be related to an increased incidence of UFs.

Several epidemiological studies have been performed to examine the association of obesity with the risk of UFs in premenopausal women with inconsistent findings.[12–33] Some studies reported a positive association between obesity and the risk of UFs,[12–25 32 33] while others showed non-significant association.[26–31] To address the lack of consensus in the literature, we performed a systematic review and meta-analysis of observational studies to quantitatively evaluate the association of obesity with the risk/prevalence of UFs.

METHODS

Search strategy

A literature search was performed using PubMed, EMBASE and Web of Science databases from 1 January 1992 to 30 May 2020. Relevant articles were screened through the following terms: ('obesity' OR 'overweight' OR 'adiposity' OR 'body mass index' OR 'BMI') AND ('uterine leiomyoma' OR 'uterine fibroid' OR 'uterine myoma'). To avoid the omission of possible original papers, we also reviewed the reference lists of significant reviews and manually identified additional articles.

Eligibility criteria

The eligibility criteria for the selected studies were as follows: (1) original papers published in English; (2) observational study designs performed in premenopausal women, such as case–control, cohort or cross-sectional study; (3) studies that examined the

correlation of overweight or obesity with the risk of UFs; (4) studies that reported effect size including OR, relative risk or HR with corresponding 95% CI or frequency distribution to infer them; (5) the exposure of interest was overweight or obesity; (6) the outcome of interest was UFs; (7) to avoid duplication, the data from the most complete and recent study were extracted when similar populations were used more than once in selected studies.

Two investigators (HQ and ZL) independently conducted the literature search. If they had different views for the inclusion of a study, it was resolved by consensus or in consultation with another reviewer (LX).

Data extraction

For the selected articles, the following key information was extracted: first author's last name, year of publication, country where the work was performed, study design, study periods, study population, age of participants, sample size (case), estimation methods of UFs, methods used to assess obesity, the OR (we showed effect estimate as OR for simplicity) with corresponding CI for categories of overweight or obesity and reported confounding factors. When multiple ORs (95% CIs) were reported, we extracted the fully adjusted estimates. In addition, we only extracted data on premenopausal women if the included studies consisted of both premenopausal and postmenopausal participants. The two investigators (HQ and ZL) independently evaluated the quality of studies included by using the Newcastle–OttawaScale,[34] which includes three dimensions: selection, comparability, exposure or outcome. A total score of ≥7 (the maximum score was 9 and the minimum score was 0) indicated high-quality.

Statistical analysis

Pooled ORs and corresponding 95% CIs were calculated to assess the association between obesity and the prevalence/risk of UFs. To address the likelihood of between-study variance, we combined study-specific ORs (95% CIs) using DerSimonian and Laird random-effect model.[35] I^2 values were used to evaluate heterogeneity among included studies. A value of $0<I^2\leq25\%$ means no heterogeneity, $25\%<I^2\leq50\%$ represents low heterogeneity, $50\%<I^2\leq75\%$ indicates moderate heterogeneity and $I^2>75\%$ shows high heterogeneity.[36] To ascertain the sources of between-study heterogeneity, subgroup analyses were conducted to address the role of potential confounders such as study design, study population, adjustment for covariates, study quality, assessment methods of obesity and UFs. In addition, a two-stage random-effect dose–response meta-analysis was performed to further examine the trend of obesity in association with risk of UFs.[37] Sensitivity analysis was done to evaluate the stability of pooled ORs. Funnel plot was conducted to assess publication bias.[38]

All data analyses were performed using Stata, version 12.0 (Stata Corporation, College Station, TX, USA). All presented p values were two-tailed with a statistical significance of <0.05.

RESULTS

Literature search

Using the search terms described earlier, we screened 489 articles from PubMed, 954 from EMBASE and 354 from Web of Science. A total of 1219 articles were reviewed through titles and abstracts after excluding 578 duplicates. Subsequently, 1175 articles were removed because they did not meet the inclusion criteria, and 44 articles were selected for full-text review. Of the 44 articles, 22 were eliminated based on our eligibility criteria: 13 articles did not report ORs with corresponding CIs, and we could not calculate the ORs using existing data; 5 articles did not report the outcome of interest; 4 articles used similar population with the most recent papers included. Finally, 22 articles met our inclusion criteria with 24 studies involving 325 899 participants and 19 593 cases were included in this meta-analysis.[12–33] Figure 1 shows the flow chart with our detailed methods for studies' selection.

