Impact of Uric Acid on the Relationship between Waist Circumference and Insulin Resistance: Results from CHARLS

Jia Zheng (1637643374@qq.com)
Shengjing Hospital of China Medical University https://orcid.org/0000-0003-1382-5135
Min Jiang
China Medical University
Yanxia Xie
Sichuan University

Research

Keywords: waist circumference, uric acid, insulin resistance, temporal relationship

Posted Date: January 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-141137/v1

Title Page

Title: Impact of Uric Acid on the Relationship between Waist Circumference and Insulin Resistance: Results from CHARLS

Running Title: the mediation effect of UA on WC - IR

Authors' full names and affiliations:

Jia Zheng [1] MD; Min Jiang [2] MD, PhD; Yanxia Xie [3] MD; .

1. Department of Clinical Epidemiology, the Fourth Affiliated Hospital of China Medical University, Shenyang 110032, P. R. China;

2. Department of Epidemiology, School of Public Health, China Medical University, Shenyang 110122, China;

3. National Office for Maternal and Child Health Surveillance of China, Department of Obstetrics, West China Second University Hospital, Sichuan University, Chengdu 610041, P. R. China.

Correspondence Author:

Jia Zheng, MD.

Department of Clinical Epidemiology, the Fourth Affiliated Hospital of China Medical University, Shenyang 110032, P. R. China;

Tel.: +86-24-62043287

Fax: +86-24-62043287

E-mail: 1637643374@qq.com

Abstract

Background

Waist circumference (WC) and uric acid (UA) are significantly related. Still, their temporal sequence and how the sequence works on future risk of insulin resistance (IR) are unknown, especially in the Chinese population.

Methods

Cross-lagged panel model was used to analyze the reciprocal, longitudinal relationships between a set of inter-related variables. The mediation model was constructed to test the impact of the relationship between WC and UA on IR.

Results

A total of 5,727 subjects in our study population were enrolled, of which 53.5% were women, and the mean age was 59.0 (SD, 8.62) years. After adjusting for traditional confounding factors, we found that a higher level of baseline WC was significantly associated with a higher level of follow-up UA (β = 0.003, P = 0.031) and follow-up triglycerides glucose index (TyG) (β = 0.003, P < 0.001);. Simultaneously, there was no statistical association between the level of baseline UA and the level of follow-up WC (β = -0.009, P = 0.951). Besides, the cross-lagged panel model showed that the baseline WC had influenced the level of follow-up UA. The mediation effects of UA on WC-IR were estimated to be 18.1% in general adults, and 36.2% in women.

Conclusions

The current study demonstrated that the higher WC levels probably preceded UA in general population, and UA mediated the relationship of WC to TyG, especially

among females. However, the mediation effect was different between men and women, and the possible mechanism would require further clarification.

Keywords: waist circumference; uric acid; insulin resistance; temporal relationship

Background

Type 2 diabetes mellitus (T2DM) is prevalent in the Chinese population, and insulin resistance (IR) is the main reason for T2DM [1]. At the same time, IR plays a crucial role in the pathophysiological mechanisms of T2DM and metabolic syndrome (MetS) [2,3]. In addition, it is closely associated with other non-communicable diseases (NCDs), including cardiovascular disease (CVD) [4-6] and cancer [7-9]. Currently, some studies have detected that one reason Asians have a higher risk of T2D and IR is the proximity of fat to the vital organs [10,11]. Therefore, early detection of IR is mandatory, especially among high-risk populations without symptoms.

Many researchers have reported that visceral fat (determined by WC) is related to IR [12-14]. Besides, some studies have found that WC is a simpler and more effective measurement indicator used to discriminate IR compared with other indicators such as waist-to-height ratio [15]. Obesity not only refers to the increase in the number or size of fat cells but also means the abnormal distribution of fat tissue in the body. Growing evidence demonstrated that abdominal adiposity assessed by WC causes more health risks than total adiposity evaluated by body mass index (BMI) [16]. Compared with BMI or waist to hip ratio, WC has been shown as a more effective indicator of visceral adiposity in epidemiological studies, which performed better in correlation with visceral fat [16].

At the same time, some studies have demonstrated that the measurement of obesity was positively related to the serum levels of UA [17-19]. The result of one prospective study has found that the increase of serum UA is related to the increased

risk of clinical diseases based on IR [20]. As we all know, serum UA's level is associated with the metabolism of glucose and lipid. In addition, the level of serum UA is also related with the increase of body fat deposition [21,22]. The data of the potential clinical role of serum UA beyond the rheumatologic field is increasing. However, the evidence regarding the predictive value of serum UA in the development of insulin resistance has not offered sufficient supporting results [23-30].

TyG levels, which are associated with insulin resistance, play a significant role in predicting the incidence of diabetes and cardiovascular disease. However, it is unclear that the WC is related to TyG and to what extent is associated with TyG.To date, there was few literature from general population studies, particularly for a prospective cohort study of Chinese adults, who are having an increase in WC and TyG. Therefore, we hypothesized the possible association of WC and TyG mediated by UA. based on this, the current study aimed to investigate the relationship between UA and TyG component to WC level. In addition, a separate subgroup analysis between men and women was conducted to evaluate the influence of the level of WC, UA, and TyG (CA) on sex.

Methods

Study population

China Health and Retirement Longitudinal Study (CHARLS) was a nationally representative survey that conducted by the National School of Development of Peking University. From June 2011 to March 2012 (baseline survey), a multistage, random cluster sampling process was performed to select a representative sample

aged ≥45 years in 10,287 households in 450 villages/urban. 17,708 individuals were enrolled in the baseline survey through face-to-face household interviews. Since recruitment, 17,708 individuals would be re-surveyed every two years using the same questionnaires as the baseline, periodically. Blood samples were collected in 2011 and 2015. The protocol of the blood-based biomarker sample collection study was approved by the ethical review committee of Peking University (IRB 00001052-11014). The detailed information regarding the CHARL has been described on the CHARLS website (http://charls.pku.edu.cn/en). The ethical committees have approved the study protocol of Peking University, and all the written informed consent has been provided by participants.

Our study was a post hoc analysis of CHARLS from 2011 to 2015. Of the 17,708 individuals at baseline, 1,099 subjects were younger than 45 years, 2,363 subjects missed contact information or refused to attend the follow-up, and 134 subjects indicated cancer or malignant tumor at baseline. Finally, 14,112 participants were eligible to participate in the follow-up. All the subjects with complete data in gender, ethnicity, smoking status, drinking status, educational level, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), BMI, and WC at 2011 and 2015 follow-up can be included in this study. In addition to this, all the subjects should have complete data on triglycerides (TG), fasting plasma glucose (FPG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), uric acid (UA), and creatinine test. The participants had cancer or malignant tumor at baseline were excluded. Finally, 5,727 subjects were included in our study.

At the same time, we used a flow chart (**Fig. 1**) to show the detailed information about the sample size of subjects and exclusion reasons in our study.

