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Original Article

Lower Serum Levels of Uric Acid in Uterine Fibroids and Fibrocystic Breast Disease Patients in Dongying City, China

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Abstract

Background: Increasing serum levels of uric acid (SUA) after menopause in women brought up a hypothesis that estrogenic effect may protectively regulate SUA. Estrogenic effect is a major etiology of uterine fibroids and fibrocystic breast disease. The study aimed to explore SUA among patients suffering from these diseases to enhance the hypothesis.

Methods: Overall, 1349 female participants were selected into three cases: Case Ⅰ having uterine fibroids (n=568), Case Ⅱ having fibrocycstic breast disease (n=608) and Case Ⅲ having uterine fibroids combining with fibrocycstic breast disease (n=173); 4206 participants without these diseases were selected as controls. Based on health check-up data from 2011 to 2012, in Dongying Shengli Oilfield Central Hospital, a cross-sectional study was conducted to examine the difference in SUA between the case and control. We adjusted covariates by generalized linear regression mode.

Results: From 19 to 44 yr, SUA of Case Ⅰ to Case Ⅲ were lower than controls by 8.46 umol/L (P=0.011), 5.88umol/L (P=0.014) and 9.39 umol/L (P=0.059), respectively. From 45-54 yr, no significant differences were between three cases and controls. In Case Ⅰ and its control: from 54-59 yr, differences were not significant; from 60 to 72 yr, SUA in Case Ⅰ was lower than the control by 32.02umol/L (P=0.003).

Conclusion: Participants of uterine fibroids and fibrocystic breast disease had a lower SUA except the stage of menopause, which indirectly supported that estrogenic effect, may protectively decrease SUA.

Keywords: Uric acid, Estrogenic effect, Leiomyoma and fibrocyst, Breast disease

Introduction

Hyperuricemia, defined as high levels of blood uric acid, is the major etiological factor of gout (1), recently, increasing serum levels of uric acid (SUA) has been found to be linked to the prevalence of the metabolic syndrome, cardiovascular diseases, cerebrovascular disease and it was found as a predictor of micro albuminuria and renal dysfunction (2-7). In recent years, the prevalence of hyperuricemia in China is dramatically increasing, about 18.66% (8). Hyperuricemia induces vascular diseases, possibly through the generation of reactive oxygen species and subsequent endothelia dysfunction, which exerts the pro-inflammatory effects (9). Kenneth Rock noted

that uric acid might be an activator of the immune system by stimulating dendritic cell maturation and T lymphocytes (10). The IL-1/IL-1R pathway maybe explained the inflammatory link between SUA and endothelial dysfunction (11). Uric acid can also inhibit endothelial generation of nitric oxide that induces lipid oxidization and impairs endothelium-dependent vasodilation (12). SUA was increasing in postmenopausal women (13), which may increase the risk of cardiovascular diseases, metabolic syndrome, diabetes and other chronic metabolic diseases (14-17). It was hypothesized that after menopause, decreasing estrogenic effect may induce hyperuricemia. One possible explanation of physical mechanisms was estrogenic signaling might decrease SUA through affecting the activity of renal (18). Estradiol could regulate renal urate transporter expression in ovariectoized mice (19). Therefore estrogenic effect may positively adjust SUA metabolism.

It is well known that stronger estrogenic effect is a major etiology of uterine fibroids and fibrocystic breast disease (20, 21). Factors increase overall lifetime exposure to estrogen, such as obesity and early menarche, are positively associated with the incidence of uterine fibroids (22). In patients suffering from uterine fibroids and fibrocystic breast disease, whether SUA are lower than the general due to stronger estrogenic effect? If so, it may offer evidence to support the role of estrogenic effect on SUA metabolism in females.

This study selected participants with uterine fibroids, fibrocystic breast disease or uterine fibroids combining with fibrocystic breast disease as cases, and participants without these diseases as controls. The objective was to explore the difference in SUA between cases and controls. Thereby, we can explore whether estrogenic effect can regulate SUA and open a new view to prevent and treat hyperuricemia in females.

