Psychological Stress and BMI in the Prevalence of Uterine Leiomyoma Among Young Adult Women: Results from Project ELEFANT

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Abstract

Background: Uterine leiomyoma (UL) is a benign tumour with a prevalence of 4-21% in Western populations and UL occurrence is associated with impaired quality of life. Few studies have studied on psychological stress with the prevalence of UL in non-Western populations. We sought to identify the association of psychological stress with the prevalence of UL and mediation by BMI.

Methods: Analysis was performed in a cross-sectional, population-based Project Young ELEFANT study. We analysed clinical data collected from young Chinese women (age 20-40; n=178205) who were residents of Tianjin, China. Work-related, social and financial stress were evaluated by questionnaire and categorised by intensity (none, low, intermediate, and high). Odds ratios of UL were determined by binary logistic regression models adjusted for age at enrolment, smoking, passive smoking, alcohol consumption, BMI, education, occupation, residence, age at menarche, parity, oral contraceptive use, and diagnosis of type 2 diabetes and hypertension.

Results: UL prevalence in young adult women was associated with psychosocial stress by cause and intensity. High levels of work-related, social and financial stress were associated with ORs (95% CI) of 1.72 (1.41, 2.10), 1.48 (1.18, 1.84) and 1.44 (1.11, 1.88) respectively. The risk of UL with psychosocial stress showed interaction with BMI, with underweight women at greatest risk.

Conclusions: In young adult Chinese women, psychological stress is associated with UL prevalence. While BMI was positively associated with UL incidence, underweight and healthy weight women with psychosocial stress showed highest risk of UL.

Introduction

The context of social determinants of mental health, such as gender and income inequality, differ between low- and middle-income countries (LMIC) and those in high income countries (HIC).[1, 2] Studies on the effects of psychological stress have been mainly conducted in HIC, despite a large health disparity in LMIC.[3] One cause of psychosocial stress that is particularly relevant to LMIC is rapid modernisation and urbanisation, which not only modifies the physical environment but also human behaviour in response to it.[4, 5] Adapting to a new environment can induce psychological stress in differing ways and intensities. Young adults are particularly vulnerable to suffering from the social and financial stress associated with the transition to an independent life, including building their own career (often associated with a heavy workload).[6] Psychological stress is known to impact upon the body's immune and endocrine systems, which may be of particular consequence to young adult women of reproductive age. Stress induces activation of the hypothalamic-pituitary-adrenal axis that is associated with suppression of the hypothalamic-pituitary-gonadal axis through decreased GnRH secretion, subsequently leading to disruption of the ovarian cycle.

Uterine leiomyoma (UL) are benign smooth muscle tumours.[7, 8] Most of cases show no or only minor symptoms, thus there are a large number of undiagnosed women with the disease. Subsequently,

estimates of the prevalence of the condition have varied considerably between studies, from 4–70%.[9, 8] Young women with UL are often untreated as the fibroids are rarely malignant, however surgical removal of the uterus or medication are required for those with severe symptoms.[10] Indeed, it is estimated that 20–50% of symptomatic women with UL endure significant negative social and economic consequences as a result of their condition.[9] Comorbidities associated with UL include iron deficiency, anaemia, hydronephrosis and miscarriage in pregnant women.[11–13] Therefore, better understanding of the risk of UL in vulnerable young adult women is critical for their health and mental wellbeing. Genetic variants, such as those within mediator complex subunit 12 (*MED12*)[14] and high-mobility group AT-hook 2 (*HMGAT2*),[15] contribute to the risk of UL, but otherwise the cause of the disease remains largely unknown. Various environmental factors, including psychological stress, obesity and diet, are known to increase the risk of UL.[16, 8, 17, 18] A recent case-control study of Chinese women reported that consumption of vegetables and fruits decreases UL risk, while obesity and low occupational intensity increase risk.[19] Perceived racial discrimination among African-American women has been reported to be associated with a modest increase in the prevalence of UL.[20] Self-reported stress levels have similarly been reported to be higher among women with symptomatic UL than those without, but this association differs by ethnicity as it was present among black women but not white women.[21] In a study of Asian women, no such association was reported between UL and stress, depression or feelings of anxiety.[19] However, to date there has been no large-scale study on psychological stress, particularly interacting with other risk factors, with the prevalence of UL in non-Western populations.