Exposures and Covariates

Information on demographics (gender, age, ethnicity, and education), lifestyle factors (smoking status and drinking status), and history of diseases (diabetes, chronic kidney disease, and hypertension) were obtained by the structured home interview. Data on health behaviours were obtained from the subjects' self-reported health questionnaire including frequency of alcohol consumption (never, less than once a month, and more than once a month), and smoking status in the past year (never, former, and current smoker). Smoking means smoking ≥ 100 cigarettes in one's all life. Data on diabetes, chronic kidney disease, and hypertension were collected by trained health staff members.

Data on collection and measurement of cholesterol indexes, fasting plasma glucose, biochemical blood indexes, and other blood pressure indexes has detailed on the CHARLS website (http://charls.pku.edu.cn/en). TG, LDL-C and HDL-C were measured using an auto-analyzer (Olympus AU640 Auto-Analyzer, Olympus Corp, Kobe, Japan). Omron™ HEM-7200 Monitor (Omron (Dalian) Co., LTD., Dalian, China) was used to measure SBP and DBP by certified investigators in the sitting position after 5 minutes rest among each measurement. The mean of 3 blood pressure values was calculated and used for our analysis. The BMI was calculated using the weight and height indicators; the formulate as follows: BMI = weight (Kg) / height^2 (m^2).

Dependent variable (Y)

The TyG index was calculated as the follows formulate: TyG = ln [fasting TG (mmol/L) * FPG (mmol/L) *0.5*159.37] [31]. TG and FPG were measured by the Enzymatic colourimetric test method.

Independent variable (X)

A soft tape measure was used to measure WC and inserted it at the navel level to measure WC at the standing pose, with a cloth measuring tape. At the same time, all participants needed to take a normal breath and exhale, holding the breath at the end of exhaling and letting the tape out slightly.

Mediators (M)

Uric acid was measured by UA Plus method, and creatinine was measured by Rate-blanked and compensated Jaffe creatinine method. These assays were performed at the Youanmen Center for Clinical Laboratory of Capital Medical University.

Statistical analysis

All analysis was performed by IBM SPSS version 22.0 and SPSS Amos 22.0. A 2-sided $P < 0.05$ was deemed statistically significant.

Percentiles was used to describe the categorical variables and mean (standard deviation, SD) to describe the continuous variables that met the normal distribution. For some continuous variables that did not meet the normal distribution, we used the median (inter-quarter range) method to describe the central and discrete trends. At the same time, we used student t test or Mann-Whitney U test or Pearson's $\chi 2$ -tests to compare the statistics significant between men and women.

We constructed a linear regression model to explore the association of whether WC (UA) predicted future variation of TyG, in which model future TyG variation was the dependent variable and baseline WC(UA) was the independent variable. First, the multicollinearity problem among independent variables was examined by the variance expansion factor (VIF). VIF > 10 was deemed multicollinearity signification. Second, we used three models to explore the association between baseline (examination at 2011) WC(UA) and future (follow-up at 2015) TyG as follows: model 1: just adjusted for baseline WC(UA); model 2: at the fundamental basis of model 1, plus baseline age, sex and ethnicity; model 3: at the basic model 2, plus baseline education, current smoking, alcohol drinking, SBP, DBP, HR, BMI, HDL-C, LDL-C, and creatinine.

Longitudinal changes of WC and UA indices were measured at two-time points. Previous study introduced the theory and application of cross-lagged panel design [32]. Overall, we can use the cross-lagged panel model to analyze the longitudinal relationships among a set of inter-related variables [33]. In Figure 2, the path with β_1 showed the effect of baseline UA on follow-up WC, β_2 showed the effect of baseline WC on follow-up UA. In addition, the values of WC, UA were adjusted by baseline and follow-up variables, respectively: sex, age, ethnicity, education, current smoking, alcohol drinking, SBP, DBP, HR, BMI, HDL-C, LDL-C, and creatinine in linear regression analyses and save residual. After this, we used Z-transformation to standardize the residuals (mean = 0; SD = 1). The model fits were evaluated by the Comparative Fit Index (CFI). Root mean square residual (RMR) <0.05 and comparative fitness index (CFI) >90 meant a relatively good model fit to the observed

198 data in the cross-lagged path model. In addition, the cross-lagged analysis model was
199 constructed in groups of men and women, separately.

200 Once the temporal relationship between WC and UA has been established, the
201 mediation model was constructed to test the impact of the relationship between WC
202 and UA on TyG. It was worth noting that the values of TyG were analyzed by linear
203 regression residual model and standardized by Z-transformation (mean=0, SD=1), too.
204 According to results of the cross-lagged path analysis model to determine the X and
205 M, X was predictor, M was mediator, TyG was the outcome. The detailed mediation
206 model was presented in Fig.3, which involved three models,
207 including $\text{Model Y} = \beta_{\text{Tol}}\,\text{X}\ (\beta_{\text{Tol}} = \text{total effect})$,
208 $\text{Model M} = \beta_1\,\text{X}\,(\beta_1 = \text{indirect effect 1})$
209 $\text{Model Y} = \beta_2\,\text{M} + \beta_{\text{Dir}}\,\text{X}\,(\beta_2 = \text{indirect effect 2}, \beta_{\text{Dir}} = \text{direct effect})$. We used the
210 formula to calculate the proportion of the mediation effect, as follows: Mediation
211 effect (%) = $\dfrac{\beta_1 \times \beta_2}{\beta_{\text{Tol}}} \times 100\%$.

212 **Results**

213 A total of 5,727 subjects in our study population were enrolled, of which 53.5% was
214 women, and the mean age was 59.0 (SD, 8.62) years. Detailed baseline and follow-up
215 characteristics of the study population were summarized in **Table 1**. By comparing the
216 difference among sex groups, the result indicated that SBP, DBP, HR, and FPG were
217 no significant difference at baseline and FPG was no significant difference at
218 follow-up.

219 **Table 2** showed the prospective association of baseline WC with follow-up UA

and TyG. After adjusting for baseline UA, age, sex, ethnicity, education, current smoking, alcohol drinking, SBP, DBP, HR, BMI, HDL-C, LDL-C, and creatinine, the result revealed that a higher level of WC was associated with a higher level of follow-up UA ($\beta = 0.003$, $P = 0.031$) and follow-up TyG ($\beta = 0.003$, $P < 0.001$).

Table 3 showed the prospective association of baseline UA with follow-up WC and TyG. We found that a higher level of UA was associated with a higher level of follow-up TyG ($\beta = 0.051$, $P < 0.001$). However, the level of baseline UA was no significantly related to the level of follow-up WC ($\beta = -0.009$, $P = 0.951$).

