

Associations of Gain in Weight-Related Anthropometric Indices with a Marker of Lipid Peroxidation: A Cohort Study Among Urban Adults in China

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Tao Xu^{1,2}
Bin Wang^{1,2}
Limin Cao^{1,2}
Weihong Qiu^{1,2}
Zhuang Zhang^{1,2}
Ailian Chen^{1,2}
Weihong Chen^{1,2}

¹Department of Occupational and Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, People's Republic of China; ²Key Laboratory of Environment and Health, Ministry of Education and Ministry of Environmental Protection, State Key Laboratory of Environmental Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, People's Republic of China

Background: Obesity is reported to be associated with oxidative stress which can cause lipid peroxidation. However, the effects of gain in various weight-related anthropometric indices on lipid peroxidation remain unclear. We aimed to examine the cross-sectional and longitudinal associations between altered weight-related anthropometric indices and a marker of lipid peroxidation among urban adults in China.

Methods: A total of 3762 participants from the Wuhan-Zhuhai cohort were included in the present study, with a follow-up of 3 years. Six weight-related anthropometric indicators were measured and calculated, including waist circumference (WC), body mass index (BMI), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), a body shape index (ABSI), and body adiposity index (BAI). Individual urinary 8-iso-prostaglandin-F_{2α} (8-iso-PGF_{2α}) was determined via enzyme-linked immunosorbent assay to evaluate lipid peroxidation. We used generalized linear models to analyze the cross-sectional and longitudinal associations of weight-related anthropometric indices with a marker of lipid peroxidation and stratified analyses to estimate effect modification.

Results: We found significant relationships between WHR, WHtR, ABSI, and urinary 8-iso-PGF_{2α} at baseline. Each 1% increase in WHR, WHtR, and ABSI was significantly associated with a 0.007, 0.004, and 0.104 increase in log-transformed 8-iso-PGF_{2α} concentration, respectively ($P < 0.05$). In longitudinal analysis, positive dose-response relationships were observed between gains in BMI, BAI, and increased 8-iso-PGF_{2α} after adjusting for potential confounders ($P_{\text{trend}} < 0.05$). We also found that gender and smoking status modified the association of BMI gain and 8-iso-PGF_{2α} increment, and such an association was more obvious in female and non-smokers.

Conclusion: Our research implied that gain in anthropometric indices may result in a higher level of lipid peroxidation.

Keywords: weight-related anthropometric indices, lipid peroxidation, obesity, cohort study

Introduction

Obesity, a widespread pandemic leading to poor health nowadays, has attracted worldwide public attention. According to the recent World Health Organization report, more than one third of the adult population were categorized as overweight or obese globally, as were over 340 million children and adolescents.¹ Several weight-related indices have been used to assess adiposity, among which body mass index (BMI) is the most widely used.² Compared with BMI, waist circumference

Correspondence: Weihong Chen
Department of Occupational and Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, People's Republic of China
Tel +86 27 83691677
Email wchen@mails.tjmu.edu.cn

(WC) and waist-to-hip ratio (WHR) have advantages in reflecting body fat distribution and measuring central obesity that is linked to greater health risks.^{3,4} Additionally, other weight-related anthropometric indices were proposed to assess the accumulation of adipose, including waist-to-height ratio (WHtR), a body shape index (ABSI), and body adiposity index (BAI). A review from Italian scholars reported that obesity may activate the innate immune system and promote oxidative stress.⁵

Oxidative stress arises from a systemic disequilibrium of oxidation–antioxidation system due to overproductions of reactive oxygen species (ROS) or reactive nitrogen species (RNS), which could contribute to the initiation and progression of obesity-related diseases.^{6–8} Cell membranes and macromolecules may be damaged once this imbalance appears. Lipids, especially polyunsaturated fatty acids, are susceptible biomolecules that could be attacked by ROS, and generate peroxides ultimately. F₂-isoprostanes (F₂-isoP) are regarded as reliable markers among numerous lipid peroxides.⁹ The 8-iso-prostaglandin-F_{2α} (8-iso-PGF_{2α}), one well-known part of F₂-isoP class, is usually detected in urine to reflect the level of lipid peroxidation.¹⁰ Some published literatures have suggested that elevated 8-iso-PGF_{2α} was associated with obesity and fat accumulation.^{11,12}