Given the sparse literature in this field, the goal of this study was to explore the association between psychological stress and UL in young Chinese women, stratified by BMI classification, as one of the commonly known risk factors of the disease. In consideration of the different sources and intensities of stress, we examined work-related, social and financial stress that was categorised by its intensity from participants enrolled in ELEFANT project.

Materials And Methods

Participants

Project Environmental and LifeStyle Factors in metabolic health throughout life-course Trajectories (ELEFANT) is composed of three cohorts: newborns; young adults; and the elderly. We utilised data from pre-menopausal women within Young ELEFANT (n = 178205) in this study. All participants were residents of Tianjin city, China. Basic demographic and clinical characteristics data were collected during routine health check-ups (Table 1).

Table 1
Basic characteristics of the study population by uterine leiomyoma

Variables	Uterine leiomyoma		<i>P</i>
	No (n = 171968)	Yes (n = 2751)	
Age (years)	28.4 (4.7)	34.1 (5.5)	< 0.001
BMI	22.6 (4.1)	23.6 (4.3)	< 0.001
Smoking status			< 0.001
yes	2071	77	
no	169897	2674	
Passive smoking			< 0.001
yes	37838	1119	
no	134130	1632	
Alcohol use			< 0.001
yes	9888	377	
no	162080	2374	
Education (years)			< 0.001
≤ 9	79687	883	
10 ~ 15	28532	453	
≥ 16	63749	1415	
Occupation			< 0.001
Manual work	129462	1520	
Non-manual work	34941	987	
Unemployment	7565	244	
Region			< 0.001
Rural	127519	1420	
Urban	44449	1331	
Age at menarche	13.9 (1.4)	13.5 (1.6)	< 0.001
Oral contraception use			0.0102
yes	1270	32	
<i>Continuous variables are expressed by means (SD).</i>			

Variables	Uterine leiomyoma		<i>P</i>
no	170698	2719	
Parity (times)			< 0.001
None	88875	1247	
≥ 1	83093	1504	
Hypertension			< 0.001
yes	5859	312	
no	166109	2439	
Type 2 diabetes			< 0.001
yes	2153	58	
no	169815	2693	
<i>Continuous variables are expressed by means (SD).</i>			

Assessment of uterine leiomyoma

Clinicians at local hospitals examined the participants by Color ultrasound to diagnose UL. The number, location and size of leiomyoma was also recorded by the clinicians. Self-reported leiomyoma was not considered in this study.

Assessment of psychological stress

Psychosocial stress was assessed by structured questionnaires, with stress categorised by form (work-related, social, and financial) and intensity (none, low, intermediate and high). The method employed incorporated shortened versions of the Occupational Stress Indicator (OSI)[22] and the Perceived Stress Scale (PSS-10),[23] which has been validated and widely utilised in China and in the world.[24]

Assessment of other variables

Demographic data, such as age at enrolment, education, occupation, lifestyles (drinking, smoking and passive smoking), age at menarche, oral contraception usage, times of parity and history of hypertension and type 2 diabetes were collected using structured questionnaires. Education was calculated by the maximum years of formal schooling and classified into three categories of ≤ 9 , $10 \sim 15$ and ≥ 16 years. Occupation was categorised as manual work, non-manual work and unemployment. The region in which the participants lived was dichotomised into rural and urban according to their registered permanent residence. Cigarette smoking (yes or no) and alcohol consumption (yes or no) were recorded, and passive smoking history dichotomised (current passive smokers vs. former or non-passive smokers). Parity was dichotomised into 0 and ≥ 1 . According to the standard protocol, we recorded anthropometric

measurements of each participant, and body mass index (BMI) was calculated as weight/height² (kg/m²). Based on the guidelines of the Department of Disease Control, Ministry of Health of the People's Republic of China (PRC), we considered participants with a BMI below 24 as healthy weight, between 24 and 28 as overweight, and a BMI higher than 28 as obese.[25]