Results of the cross-lagged path analysis of WC and UA in the general population with age ≥ 45 were shown in **Figure 2**. The $WC_{baseline} \rightarrow UA_{follow\text{-}up}$ path coefficients ($\beta_1 = 0.025$) were significantly different from 0 ($P = 0.021$). However, the $UA_{baseline} \rightarrow WC_{follow\text{-}up}$ path coefficients ($\beta_2 = 0.001$) were not significantly different from 0 ($P = 0.921$). The study results showed that widening WC at baseline resulted in an increase in UA levels at follow-up but not the increase in UA levels at baseline, leading to later WC widening. Model fitting parameters were CFI=0.991 and RMR=0.016 in the model of WC with UA. The values of CFI and RMR showed a relatively good model fit to the observed data in our cross-lagged path model.

Figure 3 showed the mediation effects of follow-up TyG on the association between baseline level of WC and follow-up level of UA, adjusted for sex, age, ethnicity, education, current smoking, alcohol drinking, SBP, DBP, HR, BMI, HDL-C, LDL-C, creatinine after excluding cancer or malignant tumour at baseline. The standardized total effect of WC on TyG was 0.06104, and the standardized direct

impact was 0.050. Indirect effect 1 and 2 formed the overall indirect effect. According to the formula in the statistics method, the overall indirect effect was 0.01104 (0.060×0.184), the percentage of the total effect mediated by follow-up UA was estimated at 18.1% ($\frac{0.01104}{0.06104} \times 100\%$).

The results of subgroup analyses between men and women were shown in **Figure 4** and **Figure 5**. For women, we found that the $WC_{baseline} \rightarrow UA_{follow\text{-}up}$ path coefficients (β_1 = 0.033) was significantly different from 0 (P = 0.014), and the $UA_{baseline} \rightarrow WC_{follow\text{-}up}$ path coefficients (β_2 = 0.019) was not significantly different from 0 (P = 0.340). However, for men, we found that the $WC_{baseline} \rightarrow UA_{follow\text{-}up}$ path coefficients (β_1 = 0.015) was not significantly different from 0 (P = 0.407), and the $UA_{baseline} \rightarrow WC_{follow\text{-}up}$ path coefficients (β_2 = -0.013) was not significantly different from 0 (P = 0.444). These results indicated that an increase in baseline WC might affect subsequent UC increases, mainly in women, not in men. For women, the percentage of the total effect mediated by follow-up UA was estimated at 36.2% ($\frac{0.01362}{0.03762} \times 100\%$).

Discussion

The results of current study were 4-fold: (1) confirming the temporal relationship between WC and UA ($WC_{baseline} \rightarrow UA_{follow\text{-}up}$); (2) verifying UA mediate on WC to TyG; (3) estimating the percentages of UA index mediation effect on WC - TyG (18.1%); (4) and finding the mediation effect of UA on WC - TyG in women not in men.

As we all know, with the change of diet structure and lifestyle, and the increase of

social pressure, the global obesity rate has shown apparent upward trend [1-3]. With the deepening of the research on the relationship between obesity and disease, abnormal fat distribution in the body, especially the accumulation of abdominal fat, has a higher correlation with the occurrence of IR [12-14]. WC is a simple and reliable measure of central obesity. Studies have demonstrated that WC can be used as an indicator to assess early insulin secretion [15]. In addition, serum UA and obesity are related to enhanced the level of IR and the incidence of MetS [20]. Some studies have demonstrated that UA was an independent risk factor for gout and some major public health threat as Parkinson's disease, renal diseases, cardiovascular, metabolic syndrome, hypertension, and even DM. WC as the obesity indicator is considered the main risk factor for hyperuricemia [21,22], however, the temporal relationship between WC and hyperuricemia is still controversial. In this study the cross-lagged path analysis was applied to explore the chicken-and-egg question as a practical statistical approach in analyzing the causal relationship among two intercorrelated variables. In current study, the result revealed that the unidirectional relationships from WC to UA. In addition, because sex may influence the level of WC, UA, and TyG (CA), we conducted a subgroup analysis between men and women separately. The unidirectional relationship from WC to UA was significantly stronger in women than that in men. UA mediated the effect of WC on TyG, and the mediation effect of UA was in women, not in men. The mechanism of gender differences needed in-depth study.

Previous study has shown that 1/2 of diabetes participants could be attributed to

286 the increased serum UA level [34]. The increased level of serum UA is known to be
287 related to hypertension, glucose intolerance, and obesity [35]. Previous study
288 demonstrated that the high level of UA predicted the development of
289 hyperinsulinemia [36]. Some studies have showed that hyperuricemia was associated
290 with adiposity and IR [23-30]. Therefore, UA's mediation effects on IR should be
291 considered when examining the association between the WC and IR. The high level of
292 UA was positively associated with the level of high-sensitivity C-reactive protein
293 (hs-CRP) [37]. Oxidative-stressed adipose tissue was a risk factor of IR because
294 oxidative-stressed adipose tissue can decrease insulin sensitivity. Simultaneously, the
295 generation of reactive oxygen species (ROS) and the levels of NADPH oxidase tissue
296 can be increased by soluble UA. Increasing serum UA can cause IR through
297 depressing the bioavailability of Nitric Oxide (NO) and leading to oxidative stress in
298 mitochondria. Viazzi et al. [38] in 2014 stated that this mechanism happened because
299 of the role of hyperinsulinemia, which acted as an excellent marker in measuring IR.
300 The rising IR-related health burden emphasizes the significance and urgency for
301 the searching and managing risk factors for IR. In addition, IR plays a substantial role
302 in the pathophysiology of T2DM and MetS. At the same time, IR is strongly
303 associated with some non-communicable diseases, including cancer and
304 cardiovascular abnormalities. In addition, IR may by increasing the risk of mortality
305 by promoting DNA damage, stimulation of mitogenesis, and the disruption of glucose
306 [39,40]. Therefore, IR is early detected and controlled is crucial, and it should be
307 carried out even in the absence of symptoms. Recently, Homeostatic Model

Assessment (HOMA-IR) is a commonly used measurement index. However, the HOMA-IR is time-consuming and expensive; some studies have developed and assessed some surrogate markers for IR [41]. One of these biomarkers is the TyG, and it has been examined in different populations with stable results, although in normal-weight adults [41]. Therefore, we used the TyG in our study as the IR's predictor.

Currently, the prevalence of abdominal obesity has increased and has been considered a major health hazard. Abdominal obesity is significantly related to the risk of mortality, CVD, and other diseases. Comparing to generalized obesity, central obesity is more closely linked to IR. WC as a predicted measure of health risk is a convenient and effective index of abdominal obesity. It has a significant, predictable association with intra-abdominal fat area and volume. One cross-sectional study of participants without diabetes demonstrated that the insulin sensitivity index significantly correlated with WC across populations [42]. Previous literature has evidenced that WC is a suitable proxy measure for central obesity [15]. Studies have found that with the increase of BMI and adipose tissue, the incidence of type 2 diabetes gradually increases [16]. However, the ratio of adipose tissue to the muscle will affect the BMI, so the situation of human adipose tissue cannot be entirely and objectively reflected. Simultaneously, increased triglyceride-rich lipoprotein secretion and impairment of clearance of these lipoproteins are the potential mechanism of central obesity leading to hypertriglyceridemia [43,44]. After controlling for BMI, WC as a marker of abdominal obesity has significantly associated with type 2

diabetes risk [45]. In addition, it has been debated that cardiometabolic diseases and IR are associated with the increase in visceral adipose tissue, and WC is a better marker of changes in fat distribution comparing to BMI. A study has shown that participants with a higher WC are more susceptible to metabolic syndrome (MetS) and diabetes caused by IR than the participants with lower WC among the same BMI [39].