To better achieve the early prevention of obesity-related diseases, further understanding on the relationship between adiposity and lipid peroxidation is necessary. Ohmori et al¹³ found that the levels of plasma 8-iso-PGF_{2α} were significantly higher in the high BMI group. In the Framingham Heart Study, positive associations of BMI and WHR with urinary 8-iso-PGF_{2α} were also documented.¹⁴ However, a cross-sectional study of 677 Japanese people showed that BMI has no significant relevance to urinary 8-iso-PGF_{2α},¹⁵ which was inconsistent with the abovementioned findings. In addition to such controversial associations, independent effects of some new weight-related anthropometric parameters, such as ABSI and BAI, on urinary 8-iso-PGF_{2α} remain largely unknown. And the study regarding the longitudinal associations of gain in weight-related anthropometric indices with urinary 8-iso-PGF_{2α} change is limited. Accordingly, we aimed to investigate the effects of different weight-related anthropometric indices on urinary 8-iso-PGF_{2α} levels, and further examine whether there are longitudinal associations between gain in weight-related anthropometric indices and altered urinary 8-iso-PGF_{2α} levels among urban adults in China.

Methods

Study Design and Population

Data used in this study were originated from the Wuhan-Zhuhai cohort, which is a community-based prospective cohort established between 2011 and 2012 as described previously.¹⁶ A total of 4812 participants aged 18–80 years who lived in the communities of Wuhan or Zhuhai city for more than 5 years were recruited at baseline survey. Participants were followed up every 3 years. In the current cross-sectional analysis, 3762 subjects were included after excluding those with a history of nephritis (n=43), missing information on 8-iso-PGF_{2α} (n=926), and weight-related anthropometric indices (n=81) at baseline. The first follow-up survey was finished after 3 years, and a total of 2777 participants were recruited. We excluded participants who had missing data on weight-related anthropometric indices (n=1069) or failed to provide sufficient urine samples (n=322). Finally, 1386 participants were included in longitudinal analysis. Participants included and excluded showed no significant difference in basic characteristics including age and gender. The study has approval from the Ethics and Human Subject Committee of Tongji Medical College, Huazhong University of Science and Technology. Written informed consent was gained from residents before participation.

Covariate Data Collection

Covariates, including basic demographic information, lifestyle (smoking status, alcohol drinking, regular physical activity, cooking status), and history of disease, were collected through face-to-face interview by professionals. Smoking status covered ever smoking (current and former smoking) and never smoking. Drinking status covered ever drinking (current and former drinking) and never drinking. Physical activity was defined as exercising regularly at least two times per week and for more than 20 minutes each time within the past 6 months. Diet information (intake frequencies of grains, fruit, vegetables, meat, and smoked each day or week) were also collected.

Weight-Related Anthropometric Indices

Every participant underwent a physical examination that included anthropometric measurements, like weight, height, WC, and hip circumference (HC). All of them were accomplished through standardized protocol and technique. In brief, height and weight were measured via weighing scale and a ruler (RGZ-120 Jiangsu Suhong

Medical Device Co., Ltd, Changzhou, China). During the measurement, participants stood upright and kept the heels, sacrum, and scapula in line. WC was done at the midpoint between the iliac crest and the lower costal margin, and HC at the maximum circumference of the buttocks. Other weight-related anthropometric indices, including BMI, WHR, WHtR, ABSI, and BAI, were calculated as follows.^{17–19}

$$\begin{aligned} \text{BMI} &= \text{Weight}(\text{kg})/\text{Height}^2(\text{m}); \\ \text{WHR} &= \text{WC}(\text{cm})/\text{HC}(\text{cm}); \\ \text{WHtR} &= \text{WC}(\text{cm})/\text{Height}(\text{cm}); \\ \text{ABSI} &= \text{WC}(\text{m})/[\text{BMI}^{2/3}(\text{kg}/\text{m}^2)\text{Height}^{1/2}(\text{m})]; \\ \text{BAI} &= [\text{HC}(\text{cm})/\text{Height}^{1.5}(\text{m})] - 18; \end{aligned}$$

The gain in weight-related anthropometric indices were derived through the values of corresponding indicators in first follow-up minus the values at baseline. Overweight ($\geq 24 \text{ kg}/\text{m}^2$) is defined based on the BMI cut-off values presented by the Working Group on Obesity in China.²⁰

Urinary 8-Iso-PGF_{2α} Determination

We collected spot morning urine to detect the levels of urinary 8-iso-PGF_{2α} that have been widely accepted in large epidemiological investigations previously. The levels of urinary 8-iso-PGF_{2α} were determined using a commercially available ELISA kit (Cayman Chemical, Ann Arbor, MI, USA) according to the manufacturer's instruction. We controlled the intra- and inter-assay coefficients of variation below 5% and 10%, respectively. Urinary 8-iso-PGF_{2α} concentration was calibrated by urinary creatinine (Cr) and finally expressed as ng/mmol Cr. Increased urinary 8-iso-PGF_{2α} for each participant is the result of 8-iso-PGF_{2α} in first follow-up minus the result at baseline.