Statistical analysis

Continuous variables were expressed by means (SD) and categorical variables were expressed by number (%). Binary logistic regression analyses were performed to estimate the odds ratios [9] and 95% confidence intervals (CIs) of UL associated with work-related, social and financial stress. Trend tests were implemented to identify trends for ORs by intensity of stress. The associations with BMI were analysed among underweight and healthy weight (BMI < 24) participants and overweight and obese (BMI ≥ 24) participants, with binary logistic regression analyses used to determine whether each of three forms of stress were associated with UL risk within BMI category. All logistic regression analyses were adjusted for age at enrolment, smoking status, passive smoking status, drinking status, BMI, education, occupation, residence, age at menarche, parity, oral contraceptive use, diabetes, and hypertension. All statistical analyses were performed using SPSS 23.

Results

Uterine leiomyoma prevalence among young Chinese women

The prevalence of UL in pre-menopausal Chinese women aged between 20 and 50 was 1.6% (2751/171968). This is lower than reported elsewhere,[9, 8] which may be due to the comparatively young age of participants (mean age: 29). BMI was higher among participants with UL (22.56 ± 4.12 kg/m² vs 23.65 ± 4.35 kg/m²; $p < 0.001$). The known risk factors for UL of alcohol consumption, first-hand and second-hand tobacco smoke exposure were each confirmed to be positively associated with UL prevalence ($p < 0.001$). Young women with longer in education (≥ 16 years), non-manual occupation and living in urban areas showed greater prevalence of UL. Younger age at menarche, use of the oral contraceptive pill and higher parity were also associated with greater UL prevalence. Women with hypertension or type 2 diabetes also had significantly higher prevalence of UL (Table 1).

Prevalence of UL by BMI

To understand the association between BMI and UL prevalence, we calculated the odd ratios [9] for UL by BMI category, *i.e.* underweight, healthy weight, overweight and obese. The analyses were adjusted for age at enrolment, smoking status, passive smoking status, drinking status, education, occupation, region, age at menarche, parity, oral contraceptive use, type 2 diabetes, and hypertension. In young Chinese women, UL prevalence was higher in participants who were overweight (OR 1.30, 95% CI, 1.18–1.42) or obese (OR

1.31, 95% CI, 1.15–1.50) compared to those who are healthy weight (reference) (Table 2). The association with BMI (numerical) and UL prevalence is in eTable 1 in the Supplement.

Table 2

Odds ratios [9] with 95% confidence intervals (95% CIs) for uterine leiomyoma by BMI and stress.

Variable	Uterine leiomyoma		Crude OR	Adjusted OR*	P for trend
	No	Yes			
BMI					
Underweight	13712	112	0.62 (0.51, 0.74)	0.71 (0.59, 0.87)	0.049
Healthy weight	113741	1541	1.00 (ref)	1.00 (ref)	
Overweight	32320	791	1.81 (1.66, 1.97)	1.30 (1.18, 1.42)	
Obesity	12195	307	1.84 (1.63, 2.08)	1.31 (1.15, 1.50)	
Stress					
Yes	36885	1209	2.87 (2.66, 3.09)	1.47 (1.34, 1.62)	-
No	135083	1542	1.00 (ref)	1.00 (ref)	
*Adjusted for age at enrolment, smoking status, passive smoking status, drinking status, education, occupation, region, age at menarche, parity, oral contraceptive use, diabetes, and hypertension.					