Materials and Methods

Study population

All participants were regular and registered staffs or retirees of enterprises and institutions in Dongying City with the benefit of free health check-up once a year. Participants were selected from health check-up records of a general hospital in Shandong Province from Jan 2011 to Jan 2012. We included 5728 female participants with an age range of 19-72 yr who had intact health check-up records.

Exclusion criteria for participants: fasting blood glucose (FBG)>8.00 mmol/L (osmotic diuresis critical point is 8.96mmol/L); AST≥100U/L or ALT≥100U/L; creatinine clearance (Ccr)<50ml-/min or blood uric nitrogen (BUN) > 9mmol/L (23); currently using diuretics, allopurinol or uricosuric agents; gout patients; surgery history of hysterectomy, mastectomy or ovarian cystectomy; current or former hormone replace therapy (HRT) users; present or past histories of endometriosis, ovarian tumors and polycystic ovarian syndrome; current in the stage of pregnancy or breastfeeding. Finally, a total of 5555 female participants were recruited. The study set up three cases: Case Ⅰ 568 uterine fibroids patients aged 19-72 yr; Case Ⅱ 608 fibrocystic breast disease patients aged 19-54 yr; Case Ⅲ 173 patients diagnosed with both uterine fibroids and fibrocystic breast disease aged 19-54 yr. The study set up two controls: Control Ⅰ 4206 people without uterine fibroids and fibrocystic breast disease aged 19-72 yr (vesus Case Ⅰ); Control Ⅱ 3762 people from Control Ⅰ excluding age above 54 yr (vesus Case Ⅱ and Case Ⅲ).

The oldest uterine fibroids patients were 72 yr old and no fibrocystic breast disease patients were older than 54 yr old. Since SUA differs in women's lifespan due to menopause, for each condition, participants were further divided into different age groups: 19-44 (reproductive period), 45-54 (menopause), 55-59 (early post-menopause) and ≥60 (post-menopause) for Case Ⅰ and Control Ⅰ; 19-44 (reproductive period) and 45-54 (menopause) for Case Ⅱ, Case Ⅲ and Control Ⅱ.

Measurements/ General Examination

Standardized interviews and self-reported questionnaires

Standardized interviews and self-reported questionnaires were used to obtain the following

information: age (in years); medical history including cardiovasculuar diseases, metabolic diseases, uterine fibroids, endometriosis, fibrocystic breast disease, ovarian tumors, polycystic ovarian syndrome and so on; operation history including hysterectomy, mastectomy, ovarian cystectomy and so on; use of prescription medication including anti-hypertensives, allopurinol, uricosuric agents, hormone use and so on; histories of pregnancy, delivery and breast feeding.

The anthropometric variables

The anthropometric variables contained weight, height and blood pressure. Weight and height were measured with the subjects wearing light clothes and no shoes. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in metres. Blood pressure (BP) was obtained from the right arm of the subject in a relaxed, sitting position after 5 min rest. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded for twice by mercury sphygmomanometers.

Laboratory Analysis

Blood samples were obtained by venipuncture in the morning after fasting overnight (at least 12 h). Laboratory test included: fasting blood glucose (FBG), total cholesterol level (T-CH), triglyceride (TG), glutamic-pyruvic transaminase (ALT), glutamic-oxalacetic transaminase (AST), blood uric nitrogen (BUN), blood creatinine (Cr) and SUA. Glomerular filtration rate (GFR), estimated by creatinine clearance (Ccr) using the Cockcroft-Gault (CG) formula: (140− age) × weight/ (serum creatinine×85).

Estrogen-dependent diseases diagnosis

All 5555 participants took gynecology and breast colour doppler ultrasound. Uterine fibroids and fibrocystic breast disease were confirmed by professional gynecologistis according to the standard protocol of the health check-up institute (24, 25).