The Finnish Diabetes Prevention Study with impaired glucose tolerance risk population showed that UA's change was significantly associated with the change in fasting insulin [46]. Serum UA as the product of purine metabolism, its level is determined by the level of purine metabolism in the liver, excretion from the kidney, and secretion from adipose tissue. Some literature proved that central obesity might be associated with hypertriglyceridemia is by increasing the triglyceride-rich lipoprotein secretion and impairing this lipoprotein clearance [43,44]. The mechanism may include the abnormal secretion of very-low-density lipoproteins related with the means that may have the abnormal secretion of very-low-density lipoproteins associated with the increased of visceral adiposity [43].

Strength and limitation

All WC, UA, and TyG measurements were carried out by trained staff under the unified and standardized measuring instrument with high repeatability. Most importantly, we controlled the subgroup analysis between males and females about the UA’ss mediation effects on WC to IR in a representative sample of the Chinese population with age over 45 years. In addition, the current study provided information

on education, current smoking, alcohol drinking, SBP, DBP, HR, BMI, HDL-C, LDL-C, and creatinine. However, excluding the missing data, only 5,727 participants included in our finally analysis.

Conclusions

The result of this research demonstrated that the baseline level of WC and UA were associated with the future risk of IR, the temporal relationship between WC and UA was $WC_{baseline} \rightarrow UA_{follow\text{-}up}$, and the mediation effect of UA on WC - TyG was found in women, not in men. Further studies are required to explore the possible underlying mechanism.

Declarations

Ethics approval and consent to participate: The procedures followed were in accordance with the ethical standards of the responsible committee of Peking University and the Chinese Center for Disease Control and Prevention, and written informed consents were obtained from all subjects or their proxies.

Consent for publication: Not applicable

Availability of data and materials: All the data can be found on the CHARLS website (http://charls.pku.edu.cn/en). The datasets analyzed during our study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: This study received no external funding.

Authors' contributions: JZ contributed conception and design of the study; JZ and MJ organized the database; YX and MJ reviewed the English language and grammar.

JZ performed the statistical analysis and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Acknowledgements: The authors are grateful to the China Health and Retirement Longitudinal Study (CHARLS) research team for providing the data.

References

1. Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. World J Diabetes 2012;3:110.

2. Cornier M-A, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, et al. The metabolic syndrome. Endocr Rev 2008;29(7):777e822.

3. Reusch JE. Current concepts in insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome. Am J Cardiol. 2002;90(5A):19G-26G.

4. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zu~niga FA. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol 2018;17(1):122.

5. Muniyappa R, Sowers JR. Role of insulin resistance in endothelial dysfunction. Rev Endocr Metab Disord 2013;14(1):5e12.

6. Ortega-Loubon C, Fern?andez-Molina M, Singh G, Correa R. Obesity and its cardiovascular effects. Diabetes Metab Res Rev 2019:e3135.

7. Arcidiacono B, Iiritano S, Nocera A, Possidente K, Nevolo MT, Ventura V, et al. Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. Exp Diabetes Res 2012;2012:789174.

8. Orgel E, Mittelman SD. The links between insulin resistance, diabetes, and cancer. Curr Diabetes Rep 2013;13(2):213e22.

9. Hernandez AV, Pasupuleti V, Benites-Zapata VA, Thota P, Deshpande A, Perez-Lopez FR. Insulin resistance and endometrial cancer risk: a systematic review and meta-analysis. Eur J Cancer A 2015;51(18):2747e58.

418 10. Kobayashi H, Nakamura T, Miyaoka K, Nishida M, Funahashi T, Yamashita S,et
419 al. Visceral fat accumulation contributes to insulin resistance, small-sized low-density
420 lipoprotein, and progression of coronary artery disease in middle-aged non-obese
421 Japanese men. Jpn Circ J 2001;65:193–9.
422 11. Goodpaster BH, Krishnaswami S, Resnick H, Kelley DE, Haggerty C, Harris TB,
423 et al. Association between regional adipose tissue distribution and both type 2
424 diabetes and impaired glucose tolerance in elderly men and women. Diabetes Care
425 2003;26:372–9.
426 12. Albu JB, Murphy L, Frager DH, Johnson JA, Pi-Sunyer FX. Visceral fat and
427 race-dependent health risks in obese nondiabetic premenopausal women. Diabetes
428 1997;46:456–62.
429 13. Carey DG, Jenkins AB, Campbell LV, Freund J, Chisholm DJ. Abdominal fat and
430 insulin resistance in normal and overweight women: direct measurements reveal a
431 strong relationship in subjects at both low and high risk of NIDDM. Diabetes
432 1996;45:633–8.
433 14. Macor C, Ruggeri A, Mazzonetto P, Federspil G, Cobelli C, Vettor R. Visceral
434 adipose tissue impairs insulin secretion and insulin sensitivity but not energy
435 expenditure in obesity. Metabolism 1997;46:123–9.
436 15. Ponnalagu Shalini D/O,Bi Xinyan,Henry Christiani Jeyakumar,Is waist
437 circumference more strongly associated with metabolic risk factors than
438 waist-to-height ratio in Asians?[J] .Nutrition, 2019, 60: 30-34.
439 16. Rankinen T, Kim SY, Perusse L, Despres JP, Bouchard C. The prediction of

abdominal visceral fat level from body composition and anthropometry: ROC analysis. Int J Obes Related Metab Disord 1999;23:801-809.

17. Gillum RF. The association of the ratio of waist to hip girth with blood pressure, serum cholesterol and serum uric acid in children and youths aged 6-17 years. J Chronic Dis 1987;40:413-20.

18. Kono S, Shinchi K, Imanishi K, Honjo S, Todoroki I. Behavioural and biological correlates of serum uric acid: a study of self-defence officials in Japan. Int J Epidemiol 1994;23:517-22.

19. Yamashita S, Matsuzawa Y , Tokunaga K, Fujioka S, Tarui S. Studies on the impaired metabolism of uric acid in obese subjects:marked reduction of renal urate excretion and its improvement by a low-calorie diet. Int J Obes 1986;10:255-64.