Psychosocial stress and UL prevalence

To analyse the association between psychosocial stress and development of UL, we calculated adjusted ORs for UL by form and intensity of stress. Within the Young ELEFANT cohort, 20.63% of young Chinese women self-reported that they were under work-related stress (8.73% low stress, 10.24% intermediate, and 1.66% high), 7.70% that they were enduring social stress (6.40% low, 1.22% intermediate, and 0.07% high) and 14.85% reported financial stress (7.62% low, 6.30% intermediate, and 0.93% high) (Table 3). The overlap between forms of self-reported psychosocial stress are shown in eFigure 1 in Additional file 1. Participants reporting multiple forms of stress showed significantly higher prevalence of UL (Table 2). Stratification of stress levels by intensity (none, low, intermediate and high) revealed a gradual increase in UL prevalence with higher levels of stress. UL prevalence was also increased by self-reported social stress (OR 1.33, 95% CI, 1.18–1.51), with a stronger effect observed with intermediate or high levels (OR 1.48, 95% CI, 1.18–1.84). With work-related stress, the ORs for UL were 1.38 (95% CI, 1.22–1.57), 1.48 (95% CI, 1.32–1.66) and 1.72 (95% CI, 1.41–2.10) with low, intermediate and high stress levels, respectively. The ORs of UL associated with financial stress increased steadily with higher levels of stress, ranging from 1.29 (95% CI, 1.14–1.46) with low levels to 1.44 (95% CI, 1.11–1.88) with high levels (Table 3). An association between stress and UL stratified by work type (manual vs non-manual) is shown in eTable 2

in Additional file 1. The analyses were adjusted for age at enrolment, smoking status, passive smoking status, drinking status, BMI, education, occupation, region, age at menarche, parity, oral contraceptive use, type 2 diabetes, and hypertension. Associations between stress and UL by age are displayed in eTable 3 in Additional file 1.

Table 3

Odds ratios [9] with 95% confidence intervals (95% CIs) for uterine leiomyoma by form and intensity of stress.

Variable	Uterine leiomyoma		Crude OR	Adjusted OR*	P for trend
	No	Yes			
Social stress					
None	159235	2301	1.00 (ref)	1.00 (ref)	< 0.001
Low	10645	353	2.28 (2.04, 2.55)	1.33 (1.18,1.51)	
Intermediate	1969	91	3.21 (2.61, 3.94)	1.48 (1.18, 1.84)	
High	119	6			
Work-related stress					
None	137701	1609	1.00 (ref)	1.00 (ref)	< 0.001
Low	14668	391	2.28 (2.04, 2.55)	1.38 (1.22, 1.57)	
Intermediate	16908	618	3.13 (2.85, 3.44)	1.48 (1.32, 1.66)	
High	2691	133	4.18 (3.49, 5.01)	1.72 (1.41, 2.10)	
Financial stress					
None	147270	1942	1.00 (ref)	1.00 (ref)	< 0.001
Low	12772	368	2.18 (1.95, 2.44)	1.29 (1.14, 1.46)	
Intermediate	10398	375	2.70 (2.41, 3.02)	1.34 (1.18, 1.51)	
High	1528	66	3.34 (2.61, 4.27)	1.44 (1.11, 1.88)	
*Adjusted for age at enrolment, smoking status, passive smoking status, drinking status, BMI, education, occupation, region, age at menarche, parity, oral contraceptive use, type 2 diabetes, and hypertension.					

High prevalence of uterine leiomyomas in BMI under 24 kg/m² with psychological stress

We observed that BMI and psychological stress were each associated with UL in the previous analysis. To examine the prevalence of UL in under/healthy weight and overweight/obese individuals self-reporting stress, we dichotomised study participants using a BMI threshold of 24 kg/m²; this is the threshold used to identify overweight/obese individuals according to Chinese guidelines.[25] The prevalence of UL in participants reporting social stress was OR 1.43 (95% CI, 1.25–1.65) among those with a BMI < 24 and 1.23 (95% CI, 1.02–1.49) for those with BMI ≥ 24 (Table 4). The ORs for UL with work-related stress were 1.60 (95% CI, 1.41–1.81) in under/normal weight participants, and 1.25 (95% CI, 1.08–1.46) for overweight/obese participants. Financial stress was associated with increased UL prevalence in both weight groupings, with an OR of 1.41 (95% CI, 1.24–1.59) for under/normal weight individuals and 1.18 (95% CI, 1.01–1.38) for overweight/obese participants. Thus, we observed that the association of UL with any form of stress was stronger in underweight/normal weight individuals in comparison to overweight and obese ones.