Statistics

Statistics analysis was performed using SAS software, version 9.1. Data was shown as mean± standard deviation. If variances were homogenious, the mean differences between groups were compared by Student's *t* test. A *P*-value of less than 0.10 was considered to be statistically significant when comparing differences between cases and control by Student's *t* test.

After adjustment for covariant variables, the associations between the two kinds of diseases and SUA were evaluated using the generalized linear regression mode. The study set SUA as the dependent variable; the presence of diseases from cases as the independent variable; risk factors selected based on results of independent-sample *t* test ($P<0.10$) as covariant variables. Compared with controls, partial regression coefficient β of cases represented differences of SUA (ug/L) between the case and control. A *P*-value of less than 0.05 was considered to be statistically significant by generalized linear regression mode.

Results

Characteristics of participants according to cases and age categories

Demographic and biochemical parameters of participants according to cases and age categories were listed in Table 1 (for uterine fibroids and control), Table 2 (for fibrocystic breast disease and control) and Table 3 (for uterine fibroids combining with fibrocystic breast disease and control).

From Table 1 (for uterine fibroids and control), totally for all ages, BMI, T-CH, TG and FBG of the case were higher compared with the control but SUA were lower. When considering age categories, from 19-44 yr, BMI, SBP, DBP, T-CH, TG and FBG of the case were higher than the control; from 45-54 yr, it was found only T-CH in the case were lower than that in the control; from 55-59 yr, BMI, SBP, DBP, T-CH, FBG and SUA of the case were lower than the control; from 60-72 yr, BMI, SBP, DBP and SUA of the case were lower than the control.

From Table 2 (for fibrocystic breast disease and control), totally for all ages, BMI, SBP, DBP, TG and SUA in the case were lower than the control. When considering age categories, from 19-44 yr, BMI, SBP, TG and SUA of the case were lower than the control; from 45-54 yr, DBP and TG of the case were lower than the control.

From Table 3 (for uterine fibroids combining with fibrocystic breast disease and control), totally for all ages, only SUA of the case were lower than the control. When considering age categories, from 19-44 yr, BMI and T-CH of the case were higher than the control; from 45-54 yr, BMI, SBP, DBP and SUA of the case were lower than the control.

Differences in SUA among cases and controls according to age categories

To compare differences of SUA between cases and controls, the study built 11 generalized linear regression models according to age categories among three cases (the note of Table 4 showed adjusted variables in different models respectively). Covariant variables entered generalized linear regression models were selected by *t* test at the standard of $P<0.10$, as follows from Table 1-3. In comparison with controls, SUA of three cases decreased by 9.62 umol/L, 4.69 umol/L and 10.91 umol/L respectively. When taking age into consideration, the decreasing SUA differed from each other. From 19 to 44 yr, SUA of Case Ⅰ to Case Ⅲ were lower than controls by 8.46 umol/L ($P=0.011$), 5.88 umol/L ($P=0.014$) and 9.39 umol/L ($P=0.059$), respectively. From 45-54 yr, no significant differences were between three cases and controls. In Case Ⅰ and its control: from 54-59 yr, differences were not significant; from 60 to 72 yr, SUA in Case Ⅰ was lower than the control by 32.02 umol/L ($P=0.003$).

Discussion

Based on a large sample of health check-up records, the study showed that people suffering from uterine fibroids, fibrocystic breast disease or uterine fibroids combined with fibrocystic breast disease had a significantly lower SUA than controls except periods of menopause and early post-menopause, which indirectly supported our primary hypothesis that estrogenic effect may positively adjust SUA metabolism in females.

In the health check-up survey, it was unrealistic to determine menopausal period through testing serum estradiol levels in a large sample. So we divided age groups based on former Chinese epidemiological data. According to Lin Li's study of 21,113 women aged 40-65 yr in 13 cities, China, age at natural menopause was most between 45 to 55 yr and only no more than 3% of women were still at menopause between 55 to 60 yr (26). So we set age groups as 19-44 (reproductive period), 45-54 (menopause), 55-59 (early post-menopause) and ≥60 (post-menopause).