20. Bombelli M, Quartitrevano F, Tadic M, et al. Uric acid and risk of new-onset metabolic syndrome, impaired fasting glucose and diabetes mellitus in a general Italian population: data from the Pressioni Arteriose Monitorate E Loro Associazioni study[J]. Journal of Hypertension, 2018, 36(7): 1492-1498.

21. Osgood K, Krakoff J, Thearle M. Serum uric acid predicts both current and future components of the metabolic syndrome. Metab Syndr Relat Disord 2013; 11:157–162.

22. Cicero AFG, Salvi P, D'Addato S, Rosticci M, Borghi C. Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: data from the Brisighella Heart Study. J Hypertens 2014; 32:57–64.

23. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K. Serum uric acid and the risk for hypertension and type 2 diabetes in Japanese men: the Osaka Health

462 Survey. J Hypertens 2001; 19:1209–1215.
463 24. Meisinger C, Thorand B, Schneider A, Stieber J, Do ¨ring A, Lo ¨wel H. Sex
464 differences in risk factors for incident type 2 diabetes mellitus: the MONICA
465 Augsburg Cohort Study. Arch Intern Med 2002; 162:82–89.
466 25. Lin KC, Tsai ST, Lin HY, Chou P. Different progressions of hypergly-cemia and
467 diabetes among hyperuricemic men and women in the kinmen study. J Rheumatol
468 2004; 31:1159–1165.
469 26. Chien KL, Chen MF, Hsu HC, Chang WT, Su TC, Lee YT, Hu FB. Plasma uric
470 acid and the risk of type 2 diabetes in a Chinese community. Clin Chem 2008;
471 54:310–316.
472 27. Nan H, Qiao Q, Soderberg S, Pitka ¨niemi J, Zimmet P, Shaw J, et al. Serum uric
473 acid and incident diabetes in Mauritian Indian and Creole populations. Diabetes Res
474 Clin Pract 2008; 80:321–327.
475 28. Kramer CK, von Mu ¨hlen D, Jassal SK, Barret-Connor E. Serum uric acid levels
476 improve prediction of incident type 2 diabetes in individuals with impaired fasting
477 glucose: the Rancho Bernardo Study. Diabetes Care 2009; 32:1272–1273.
478 29. Zhang ML, Gao YX, Wang X, Chang H, Huang GW. Serum uric acid and
479 appropriate cutoff value for prediction of metabolic syndrome among Chinese adults.
480 J Clin Biochem Nutr 2013; 52:38–42.
481 30. Chen JH, Hsieh CH, Liu JS, Chuang TJ, Chang HW, Huang CL, et al. The power
482 of serum uric acid in predicting metabolic syndrome diminishes with age in an elderly
483 Chinese population. J Nutr Health Aging 2016;20:912–917.

484 31. Sánchez-Íñigo L, Navarro-González D, Fernández-Montero A, Pastrana-Delgado
485 J, Martínez JA. The TyG index may predict the development of cardiovascular events.
486 Eur J Clin Investig 2016;46:189-97.
487 32. von Salisch M, Zeman JL. Pathways to reciprocated friendships: a cross-lagged
488 panel study on young adolescents' anger regulation towards friends. J Youth Adolesc
489 2018;47:673e87.
490 33. Kivimäki M, Feldt T, V ahtera J, Nurmi JE. Sense of coherence and health:
491 evidence from two cross-lagged longitudinal samples. Soc Sci Med. 2000; 50:583–97.
492 34. Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. High serum uric
493 acid as a novel risk factor for type 2 diabetes. Diabetes Care. 2008;31(2):361-362.
494 35. Rathmann W, Haastert B, Icks A, Giani G, Roseman JM. Ten-year change in
495 serum uric acid and its relation to changes in other metabolic risk factors in young
496 black and white adults: the CARDIA study. Eur J Epidemiol. 2007;22(7):439-445.
497 36. Carnethon MR, Fortmann SP, Palaniappan L, Duncan BB, Schmidt MI,
498 Chambless LE. Risk factors for progression to incident hyperinsulinemia: the
499 Atherosclerosis risk in communities study, 1987–1998. Am J Epidemiol
500 2003;158:1058–67.
501 37. Zhu Y, Hu Y, Huang T, Zhang Y, Li Z, Luo C, Luo Y, Yuan H, Hisatome I,
502 Yamamoto T, Cheng J: High uric acid directly inhibits insulin signalling and induces
503 insulin resistance. Biochem Biophys Res Commun 2014, 447(4):707–714.
504 38. Viazzi F, Garneri D, Leoncini G, Gonnella A, Muiesan ML, Ambrosioni E, et al.
505 Serum uric acid and its relationship with metabolic syndrome and cardiovascular risk

506 profifile in patients with hypertension: insights from the I-DEMAND study. Nutr
507 Metabol Cardiovasc Dis 2014;24(8):921e7.
508 39. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet
509 2005;365:1415e28.
510 40. Reddy KJ, Singh M, Bangit JR, Batsell RR. The role of insulin resistance in the
511 pathogenesis of atherosclerotic cardiovascular disease: an updated review. J
512 Cardiovasc Med (Hagerstown); 2010.
513 41. Simental-Mendía LE, Rodríguez-Moran M, Guerrero-Romero F. The product of
514 fasting glucose and triglycerides as surrogate for identifying insulin resistance in
515 apparently healthy subjects. Metab Syndrome Relat Disord 2008;6(4): 299e304.
516 42. Martínez-Larrad MT, Lorenzo C, González-Villalpando C, Gabriel R, Haffner SM,
517 Serrano-Ríos M. Associations between surrogate measures of insulin resistance and
518 waist circumference, cardiovascular risk and the metabolic syndrome across Hispanic
519 and non-Hispanic white populations. Diabet Med. 2012;29(11):1390-1394.
520 43. Björnson E, Adiels M, Taskinen MR, Borén J. Kinetics of plasma triglycerides in
521 abdominal obesity. Curr Opin Lipidol. 2017;28(1):11-18.
522 44. Carpentier AC. Hypertriglyceridemia Associated With Abdominal Obesity:
523 Getting Contributing Factors Into Perspective. Arterioscler Thromb Vasc Biol.
524 2015;35(10):2076-2078.
525 45. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal
526 adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J
527 Clin Nutr. 2005; 81(3):555–63.

528 **46.** Niskanen L, Laaksonen DE, Lindstro¨m J, et al. Serum uric acid as a harbinger of
529 metabolic outcome in subjects with impaired glucose tolerance. Diabetes Care
530 2006;29:709–11.
531

Figure legends

Fig.1. Flow chart of participants included in this study after inclusion and exclusion.

Fig.2. Cross-lagged path analysis of WC and UA index(n=5727), agjusted for baseline and follow-up variables, respectively: sex, age, ethnicity, education, current smoking, alcohol drinking. r1=synchronous correlations; r2, r3 = tracking correlations; r1, r2 = cross-lagged path coefficients; R2 = variance explained); * represent coefficients different from 0, $P < 0.001$; CFI = 0.991, RMR = 0.016

Fig.3. Mediation effect of UA index on the WC-TyG association (n =5727), * represent coefficients different from 0, $P < 0.001$.