Table 4

Odds ratios [9] with 95% confidence intervals (95% CIs) for uterine leiomyoma by psychological stress and BMI.

BMI < 24			BMI ≥ 24			
	Uterine leiomyoma		Adjusted OR*	Uterine leiomyoma		Adjusted OR*
	No	Yes		No	Yes	
Social stress						
No	117947	1362	1.00 (ref)	41288	939	1.00 (ref)
Yes	9506	291	1.43 (1.25, 1.65)	3227	159	1.23 (1.02,1.49)
Work-related stress						
No	102292	929	1.00 (ref)	35409	680	1.00 (ref)
Yes	25161	724	1.60 (1.41,1.81)	9106	418	1.25 (1.08, 1.46)
Financial stress						
No	109462	1147	1.00 (ref)	37808	795	1.00 (ref)
Yes	17991	506	1.41 (1.24, 1.59)	6707	303	1.18 (1.01, 1.38)
*Adjusted for age at enrolment, smoking status, passive smoking status, drinking status, education, occupation, region, menarche age, parity, oral contraceptive use, diabetes, and hypertension.						

Interaction between BMI and psychological stress on uterine leiomyoma prevalence

We examined interactions between BMI and psychological stress upon the prevalence of UL (Table 5). In this study, we observed that interaction between stress and underweight (OR 1.16, 95% CI, 1.00-1.34), overweight (OR 0.92, 95% CI, 0.85-1.00) and obesity (OR 0.90, 95% CI, 0.81-1.00) was significant in increasing the ORs for UL.

Table 5
Interaction between BMI and stress for uterine leiomyoma risk.

BMI classification	Stress	Uterine leiomyoma	
		Crude OR (95% CI)	Adjusted* OR (95% CI)
Underweight	no	0.48 (0.42, 0.55)	0.71 (0.61, 0.82)
	yes	1.15 (1.00, 1.34)	1.16 (1.00, 1.34)
Healthy weight	no	1.00 (ref)	1.00 (ref)
	yes	1.71 (1.61, 1.81)	1.26 (1.18, 1.34)
Overweight	no	1.53 (1.42, 1.66)	1.20 (1.11, 1.30)
	yes	0.90 (0.84, 0.98)	0.92 (0.85, 1.00)
Obesity	no	1.54 (1.40, 1.71)	1.22 (1.10, 1.36)
	yes	0.92 (0.83, 1.01)	0.90 (0.81, 1.00)
*Adjusted for age at enrolment, passive smoking status, drinking status, education, region, age at menarche, and hypertension. Result of likelihood test for interaction variable BMI*stress is significant (P = 0.0029, df = 3).			

Discussion

In Chinese young adult women, psychological stress increased the prevalence of uterine leiomyomas in an intensity-dependent manner. High intensity of work-related stress was the strongest risk factor for the disease over other forms of stress. Interestingly, the association of stress with uterine leiomyomas prevalence was higher in under or healthy weight young women than overweight or obesity. To the best of our knowledge, our study is the first to report an association between psychosocial stress and uterine leiomyomas in an Asian population, and the first to identify an interaction with BMI.

Evidence from clinical, molecular and pharmacological studies has supported the implication of the sex hormones in the development and maintenance of uterine leiomyomas, as hormonally-responsive neoplasms.[26, 27] Psychosocial stress may subsequently promote the development of UL through hormonal imbalance, and particularly through the action of cortisol. This stress hormone is released by

activation of the hypothalamic-pituitary- adrenal gland axis under stress, and in turn regulates the secretion of a number of other hormones, including glucocorticoids, catecholamines, growth hormone, prolactin, oestrogen and progesterone.[28–30] *In vitro* studies have demonstrated increased secretion of ovarian steroids after stress hormone exposures[31] while, conversely, suppression of circulating gonadotropins and gonadal steroid hormones has been observed in non-human primates undergoing stressful conditions, leading to abnormal menstrual cycle and impairment of reproductive function.[32]. This is supported by evidence from a human population study that increased cortisol levels are associated with altered production of reproductive hormones and subsequently alterations in the menstrual cycle.[33] However, the few studies that have examined the interplay of cortisol and reproductive hormones frequently show contrasting findings, and therefore much further work is required to elucidate the mechanisms underpinning the association between UL and psychosocial stress.