In our study, the oldest uterine fibroids patients were 72 yr old, so we set the highest age category as 60-72 yr in the case of uterine fibroids. Some scholars may doubt that after menopause, as the ovaries's function declines, some uterine fibroids tend to atrophy without estrogenic effect. There is no need to include women after 60 yr old. However, uterine fibroids are still the most common benign tumors in postmenopausal women (27). Bachmann suggested that after menopause, ovaries still continue to produce testosterone, and peripheral tissues metabolize testosterone to active estrogen (28). Additionally, adipose tissue is able to produce increasing levels of estrogen with age at the time of menopause (29). On the other hand, the estrogen receptor-alpha (ER-α, a kind of estrogen receptors (ERs), estrogen becomes functional mainly in the presence of ER-α (30))gene polymorphisms have been reported to be associated with uterine leiomyoma risk (31), which have no relationships with aging. So, it is reasonable to include participants among the age category of 60-72 yr.

Fibrocystic breast disease become most evident in women between 35 and 55 yr of age (32). It is caused by a proliferation of epithelial cells in the lobulo-alveolar region. After menopause, women's breast epithelial tissue has become atrophic with changed respond to hormonal messengers (32). Generally, in post-menopausal

women, few of them suffer from this kind of disease. So in this study, no patients of fibrocystic breast disease were older than 54 yr old.

The two key steps in keeping normal SUA are synthesis in liver and excretion in kidney. We excluded participants whose liver and kidney function were damaged judged by laboratory indexs: transaminases that reflect liver function; Ccr and BUN that reflect glomerular filtration function. Moreover, osmotic diuresis due to hyperglycaemia can decrease SUA pathologically, so we excluded people whose FBG>8.00 mmol/L. Uterine fibroids and fibrocystic breast disease were related to body size, diabetes and atherosclerosis (33-35) and these factors also influence uric acid metabolism (2). To keep comparative groups matched, we adjusted BMI, SBP, DBP, T-CH, TG and FBG by generalized regression model. However, we did not include Ccr as an adjusted variable like former studies did, because maybe Ccr is an intermediary variable in the analysis between estrogenic effect and SUA (36). Moreover, from Table 1-3, it was found that differences of these parameters between 3 pairs of cases and controls were variated according to age categories, so the study built 11 individual generalized linear regression models to fit for different conditions referred to diseases and age.

Stronger estrogenic effect (higher level of estrogen binding higher express of ERs) than normal plays an important part in the etiology of uterine fibroids and cyclomastopathy (30, 37). It has been reported that estrogenic effect can regulate the metabolism of SUA (18). In renal, estrogen induces fractional excretion of uric acid and higher levels of estradiol leads a lower postsecretory tubular reabsorption of urate (18). Moreover, ER-α activity is asociated with regulation of metabolism (38). Wang W indicated that gene polymorphism of ER-α affects SUA reduction after bariatric surgery (39). Therefore, due to higher estrogenic effect on regulation of SUA, participants with uterine fibroids and fibrocystic breast disease in our study had lower SUA than controls.

When exploring SUA in uterine fibroids patients according to age categories, although in groups of reproductive period and post-menopause period, SUA in cases were all lower than controls, but differed in ranges. In the age category of 19-44 yr (reproductive period), the case was 9.62umol/L lower than control, which is not as great as that in the age category of 60-72 yr (the case was 32.02 umol/L lower than control). The possible reason may be: the physiological effect of estrogen are realized by enough levels of estrogen binding active ERs. In the reproductive period, no matter in the case or the control, generally, endogenous estrogen level is relatively higher overall, which can ensure the normal regulation on metabolism. Thus, SUA of the control was relatively lower (237.05 umol/L) compared with participants after menopause (271.22 umol/L). And more sensitive ERs of the case might lead slightly lower SUA than the control.