Fig.4. In men: Cross-lagged path analysis of WC and UA index(n=2663), agjusted for baseline and follow-up variables, respectively: sex, age, ethnicity, education, current smoking, alcohol drinking, SBP, DBP, HR, BMI, HDL-C, LDL-C, and creatinine. r1=synchronous correlations; r2, r3 = tracking correlations; r1, r2 = cross-lagged path coefficients; R2 = variance explained); * represent coefficients different from 0, $P < 0.001$; CFI = 0.995, RMR = 0.015; In women: Cross-lagged path analysis of WC and UA index(n=3064), agjusted for baseline and follow-up variables, respectively: sex, age, ethnicity, education, current smoking, alcohol drinking, SBP, DBP, HR, BMI, HDL-C, LDL-C, and creatinine. r1=synchronous correlations; r2, r3 = tracking correlations; r1, r2 = cross-lagged path coefficients; R2 = variance explained); * represent coefficients different from 0, $P < 0.001$; CFI = 0.984, RMR = 0.019

Fig.5. Mediation effect of UA index on the WC-TyG association (n =3064) in women, * represent coefficients different from 0, $P < 0.001$.

Figures

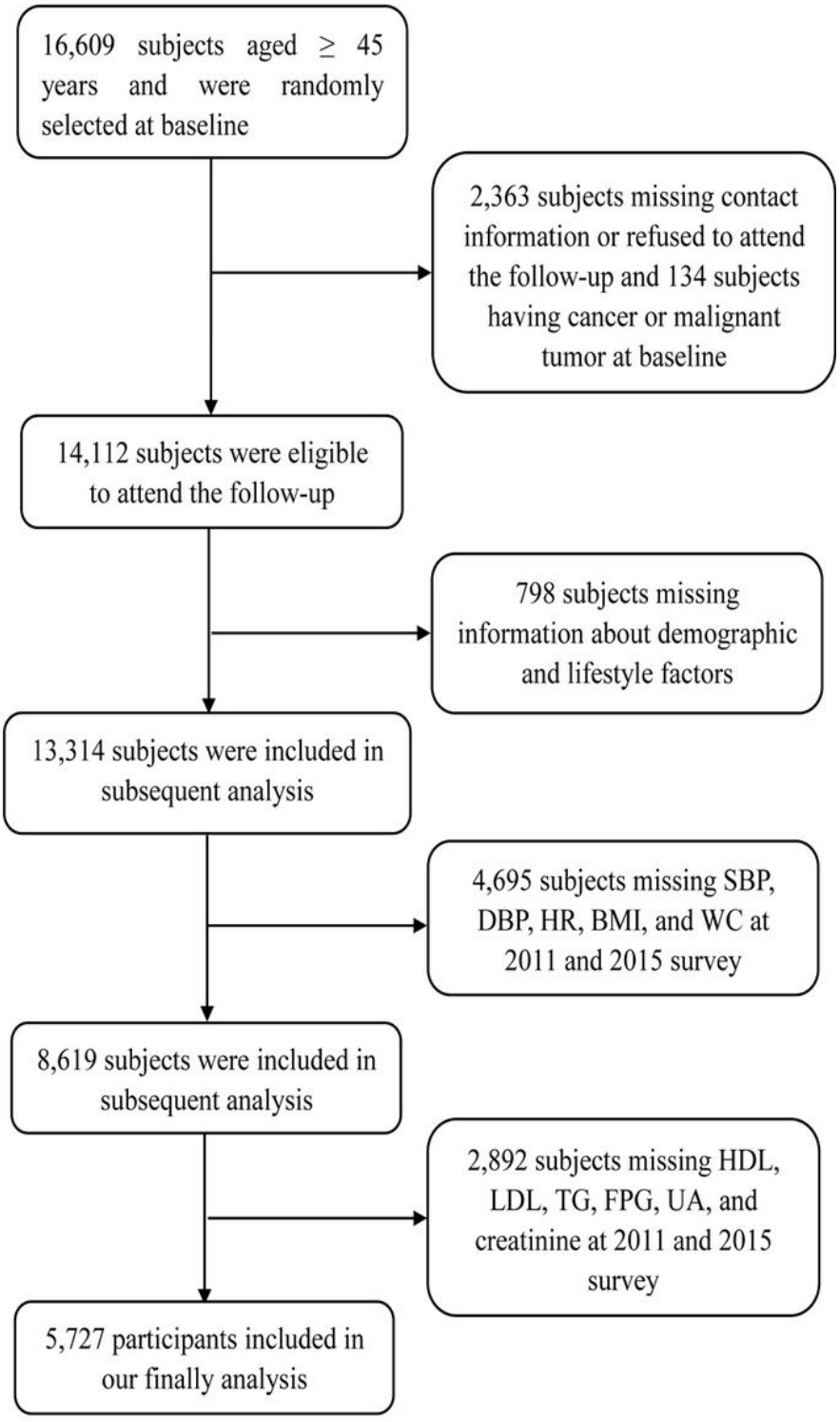

Figure 1

Flow chart of participants included in this study after inclusion and exclusion.