Baseline characteristics

For all the studies included, the years of publication ranged from 1998 through 2019. As for study design, 14 were case–control studies,[12 15 17–19 22 24 26 29–33] 4 cohort studies[13 20 23 27] and 6 cross-sectional studies.[14 16 21 25 28] Looking at study region, 10 studies were performed in North America,[12 13 16 20 23–25 30] 1 in Africa,[14] 9 in Asia[15 17–19 22 26 27 32 33] and 4 in Europe.[21 28 29 31] With respect to adjustment for confounders, 18 studies were adjusted[12 13 15 18–25 27 28 30–32] and 6 unadjusted.[14 16 17 26 29 33] When evaluating study quality, 17 studies were deemed to be high quality,[12 13 18–28 30 31] and 7 low quality.[14–16 18 29 32 33]

For reports of menstrual status, 19 studies included premenopausal women,[12–24 26 27 29 31 33] 5 studies contained a small number of postmenopausal participants[25 28 30 32]; as for the assessment approaches of UFs, 17 studies used ultrasound and/or surgery,[12–15 17–20 22 23 25 26 29 31–33] 5 were based on self-report[16 24 28 30] and 2 reported clinical diagnosis.[21 27] Regarding obesity, 23 studies focused on BMI,[12–17 19–33] 4 on weight change since age 18,[13 20 23 27] 5 on waist-to-hip ratio[13 20 22 26 32] and 4 on waist circumference.[18 20 22 32] The basic information for the included articles and quality assessment scores are presented in online supplemental file 3.

Association of obesity with the risk of UFs

We found that there was a positive association between obesity and the risk of UFs (OR, 1.19; 95% CI, 1.09 to 1.29; p=0.00; figure 2), through combining ORs of risk of UFs for the highest obesity degree defined in original articles. For the highest versus reference category of BMI, the pooled OR of risk of UFs was 1.19 (95% CI 1.09 to 1.31). For the waist-to-hip ratio, the pooled OR was 1.95 (95% CI 1.23 to 3.08) when comparing the highest waist-to-hip ratio to reference waist-to-hip ratio. For weight change since age 18, the pooled OR risk of UFs was 1.26 (95% CI 1.12 to 1.42) when comparing the highest weight change to reference weight change over time. We found a similar trend for waist circumference with a pooled OR risk of UFs of 1.47 (95% CI 0.95 to 2.28) when comparing the high waist circumference to the reference category. These results are shown in table 1.

Subgroup meta-analysis

To explore possible sources of between-study heterogeneity, subgroup analyses were conducted using potential confounders including study design, study population, adjustment for covariates, study quality and assessment methods of UFs. As shown in table 1, the pooled ORs for case–control, cohort and cross-sectional studies were 1.12 (0.99 to 1.27), 1.17 (1.10 to 1.25) and 1.53 (1.12 to 2.09), respectively. The pooled ORs for studies by region were 1.24 (1.10 to 1.40) in North America, 1.30 (1.09 to 1.55) in Asia, 0.95 (0.72 to 1.26) in Europe and 3.54 (1.81 to 6.89) in Africa. The pooled ORs for ultrasound and/or surgery 1.18 (1.07 to 1.31), self-reported 1.14 (0.90 to 1.45) and clinical diagnosis methods 1.29 (1.09 to 1.53) were within a similar range. However, we found a decrease in the estimates between