However, among people of 60-72 yr (post-menopause period), in general, endogenous estrogen level is lower than premenopause because of weakened ovarian function. Therefore it is reasonable that after menopause, losing protection of estrogenic effect, females are likely to suffering from hyperuricemia (13). However, in people with uterine fibroids, a stronger ER-α immunoreactivity was observed in the post-menopausal group compared with the premenopausal group (40). High activity of ERs keep people with uterine fibroids after menopause can still have strong estrogenic effect, which can protectively decrease SUA in a certain degree. In the group of post-menopause period, the differece of SUA was the most significant between the case and control.

Moreover, if estrogenic effect can decrease SUA, in menopause (45-54 yr old) group and early post-menopause (55-59 yr old) group, why we found that the difference of SUA was not obvious between the case and control (*P*-values are 0.725 and 0.21 separately)? Possible explanation of the result is that throughout menopause, levels of different hormones rise and fall: 1- The abnormal metabolism of female is due to raised level of androgens (41, 42). Androgens' effect may influence SUA more significantly than estrogenic effect. 2-The eccentric raised level of

glucocorticoid may hamper the activity of estrogen (43, 44).

How estrogeic effect realizes its function on SUA? Whether it is relied on higher level of estrogen or stronger effect of ERs?

Many studies have explored the role of estrogen (especially exogenous estrogen) for adjusting SUA. Sumino H et al. showed that hormone replacement therapy (HRT) reduced SUA in certain group of postmenopausal women with hyperuricaemia (45). Based on the Third National Health and Nutrition Examination Survey, Hak et al. got similar results (13). However, after using HRT, SUA did not change significantly in postmenopausal women (36). Maybe, the controversial outcomes from HRT were due to different effects of ERs among individuals.

Recently, it is found that ERs, especially ER-α play an essential role in the realization of estrogenic effect, which differs according to their genotypes (39, 46). Moreover, stronger effect of ER-α plays an important part in the etiology of uterine fibroids and fibrocystic breast disease (37, 47). Brandon discoverd that ERs gene expression increased in leiomyoma compared with normal myometrium (48). So maybe, stronger effect of ERs may be another mechanism for lower SUA in uterine fibroids and fibrocystic breast disease patients compared with controls in our study.

Only with health check-up data, we cannot be sure which one, higher level of estrogen or stronger effect of ERs, is more important for estrogenic effect on SUA. Further studies can focus on: 1) explore ERs' functions for regulating SUA through immunohistochemistry from related biopsy samples or ex-vivo experiments; 2) compare serum active estrogen's levels (like estradiol) from patients of uterine fibroids and fibrocystic breast disease with the general.

This study also has some limitations. Since this is a cross–sectional study, we couldn't determine a casual relationship. In addition we did not partition disease grades according to the severity of uterine fibroids and fibrocystic breast disease, so we could not analyze dose-response of exposure and outcome.

Conclusion

Participants of uterine fibroids and fibrocystic breast disease had a lower SUA except the stage of menopause. That may indirectly support that estrogenic effect can protectively keep SUA at a relatively lower level in females.

Ethical consideration

This study was approved by the Ethics Committee of School of Public Health, Shandong University and informed oral consent was obtained from each participant. Since many individuals invovled in this study were workers from rural areas, some of whom were illiterate, the informed consent was read and explained by investigators, and participants were told that their health examination data might be applied for reaserch without private information leakage (including name, contact information and so on). The whole process was recorded by voice recorders (recorder pens), which can supervise behaviors of investigators and keep qualities of the survey.