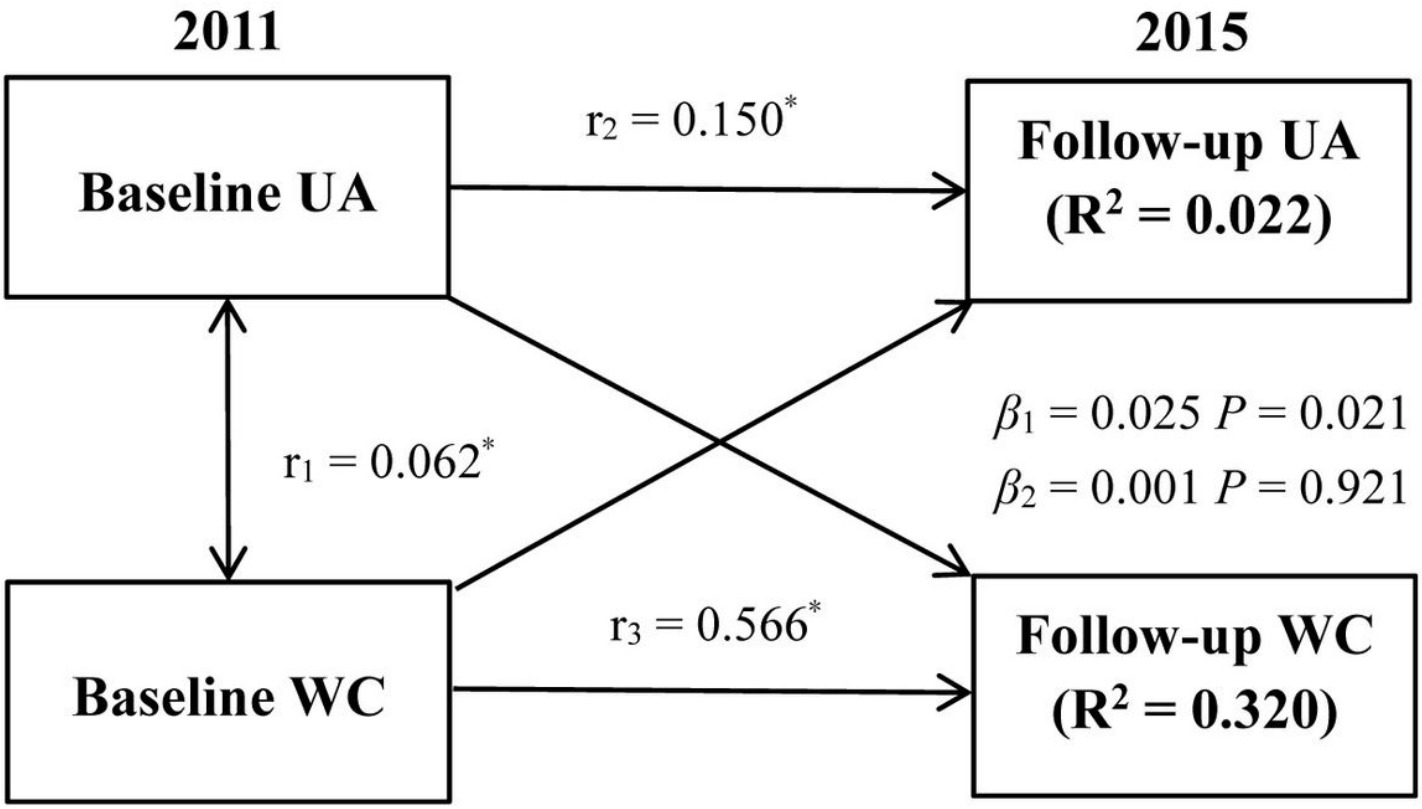

Figure 2

Cross-lagged path analysis of WC and UA index(n=5727), agjusted for baseline and follow-up variables, respectively: sex, age, ethnicity, education, current smoking, alcohol drinking. r1=synchronous correlations; r2, r3 = tracking correlations; r1, r2 = cross-lagged path coefficients; R2 = variance explained); * represent coefficients different from 0, P < 0.001; CFI = 0.991, RMR = 0.016

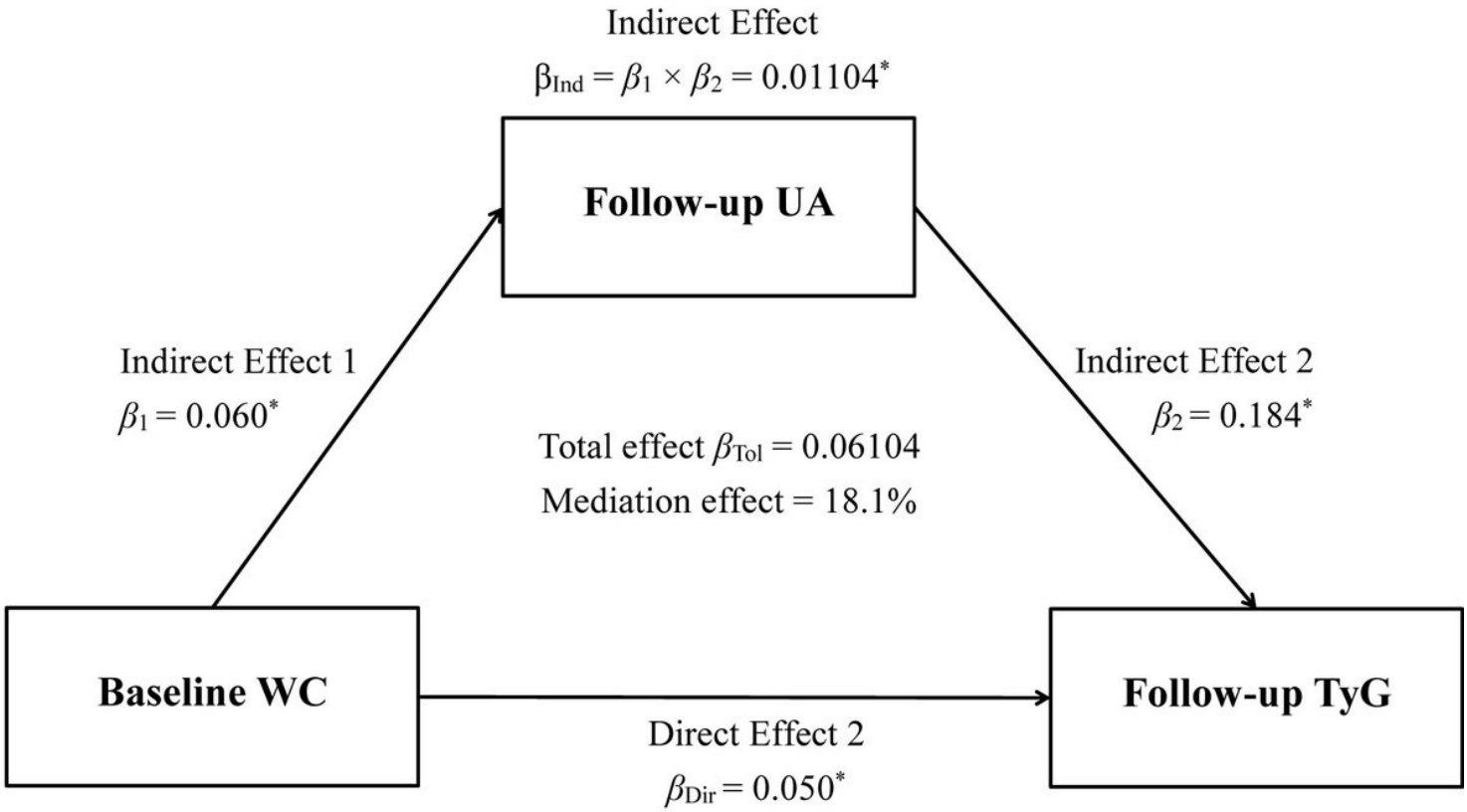

Figure 3

Mediation effect of UA index on the WC-TyG association (n =5727), * represent coefficients different from 0, P < 0.001.