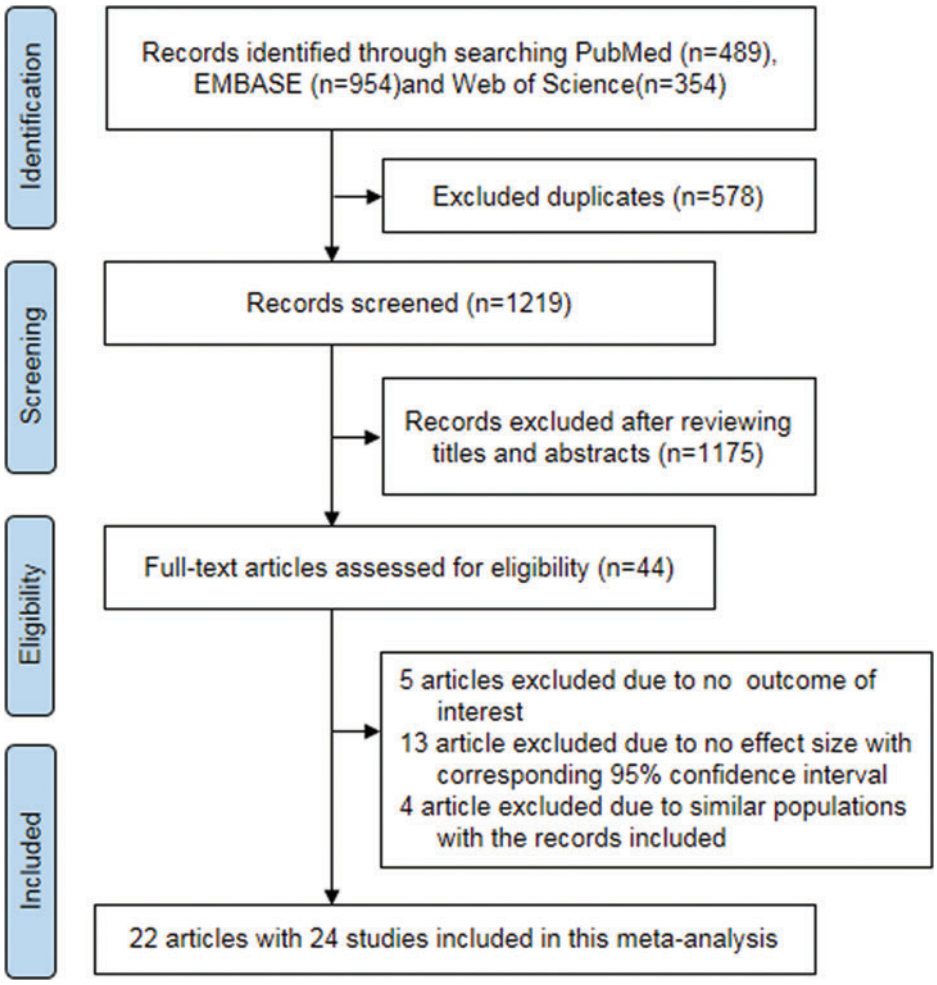

Figure 1 Flow diagram of literature search.

the unadjusted 1.73 (1.01 to 2.96) and adjusted 1.16 (1.06 to 1.27) covariates of the pooled ORs.

Dose–response analysis for BMI, weight change since age 18, waist-to-hip ratio and waist circumference

A two-stage random-effect dose–response meta-analysis for BMI, weight change since age 18, waist-to-hip ratio and waist circumference was performed (results are shown in figure 3). In the first step, a restricted cubic spline model with four knots at the 3rd, 35th, 65th and 95th percentiles was constructed; in the second step, study-specific ORs and corresponding CIs were combined through a multivariate random-effect model using restricted maximum likelihood.

The results of our dose–response analyses indicated that there was a non-linear association between obesity and the prevalence of UFs. For BMI, we found an inverse J-shaped pattern based on 14 studies.[12–14 16 20–23 25–27 32 33] For the weight change since age 18, we found a parabola pattern based on four studies.[13 20 23 27] When we evaluated the waist-to-hip ratio, we found a relatively horizontal line pattern based on five studies.[13 20 22 26 32] Finally, for waist circumference, we found a flat right-skewed bell curve based on three studies.[20 22 32]

Sensitivity analysis and evaluation of publication bias

Through removing one study at a time, the pooled ORs (95% CIs) ranged from 1.161 (1.068 to 1.262) to 1.243 (1.106 to 1.397), suggesting that the combined effect estimates were relatively robust (see online supplemental file 1). Additionally, obvious asymmetry was not found in funnel plots (see online supplemental file 2), indicating that no obvious publication bias was found in these studies.

DISCUSSION

Positive association between obesity and the risk of UFs

There are several observational studies assessing the association between obesity and the risk/prevalence of UFs. Interestingly, the findings of these studies are highly variable and inconsistent. Perhaps one of the reasons for wide discrepancies between studies can be the relatively small sample size and insufficient analytical power to determine the association in some of the studies. Our meta-analysis to evaluate the association of obesity with the risk of UFs presents an integrated evaluation of current studies' findings. In this meta-analysis, 22 articles with 24 studies involving 325 899 participants and 19 593 cases were evaluated. Our pooled result showed a positive association between the measures of obesity and the prevalence/risk of UFs (OR, 1.19; 95% CI, 1.09 to 1.29; p=0.00). This finding suggests there is room for an intervention aiming at reducing the incidence of UFs in premenopausal women, especially when the pathogenesis of UFs is still unclear.

For BMI and weight change since age 18, this meta-analysis suggested that participants classified with obesity had 17% and 26% higher risk of UFs than participants without obesity. Additionally, we found a non-linear dose–response for BMI,