Our study demonstrated a dose-dependent increase in UL risk with higher intensity of stress. While we also observed a differential effect by form of self-reported stress (e.g. financial), these may be proxies for the intensity of stress felt by the individual. The hypothesis that the level of stress endured by an individual is associated with UL risk is further supported by studies elsewhere. Within the Nurses' Health Study, sexual and physical abuse in childhood was demonstrated to be associated with increased risk of UL in premenopausal women, with a dose-response reported between severity and duration of abuse and UL risk.[34] Similarly, Vines *et al*/reported an association between the number of self-reported major life events with respect to stress intensity and UL incidence, with higher prevalence among black women with severe stress compared with those no or mild stress.[35]

Previous epidemiological studies report a positive association between BMI and UL,[36, 37] or an inverse J-shaped association.[38] In this study, leiomyoma prevalence was higher among women who were underweight and of a healthy weight in comparison to those who are overweight or obese. Similar results are reported in the Black Women's Health Study, where increased risk of leiomyoma was reported in women with a BMI of 27.5–29.9 kg/m² and lower risk in women with a BMI of ≥ 30 kg/m², indicating an inverse J-shaped association[38] that has also been reported in Asian women.[39] Psychological stress is known to impair the immune system and is associated with increased body weight.[16] Our observation of an interaction between BMI and psychosocial stress underlines that a complex interaction exists between key risk factors for uterine leiomyoma.

A limitation of the present study is that cortisol level, as a biomarker of stress, was not available in the study participants. However, this is the first study to report on the effects of different forms and intensities of psychosocial stress upon UL risk using a validated psychological stress measurement in a large number of young women. The data in the present study was also analysed cross-sectionally, and therefore the association between prevalence of UL with stress needs further study to examine causal relationships with genetic factors using follow-up data in a prospective study.

Conclusions

We report that uterine leiomyoma prevalence in young adult women is increased by psychological stress, with risk greatest among those individuals reporting high intensity of stress. The association was stronger in underweight and healthy weight women in comparison to overweight and obese individuals. Further work is required to elucidate the complex interplay of stress, obesity and hormonal imbalance in the modification of UL risk.

Abbreviations

UL, Uterine leiomyoma; ORs, Odds ratios; LMIC, low- and middle-income countries; HIC, high income countries; *MED12*, mediator complex subunit 12; *HMGA2*, high-mobility group AT-hook 2.

Declarations

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Authors' contributions

conceptualization, L.G. and S.H.; methodology, J.F. and E.C.; formal analysis, R.S. and B.Y.; investigation, B.Y.; resources, Y.Z., C.L., H.L., R.Z. and X.G.; data curation, B.Y., R.S., J.F., C.O.Y.; writing—original draft preparation, B.Y. and T.M.B.; writing—review and editing, H.M.B., B.Y. and P.H.L.; visualization, S.H., H.M.B. and L.G.; supervision, S.H. and H.M.B.; project administration, L.G., S.H. and H.M.B.; funding acquisition, L.G., X.G. and Y.Z.

Availability of data and materials

The datasets used during the current study are available from the corresponding authors on reasonable request.

Code availability

All codes from this study are available from the corresponding authors on reasonable request.

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Competing interests

All authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

All procedures and study protocols were approved by the ethical committee of Tianjin Medical University (TMUHEMEC2016022). The study was conducted in accordance with the principles of the Declaration of Helsinki. All participants signed written informed consent before inclusion in the study.

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