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Table 1: Demographic data and laboratory parameters in the case of uterine fibroids and control

Parameter	Total age		19-44		45-54		55-59		60-72	
	Control (n=4206)	Case (n=568)	Control (n=2973)	Case (n=254)	Control (n=790)	Case (n=199)	Control (n=159)	Case (n=66)	Control (n=284)	Case (n=49)
BMI (kg/cm^2)	22.88 (3.42)	23.52 (3.67)[b]	22.27 (3.27)	23.25 (2.93)[b]	23.83 (3.16)	24.15 (2.99)	25.06 (3.12)	21.87 (6.87)[b]	25.39 (3.52)	24.52 (2.59)[a]
SBP (mm Hg)	124.20 (20.14)	123.22 (26.75)	119.44 (16.63)	125.00 (17.84)[b]	129.06 (20.17)	128.87 (16.89)	140.87 (22.44)	106.21 (45.35)[b]	151.23 (22.71)	113.94 (46.71)[b]
DBP (mm Hg)	76.44 (11.96)	76.55 (16.15)	74.45 (11.05)	77.87 (10.92)[b]	80.09 (12.75)	80.64 (11.64)	83.18 (12.33)	66.85 (26.38)[b]	83.35 (12.34)	67.47 (25.15)[b]
T-CH (mg/dL)	4.71 (0.95)	4.98 (1.03)[b]	4.48 (0.84)	4.80 (0.82)[b]	5.18 (0.93)	5.04 (0.95)[a]	5.49 (0.84)	5.24 (1.32)[a]	5.47 (0.93)	5.30 (1.60)
TG (mg/dL)	1.11 (0.82)	1.24 (0.78)[b]	0.99 (0.73)	1.07 (0.69)[a]	1.28 (0.85)	1.28 (0.71)	1.61 (1.24)	1.38 (0.69)	1.63 (0.91)	1.69 (1.27)
FBG (mmol/L)	4.99 (0.59)	5.10 (0.73)[b]	4.91 (0.53)	5.05 (0.52)[b]	5.11 (0.61)	5.14 (0.61)	5.25 (0.64)	5.03 (1.11)[a]	5.44 (0.80)	5.27 (1.31)
SUA (umol/L)	242.51 (55.62)	237.23 (57.51)[b]	237.05 (53.17)	233.03 (50.12)	248.10 (54.76)	245.56 (58.97)	265.53 (64.44)	236.30 (67.06)[b]	271.22 (63.81)	226.37 (69.93)[b]

Note: values expressed as mean (SD); [a] $P<0.10$, [b] $P<0.05$ / Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-CH, total cholesterol level; TG, triglyceride; FBG, fasting blood glucose; SUA, serum levels of uric acid.

Table 2: Demographic data and laboratory parameters in the case of fibrocystic breast disease and control

Parameter	All age		19-44		45-54	
	Control (n=3762)	Case (n=608)	Control (n=2973)	Case (526)	Control (789)	Case (82)
BMI (kg/cm^2)	22.60 (3.31)	22.08 (2.62)[b]	22.27 (3.27)	21.88 (2.61)[b]	23.83 (3.16)	23.36 (2.33)
SBP (mm Hg)	121.46 (17.86)	119.06 (14.64)[b]	119.44 (16.63)	117.97 (14.25)[a]	129.06 (20.17)	126.07 (15.29)
DBP (mm Hg)	75.63 (11.65)	74.33 (10.25)[b]	74.45 (11.05)	73.84 (10.13)	80.09 (12.75)	77.50 (10.52)[a]
T-CH (mg/dL)	4.62 (0.91)	4.60 (0.86)	4.48 (0.84)	4.52 (0.83)	5.18 (0.93)	5.12 (0.88)
TG (mg/dL)	1.05 (0.76)	0.93 (0.63)[b]	0.99 (0.73)	0.91 (0.64)[b]	1.28 (0.85)	1.10 (0.0.57)[a]
FBG (mmol/L)	4.95 (0.55)	4.93 (0.47)	4.91 (0.53)	4.91 (0.46)	5.11 (0.61)	5.03 (0.51)
SUA (umol/L)	239.37 (53.69)	230.99 (52.72)[b]	237.05 (53.17)	228.84 (51.9)[b]	248.10 (54.76)	244.73 (56.08)