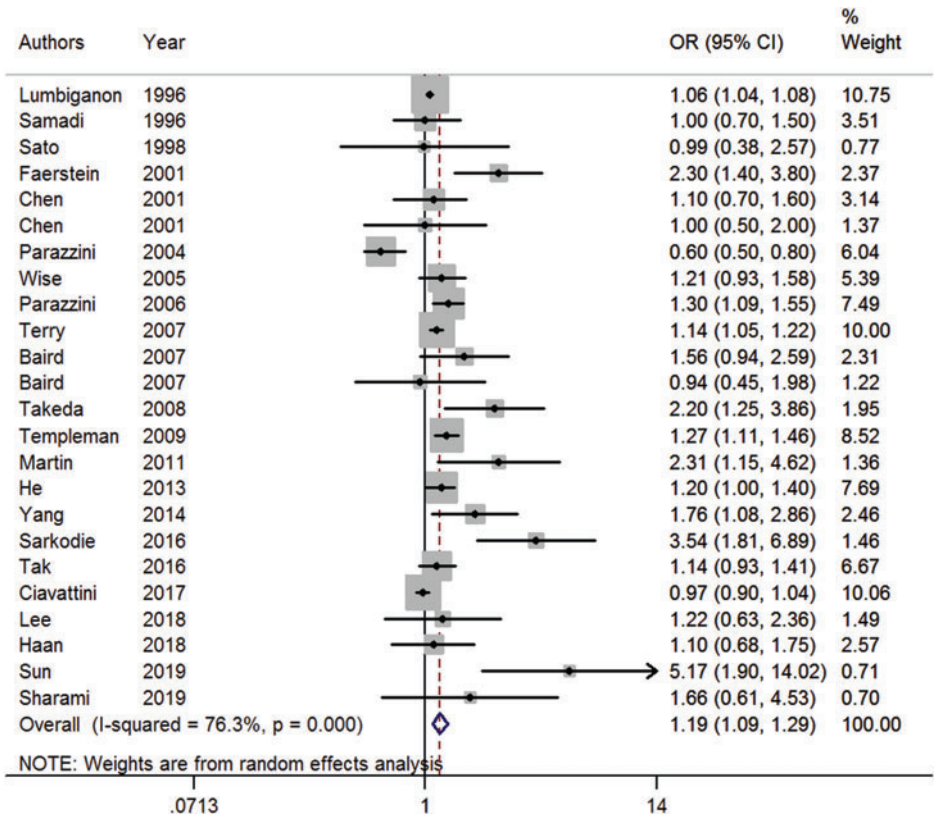

Figure 2 Forest plot of included studies. OR (95% CI). The size of the grey box is positively proportional to the weight assigned to each study, which is inversely proportional to the SE of the OR. The horizontal lines represent the 95% CI.

Table 1 Pooled ORs of subgroup analyses for the association between obesity and the risk of UFs

Subgroups	Studies (n)	Pooled ORs (95% CIs)	P value	Study heterogeneity	
				I^2	P value
All studies	24	1.19 (1.09 to 1.29)	0.000	76.3%	0.000
Estimation methods of obesity					
BMI	23	1.19 (1.09 to 1.31)	0.000	77.2%	0.000
Weight change since age 18	4	1.26 (1.12 to 1.42)	0.000	61.7%	0.050
Waist-to-hip ratio	5	1.95 (1.23 to 3.08)	0.004	91.6%	0.000
Waist circumference	4	1.47 (0.95 to 2.28)	0.080	83.5%	0.000
Study design					
Case–control	14	1.12 (0.99 to 1.27)	0.060	78.7%	0.000
Cohort	4	1.17 (1.10 to 1.25)	0.000	0.0%	0.591
Cross-sectional	6	1.53 (1.12 to 2.09)	0.008	59.4%	0.031
Region					
North America	10	1.24 (1.10 to 1.40)	0.001	39.9%	0.092
Asia	9	1.30 (1.09 to 1.55)	0.004	66.1%	0.003
Europe	4	0.95 (0.72 to 1.26)	0.724	88.9%	0.000
Africa	1	3.54(1.81 to 6.89)	0.000	–	–
Adjustment					
Yes	18	1.16 (1.06 to 1.27)	0.002	74.2%	0.000
No	6	1.73 (1.01 to 2.96)	0.044	82.4%	0.000
Study quality					
High	17	1.14 (1.03 to 1.25)	0.008	70.6%	0.000
Low	7	1.76 (1.26 to 2.47)	0.001	85.7%	0.000
Menstrual status					
Premenopausal	19	1.17 (1.07 to 1.28)	0.000	78.8%	0.000
Premenopausal and a few postmenopausal	5	1.35 (0.89 to 2.04)	0.155	62.4%	0.031

Continued

Table 1 Continued

Subgroups	Studies (n)	Pooled ORs (95% CIs)	P value	Study heterogeneity	
				I^2	P value
Assessment methods of UFs					
Ultrasound and/or surgery	17	1.18 (1.07 to 1.31)	0.001	81.6%	0.000
Self-reported	5	1.14 (0.90 to 1.45)	0.261	13.1%	0.330
Clinical diagnosis	2	1.29 (1.09 to 1.53)	0.003	0.0%	0.855

BMI, body mass index; UFs, uterine fibroids.