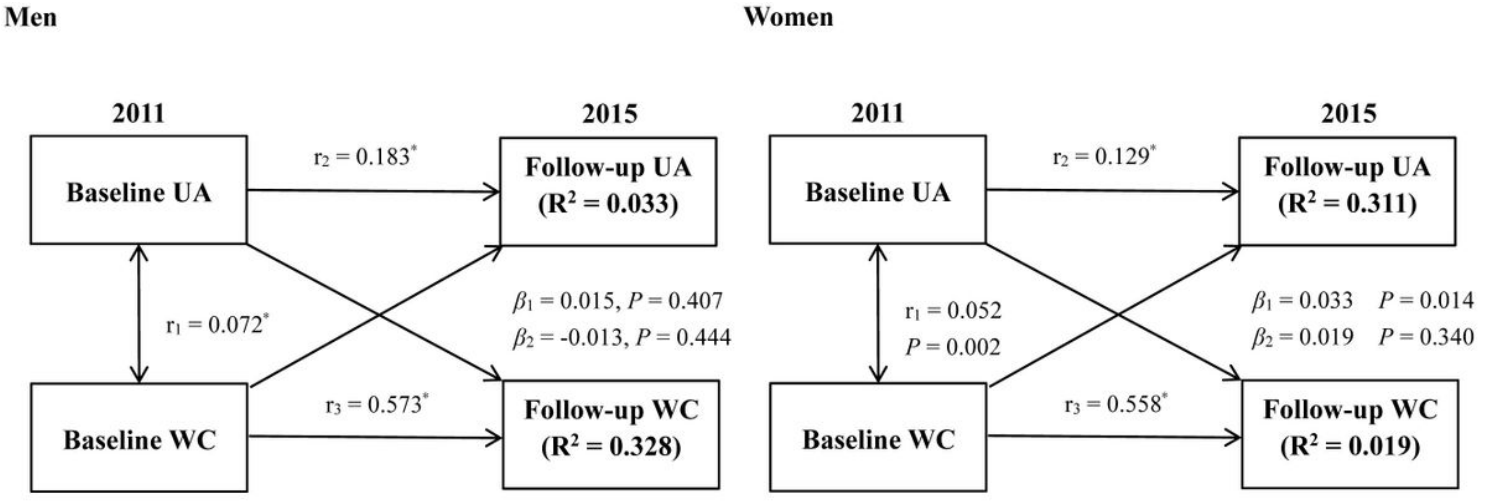

Figure 4

In men: Cross-lagged path analysis of WC and UA index(n=2663), agjusted for baseline and follow-up variables, respectively: sex, age, ethnicity, education, current smoking, alcohol drinking, SBP, DBP, HR, BMI, HDL-C, LDL-C, and creatinine. r1=synchronous correlations; r2, r3 = tracking correlations; r1, r2 = cross-lagged path coefficients; R2 = variance explained); * represent coefficients different from 0, P < 0.001; CFI

= 0.995, RMR = 0.015; In women: Cross-lagged path analysis of WC and UA index(n=3064), agjusted for baseline and follow-up variables, respectively: sex, age, ethnicity, education, current smoking, alcohol drinking, SBP, DBP, HR, BMI, HDL-C, LDL-C, and creatinine. r1=synchronous correlations; r2, r3 = tracking correlations; r1, r2 = cross-lagged path coefficients; R2 = variance explained); * represent coefficients different from 0, P < 0.001; CFI = 0.984, RMR = 0.019

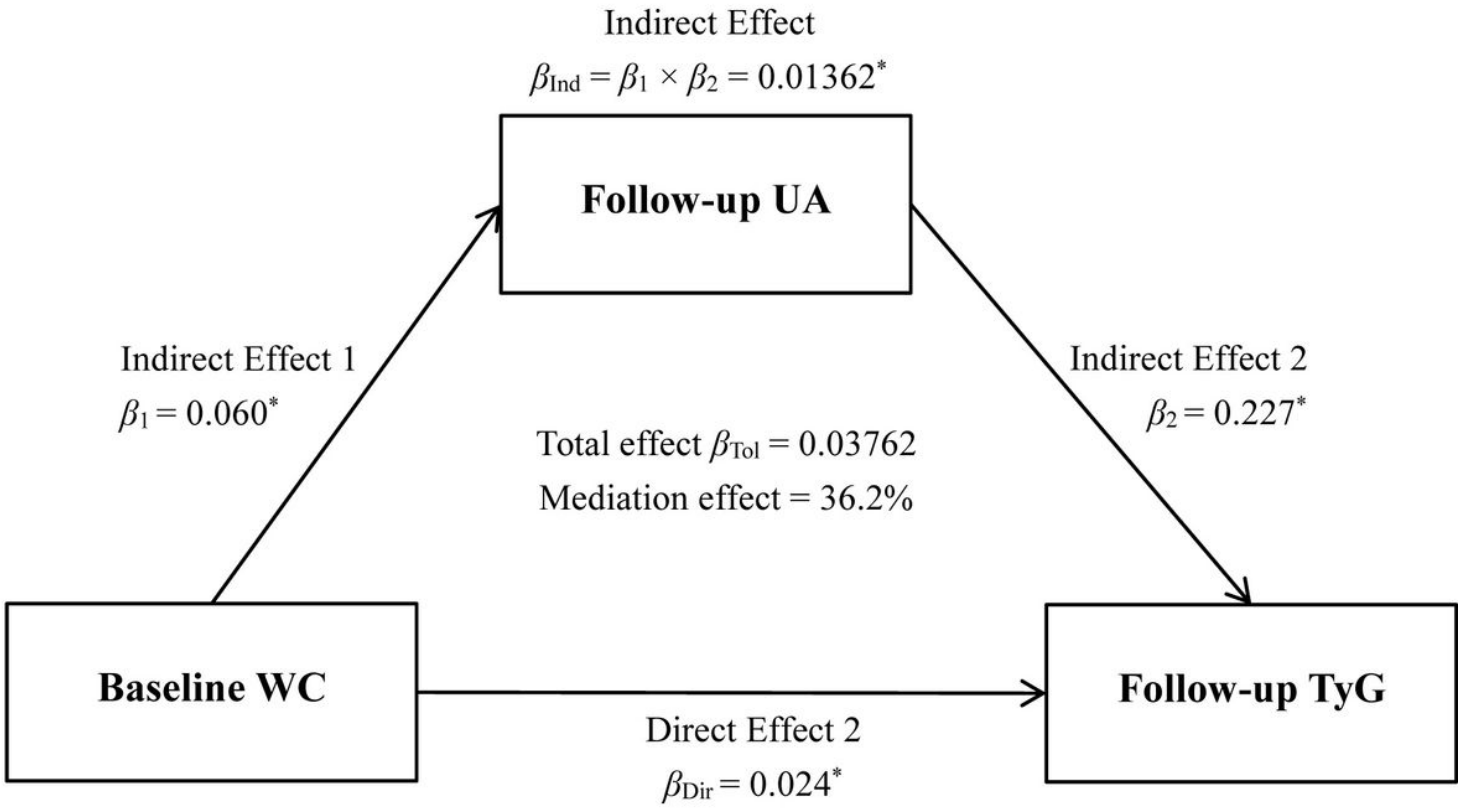

Figure 5

Mediation effect of UA index on the WC-TyG association (n =3064) in women, * represent coefficients different from 0, P < 0.001.