Note: values expressed as mean (SD); [a] $P<0.10$, [b] $P<0.05$

Table 3: Demographic data and laboratory parameters in the case of uterine fibroids combining with fibrocystic breast disease and control

Parameter	All age		19-44		45-54	
	Control (n=3762)	Case (n=173)	Control (n=2973)	Case (110)	Control (789)	Case (63)
BMI (kg/cm²)	22.60 (3.31)	22.59 (2.29)	22.27 (3.27)	22.73 (2.44) [a]	23.83 (3.16)	22.36 (1.99) [a]
SBP (mm Hg)	121.46 (17.86)	121.60 (12.10)	119.44 (16.63)	120.67 (12.12)	129.06 (20.17)	123.22 (11.98) [b]
DBP (mm Hg)	75.63 (11.65)	75.63 (9.28)	74.45 (11.05)	74.82 (9.56)	80.09 (12.75)	77.03 (8.65) [b]
T-CH (mg/dL)	4.62 (0.91)	4.86 (0.85)	4.48 (0.84)	4.72 (0.81) [b]	5.18 (0.93)	5.11 (0.83)
TG (mg/dL)	1.05 (0.76)	1.02 (0.52)	0.99 (0.73)	0.93 (0.46)	1.28 (0.85)	1.17 (0.59)
FBG (mmol/L)	4.95 (0.55)	4.99 (0.42)	4.91 (0.53)	4.96 (0.43)	5.11 (0.61)	5.03 (0.39)
SUA (umol/L)	239.37 (53.69)	230.67 (46.30)[b]	237.05 (53.17)	230.65 (43.07)	248.10 (54.76)	230.72 (51.83) [a]

Note: values expressed as mean (SD); [a] $P<0.10$, [b] $P<0.05$

Table 4: Differences in SUA (umol/L) among cases and controls of different age groups by generalized linear regression

Disease	All age			<45			45-54			55-59			60-72		
	β	*β*-SE	*P*-value	*β*	*β*-SE	*P*-value	*β*	*β*-SE	*P*-value	*β*	*β*-SE	*P*-value	*β*	*β*-SE	*P*-value
Uterine fibroids															
Control	0	.	.	0	.	.	0	.	.	0	.	.	0	.	.
Case	**-9.62[a]**	**2.38**	**<0.001**	**-8.46[b]**	**3.32**	**0.011**	1.54[c]	4.38	0.725	-13.36[d]	10.60	0.21	**-32.02[e]**	**10.69**	**0.003**
fibrocystic breast disease															
Control	0	.	.	0	.	.	0	.	.	.	.	.	.	.	.
Case	**-4.6[f]**	**2.23**	**0.035**	**-5.88[g]**	**2.40**	**0.014**	0.10[h]	.	0.987	.	.	.	.	.	.
Uterine fibroids combining with fibrocystic breast disease															
Control	0	.	.	0	.	.	0	.	.	.	.	.	.	.	.
Case	**-10.91[i]**	**4.11**	**0.008**	**-9.39[j]**	**4.97**	**0.059**	10.32[k]	6.91	0.14	.	.	.	.	.	.

Note: [a] adjusted for BMI, T-CH, TG, FBG and age; [b] adjusted for BMI, SBP, DBP, TG, T-CH and FBG ; [c] adjusted for T-CH ; [d] adjusted for BMI, SBP, DBP, T-CH and FBG ; [e] adjusted for BMI, SBP and DBP; [f] adjusted for BMI, SBP, DBP, TG and year ; [g] adjusted for BMI, SBP and TG ; [h] adjusted for DBP and TG ; [i] adjusted age ; [j] adjusted for BMI and T-CH ; [k] adjusted for BMI, SBP and DBP.