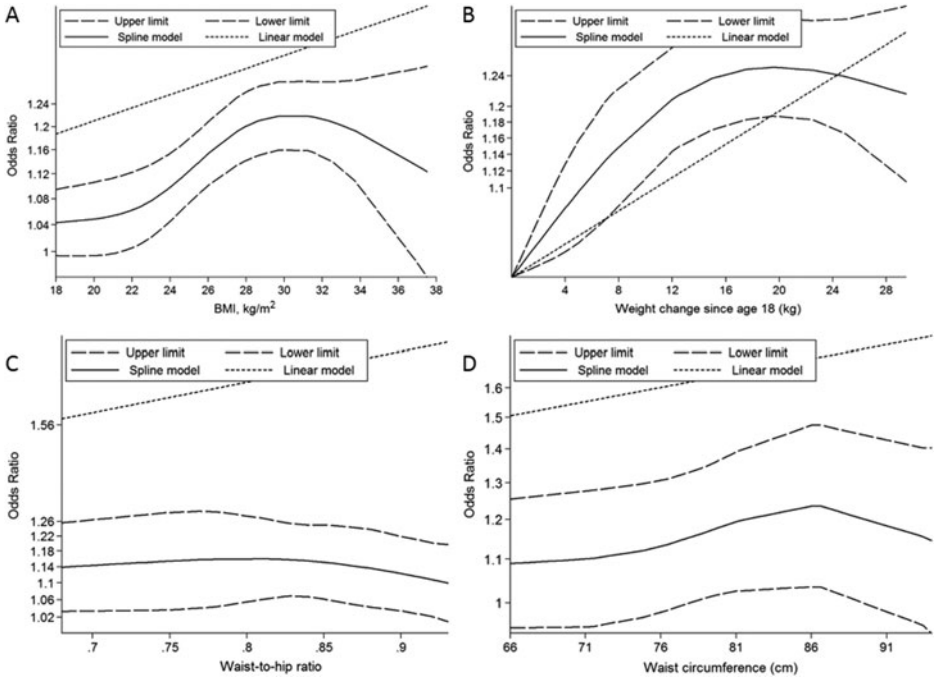

Figure 3 Dose–response analysis between obesity and the risk of UFs. (A) Dose–response analysis between BMI and riskof UFs, (B) Dose–response analysis between weight change since age 18 and the risk of UFs, (C) Dose–response analysis between waist-to-hip ratio and the risk of UFs, (D) Dose–response analysis between waist circumference and the risk of UFs. BMI, body mass index; UFs, uterine fibroids. The solid line and the long dash line represent the estimated ORs and corresponding 95% CIs.

weight change since age 18 and waist circumference in association with risk of UFs. Yet, our results might underestimate the overall correlation between obesity and the risk of UFs, since the pooled ORs reported in table 1 were calculated using the high level of obesity. In addition, the combined OR of waist-to-hip ratio with the risk/prevalence of UFs was relatively higher, but the inclusion of Sun's study[32] skewed our result away from the null. Furthermore, dose–response analysis also showed that the correlation of waist-to-hip ratio with UFs was not strong.

Latent mechanisms to explain the association between obesity and the risk of UFs

Although the underlying mechanisms implicated in obesity associated with an increased risk of UFs remain unclear, several theoretical pathways for this association have been proposed. One of these pathways suggests an increased conversion of adrenal androgens to oestrone by adipose tissue promotes the incidence of UFs.[39–41] As an endocrine organ, adipose tissue is responsible for the peripheral conversion of circulating androgens to oestrone. Characterised by an increased proliferation of smooth muscle cells and an overproduction of extracellular matrix (ECM), UFs are known to be oestrogen- and progesterone-dependent and have an increased sensitivity to sex steroid hormones. Thus, increased body fat may result in an overproduction of oestrogens, with enhanced cell proliferation of UFs.[40 41]

Another mechanism could be increased oestrogen and progesterone or decreased production of SHBG is able to advance the occurrence of UFs. Increased cholesterol biosynthesis in overweight women could promote oestrogen and progesterone production and then induce UFs.[42] Simvastatin, a 3-hydroxy-3-methyl-glutaryl -CoA reductase inhibitor, is reported to have a differential effect on leiomyoma and myometrial cells at concentrations regularly achieved clinically, including breakdown of the leiomyoma ECM and induction of the apoptotic pathway.[40 42] Increased unbound circulating oestrogen levels are common in overweight women due to reduced hepatic production of SHBG. Consequently, circulating oestrogens may stimulate cell proliferation of UFs.[43]

A third potential pathway suggests excessive fat accumulation contributes to secretion of adipokines and inflammatory cytokines. Adipose tissue is now recognised not only a reservoir for energy but an immune organ. In the context of obesity caused by increased food intakes and/or decreased physical activities, the development of insulin resistance (IR) is considered to be initiated by inflammation of adipose tissue.[44 45] These adipokines and inflammatory cytokines then activate key pathways related to inflammation, proliferation, autophage and mitosis, and subsequently induce the onset of UFs.[46 47]

UFs are also growth factors dependent, with the abundance of fibrotic connective tissue and ECM components as one important feature. Transforming growth factor (TGF)-family as one of the most important regulators of the fibrosis processes may contribute to UFs through Smad pathway, PI3K/Akt/mTOR pathway, the Ras/Raf/MEK/ERK signalling cascade and focal adhesion kinase pathway.[48 49] Tumour necrosis factor alpha secreted by adipocytes enhances the proliferation of UFs by functioning through NF-κB, JNKs and p38-MAPKs.[46 47 50 51]

The metabolic syndrome which usually co-exists with obesity can result in the presence of UFs and be another pathway that needs to be considered. Hyperglycaemia, along with IR, has been observed to increase unbound circulating sex steroid hormones and to promote UFs' cell growth by altering the tyrosine kinase signal pathway.[17] However, the association between UFs and IR still needs further elucidation. Hypertension might promote the onset of UFs through vasoactive peptides (eg, TGF-β) stimulating uterine smooth muscle cells' proliferation and vascular remodelling.[18] Dyslipidemia, induced by abnormal lipid metabolism, is partly regulated by oestrogens, thus related to oestrogen-dependent UFs.[22]

Unhealthy lifestyles related to obesity, including reduced physical activity, diet poor in fruits and vegetables, may also increase the risk of UFs.[15] One possible reason can be irregular physical activity is responsible for decreased SHBG levels and increased insulin and sex hormone levels. These proposed relationships need to be further explored in the future.[17 18 22]

Potential explanations for the non-linear dose–response

Potential explanations could be as follows for our finding of a non-linear pattern of association between obesity and the risk/prevalence of UFs. Thin or very obese women usually have decreased menstrual cycling compared to normal-weight women,[52] which reduces the risk of UFs through lowering levels of circulating oestrogens and progesterone. In addition, visceral fat, compared to subcutaneous fat, is easier to promote the production of proinflammatory cytokines and is associated with higher IR and hyperinsulinaemia. All of these factors are able to induce the onset of UFs.[29]

Examining possible confounding factors through subgroup analysis

In a meta-analysis, between-study heterogeneity is inescapable. We examined some of the main possible causes that could result in high between-study heterogeneity. Generally, study design, study quality, study population, the region in which the study was conducted, adjustment for covariates, the diagnostic methods of disease and the estimation methods of exposure may be sources of between-study heterogeneity. We performed subgroup analyses to minimise these sources of variation, but our between-study heterogeneity did not decrease significantly among most subgroups. Fortunately, our sensitivity analysis indicated that the pooled ORs were not substantially influenced by none of the studies except for combined ORs for waist-to-hip ratio, suggesting that the overall outcome was relatively robust.

Strengths and limitations

This meta-analysis has several strengths. First, 24 studies were included, which provided a large sample size to evaluate our hypotheses. Second, the possible confounder effects were controlled in most of the original studies included in our study when examining the effect of obesity on the occurrence of UFs. Third, the summary ORs were stable when sensitivity analysis was conducted by removing one study at a time (leave-one-out approach). Fourth, to assess and ascertain the association of obesity with the risk of UFs, different measures were used, which include the highest versus reference category of BMI, weight change since age 18, waist-to-hip ratio, waist circumference and dose–response analyses.

There were several limitations in this meta-analysis. First, in spite of a series of subgroup analyses, I^2 values of between-study heterogeneity did not reduce substantially, which indicated that there must be some unaccounted potential background confounding factors. To minimise the influence of between-study heterogeneity, we constructed a random-effect model. Second, covariates were inconsistent though most studies included performed adjustment for confounders. Third, some studies included contained a small number of perimenopausal and even postmenopausal women, who were unable to be removed from all participants according to the demographic characteristics of original studies. Fourth, race was indicated to be strongly associated with UFs by previous epidemiological studies.[53 54] However, we could not carry out subgroup analysis stratified by race and/or ethnicity since most original articles did not provide race characteristic of participants except for whites and African-Americans mentioned in some studies. Additionally, information bias might be a concern, since we collected data on weight change since age 18 and self-reported UFs. Given all the aforementioned limitations, our results may be prone to underestimation of our pooled ORs or perhaps shifting our findings towards the null.

CONCLUSIONS

Obesity is associated with an increased risk/prevalence of UFs. The association between obesity and the risk/prevalence of UFs is non-linear. Future studies should be continued to evaluate the associations of obesity with the risk of UFs using large prospective cohort studies in different races and ethnic groups.

What is already known on this subject

- UFs are highly prevalent in women of reproductive age around the world. Unfortunately, the pathogenesis of UFs is unclear except for its oestrogen- and progesterone-dependent characteristics. One of the mechanisms suggests excess adipose tissue may increase the level of circulating oestrogens, along with enhanced cell proliferation of UFs. Several mechanistic and observational studies have examined the association of obesity with the risk of UFs.

What this study adds

- This study adds evidence for the association between obesity and an elevated risk/prevalence of UFs. Additionally, our findings indicate that the association of BMI, weight change since age 18, waist-to-hip ratio and waist circumference with risk of UFs is non-linear.

Author affiliations
[1]School of Public Health, Weifang Medical University, Weifang, China
[2]School of Basic Medicine, Qingdao University, Qingdao, China
[3]Key Lab for Immunology in Universities of Shandong Province, School of Basic Medicine, Weifang Medical University, Weifang, China
[4]School of Public Health, University at Albany, State University of New York, New York, USA

Contributors HQ and LX conceived and designed the study. HQ, ZL and LX extracted data. HQ, FG and XL performed the data analyses. HQ, ZL and EV wrote the paper, and LX edited the manuscript. All authors reviewed the manuscript.

Funding This work was supported by the National Natural Science Foundation of China (No.32000495, No.81470815, No.81270460 and No.81500414), the Project of Shandong Province Higher Educational Science and Technology Program (No. J18KA290) and Project Funding approved by the National Medical Degree Postgraduate Education Steering Committee (C-YX20190201-09).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Luo Xu http://orcid.org/0000-0002-9092-3823

REFERENCES

1 Yu O, Scholes D, Schulze-Rath R, *et al.* A US population-based study of uterine fibroid diagnosis incidence, trends, and prevalence: 2005 through 2014. *Am J Obstet Gynecol* 2018;219:e1–.e8-.
2 Merrill RM. Hysterectomy surveillance in the United States, 1997 through 2005. *Med Sci Monit* 2008;14:Cr24–31.
3 Cardozo ER, Clark AD, Banks NK, *et al.* The estimated annual cost of uterine leiomyomata in the United States. *Am J Obstet Gynecol* 2012;206:e1–9.
4 Pavone D, Clemenza S, Sorbi F, *et al.* Epidemiology and risk factors of uterine fibroids. *Best Pract Res Clin Obstet Gynaecol* 2018;46:3–11.
5 Commandeur AE, Styer AK, Teixeira JM. Epidemiological and genetic clues for molecular mechanisms involved in uterine leiomyoma development and growth. *Hum Reprod Update* 2015;21:593–615.
6 Swinburn BA, Kraak VI, Allender S, *et al.* The global syndemic of obesity, undernutrition, and climate change: the lancet commission report. *Lancet* 2019;393:791–846.
7 Arroyo-Johnson C, Mincey KD. Obesity epidemiology worldwide. *Gastroenterol Clin North Am* 2016;45:571–9.
8 Hruby A, Manson JE, Qi L, *et al.* Determinants and consequences of obesity. *Am J Public Health* 2016;106:1656–62.
9 Pandey S, Bhattacharya S. Impact of obesity on gynecology. *Women's Health (London, England)* 2010;6:107–17.
10 Azziz R. Reproductive endocrinologic alterations in female asymptomatic obesity. *Fertil Steril* 1989;52:703–25.
11 Maggio M, Lauretani F, Basaria S, *et al.* Sex hormone binding globulin levels across the adult lifespan in women: the role of body mass index and fasting insulin. *J Endocrinol Invest* 2008;31:597–601.
12 Faerstein E, Szklo M, Rosenshein N. Risk factors for uterine leiomyoma: a practice-based case-control study. I. African-American heritage, reproductive history, body size, and smoking. *Am J Epidemiol* 2001;153:1–10.
13 Terry KL, De Vivo I, Hankinson SE, *et al.* Anthropometric characteristics and risk of uterine leiomyoma. *Epidemiology* 2007;18:758–63.
14 Sarkodie BD, Botwe BO, Adjei DN, *et al.* Factors associated with uterine fibroid in Ghanaian women undergoing pelvic scans with suspected uterine fibroid. *Fertility Research and Practice* 2016;2:9.
15 He Y, Zeng Q, Dong S, *et al.* Associations between uterine fibroids and lifestyles including diet, physical activity and stress: a case-control study in China. *Asia Pac J Clin Nutr* 2013;22:109–17.
16 Martin CL, Huber LR, Thompson ME, *et al.* Serum micronutrient concentrations and risk of uterine fibroids. *J Womens Health (Larchmt)* 2011;20:915–22.
17 Takeda T, Sakata M, Isobe A, *et al.* Relationship between metabolic syndrome and uterine leiomyomas: a case-control study. *Gynecol Obstet Invest* 2008;66:14–17.
18 Tak YJ, Lee SY, Park SK, *et al.* Association between uterine leiomyoma and metabolic syndrome in parous premenopausal women: a case-control study. *Medicine (Baltimore)* 2016;95: e5325.
19 Lumbiganon P, Rugpao S, Phandhu-fung S, *et al.* Protective effect of depot-medroxyprogesterone acetate on surgically treated uterine leiomyomas: a multicentre case: control study. *Br J Obstet Gynaecol* 1996;103:909–14.
20 Wise LA, Palmer JR, Spiegelman D, *et al.* Influence of body size and body fat distribution on risk of uterine leiomyomata in U.S. black women. *Epidemiology* 2005;16:346–54.
21 Parazzini F. Risk factors for clinically diagnosed uterine fibroids in women around menopause. *Maturitas* 2006;55:174–9.
22 Yang Y, He Y, Zeng Q, *et al.* Association of body size and body fat distribution with uterine fibroids among Chinese women. *J Womens Health (Larchmt)* 2014;23:619–26.
23 Templeman C, Marshall SF, Clarke CA, *et al.* Risk factors for surgically removed fibroids in a large cohort of teachers. *Fertil Steril* 2009;92:1436–46.
24 Chen CR, Buck GM, Courey NG, *et al.* Risk factors for uterine fibroids among women undergoing tubal sterilization. *Am J Epidemiol* 2001;153:20–6.
25 Baird DD, Dunson DB, Hill MC, *et al.* Association of physical activity with development of uterine leiomyoma. *Am J Epidemiol* 2007;165:157–63.
26 Sato F, Nishi M, Kudo R, *et al.* Body fat distribution and uterine leiomyomas. *J Epidemiology/Japan Epidemiological Association* 1998;8:176–80.
27 Lee JE, Song S, Cho E, *et al.* Weight change and risk of uterine leiomyomas: Korea Nurses' Health Study. *Curr Med Res Opin* 2018;34:1913–19.
28 Haan YC, Diemer FS, Van Der Woude L, *et al.* The risk of hypertension and cardiovascular disease in women with uterine fibroids. *J Clin Hypertens* 2018;20:718–26.
29 Ciavattini A, Delli Carpini G, Moriconi L, *et al.* The association between ultrasound-estimated visceral fat deposition and uterine fibroids: an observational study. *Gynecol Endocrinol* 2017;33:634–7.
30 Samadi AR, Lee NC, Flanders WD, *et al.* Risk factors for self-reported uterine fibroids: a case-control study. *Am J Public Health* 1996;86:858–62.
31 Parazzini F, Chiaffarino F, Polverino G, *et al.* Uterine fibroids risk and history of selected medical conditions linked with female hormones. *Eur J Epidemiol* 2004;19:249–53.
32 Sun K, Xie Y, Zhao N, *et al.* A case-control study of the relationship between visceral fat and development of uterine fibroids. *Exp Ther Med* 2019;18:404–10.
33 Sharami SH, Fallah Arzpeyma S, Shakiba M, *et al.* Relationship of uterine fibroids with lipid profile, anthropometric characteristics, subcutaneous and preperitoneal fat thickness. *Arch Iran Med* 2019;22:716–21.
34 Ofek Shlomai N, Rao S, Patole S. Efficacy of interventions to improve hand hygiene compliance in neonatal units: a systematic review and meta-analysis. *Eur J Clin Microbiol Infect Dis* 2015;34:887–97.
35 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
36 Higgins JP, Thompson SG, Deeks JJ, *et al.* Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
37 Orsini N, Li R, Wolk A, *et al.* Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol* 2012;175:66–73.
38 Egger M, Davey Smith G, Schneider M, *et al.* Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
39 Ilaria S, Marci R. From obesity to uterine fibroids: an intricate network. *Curr Med Res Opin* 2018;34:1877–9.
40 Wise LA, Laughlin-Tommaso SK. Epidemiology of uterine fibroids: from menarche to menopause. *Clin Obstet Gynecol* 2016;59:2–24.
41 Soave I, Marci R. From obesity to uterine fibroids: an intricate network. *Curr Med Res Opin* 2018;34:1877–9.
42 Malik M, Britten J, Borahay M, *et al.* Simvastatin, at clinically relevant concentrations, affects human uterine leiomyoma growth and extracellular matrix production. *Fertil Steril* 2018;110:1398–407.e1.
43 Moravek MB, Yin P, Ono M, *et al.* Ovarian steroids, stem cells and uterine leiomyoma: therapeutic implications. *Hum Reprod Update* 2015;21:1–12.
44 Jin T, Jiang Z, Luan X, *et al.* Exogenous orexin-a microinjected into central nucleus of the amygdala modulates feeding and gastric motility in rats. *Front Neurosci* 2020;14:274.
45 Stolarczyk E. Adipose tissue inflammation in obesity: a metabolic or immune response? *Curr Opin Pharmacol* 2017;37:35–40.

46 Ciebiera M, Wlodarczyk M, Zgliczynska M, *et al.* The role of tumor necrosis factor alpha in the biology of uterine fibroids and the related symptoms. *Int J Mol Sci* 2018;19:3869.
47 Zhan L, Yao S, Sun S, *et al.* NLRC5 and autophagy combined as possible predictors in patients with endometriosis. *Fertil Steril* 2018;110:949–56.
48 Ciebiera M, Wlodarczyk M, Wrzosek M, *et al.* Role of transforming growth factor beta in uterine fibroid biology. *Int J Mol Sci* 2017;18:2435.
49 Bao H, Sin TK, Zhang G. Activin A induces leiomyoma cell proliferation, extracellular matrix (ECM) accumulation and myofibroblastic transformation of myometrial cells via p38 MAPK. *Biochem Biophys Res Commun* 2018;504:447–53.
50 Vignini A, Sabbatinelli J, Clemente N, *et al.* Preperitoneal fat thicknesses, lipid profile, and oxidative status in women with uterine fibroids. *Reprod Sci* 2017;24:1419–25.
51 Nair S, Al-Hendy A. Adipocytes enhance the proliferation of human leiomyoma cells via TNF-alpha proinflammatory cytokine. *Reprod Sci* 2011;18:1186–92.
52 Rich-Edwards JW, Spiegelman D, Garland M, *et al.* Physical activity, body mass index, and ovulatory disorder infertility. *Epidemiology* 2002;13:184–90.
53 Sparic R, Mirkovic L, Malvasi A, *et al.* Epidemiology of uterine myomas: a review. *Int J Fertility and Sterility* 2016;9:424–35.
54 Stewart EA, Cookson CL, Gandolfo RA, *et al.* Epidemiology of uterine fibroids: a systematic review. *BJOG* 2017;124:1501–12.