Statistical Analysis

Urinary 8-iso-PGF_{2α} concentration was log-transformed because of its right skewed distribution. Demographic characteristics across urinary 8-iso-PGF_{2α} quartiles were compared using one-way ANOVA for continuous variables and Chi-square test for categorical variables.

The associations of weight-related and gain in weight-related anthropometric indices with urinary 8-iso-PGF_{2α} and altered urinary 8-iso-PGF_{2α} levels were evaluated using generalized linear models with adjustment for potential confounders, including age, gender, city, education, smoking status, alcohol drinking, physical activity, cooking meals at home, intake frequency of each kind of food

(fruit, meat, smoked), history of hypertension, diabetes, and coronary heart disease.

Continuous models were used to calculate the regression coefficient and 95% confidence intervals of altered urinary 8-iso-PGF_{2α} by each 1-unit increase in weight-related anthropometric indices, and categorical models to estimate regression coefficient of urinary 8-iso-PGF_{2α} change across quartiles of different anthropometric indices gain. Furthermore, we assessed the relationships between altered urinary 8-iso-PGF_{2α} and transition of overweight status during a 3-year period in two models. One was adjusted for single study factor, and another for all potential confounders. Statistical modification was performed by inputting an interaction term of interested weight-related anthropometric indices multiplied by the stratification covariates (age, gender, smoking status, alcohol consumption, and physical activity) in the generalized linear models, so as to clarify the modification effect of baseline demographic characteristics. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline Characteristics of Participants

The 8-iso-PGF_{2α} concentrations of all participants in urine samples ranged from 38.01–108.39 ng/mmol Cr, with a median value of 61.75 ng/mmol Cr. Baseline characteristics of the study population by quartiles of urinary 8-iso-PGF_{2α} concentration are shown in Table 1. The mean age of 3762 subjects (1156 male, 30.73%) was 52.07±13.56 years old. Male individuals, cigarette smokers, alcohol drinkers, and those who ate vegetables, fruits, and smoked food frequently were more likely to have a higher urinary 8-iso-PGF_{2α} level, whereas the results were the opposite among individuals who exercise regularly, eat more meat, and usually cook meals at home ($P < 0.05$). As for weight-related anthropometric parameters, no differences were found across urinary 8-iso-PGF_{2α} quartiles except for WHR and ABSI.

Cross-Sectional Associations of Weight-Related Anthropometric Indices with Urinary 8-Iso-PGF_{2α}

The cross-sectional relationships between various weight-related anthropometric indices and urinary 8-iso-PGF_{2α} in all participants and subgroups of non-overweight and overweight are shown in Table 2. With adjustment for

Table 1 Baseline Characteristics of Study Population by Quartiles of Urinary 8-Iso-PGF_{2α} Concentration (N=3762)

Characteristics	All Participants	Quartiles of Total Urinary 8-Iso-PGF _{2α} Levels, ng/mmol Cr				P*
		Quartile 1 (<38.01)	Quartile 2 (38.01– 61.75)	Quartile 3 (61.75–108.39)	Quartile 4 (≥108.39)	
No, observations	3762	940	941	940	941	
Age (years, mean±SD)	52.07±13.56	51.48±13.17	51.84±13.28	51.92±13.75	53.05±14.00	0.0706
Gender, n (%)						0.0023
Female	2606 (69.27)	696 (74.04)	649 (68.97)	632 (67.23)	629 (66.84)	
Male	1156 (30.73)	244 (25.96)	292 (31.03)	308 (32.77)	312 (33.16)	
Education, n (%)						0.0016
Middle school or below	2280 (60.61)	590 (62.77)	593 (63.02)	567 (60.32)	530 (56.32)	
High school	1020 (27.11)	222 (23.62)	232 (24.65)	274 (29.15)	292 (31.03)	
University or beyond	462 (12.28)	128 (13.62)	116 (12.33)	99 (10.53)	119 (12.65)	
Smoking status, n (%)						<0.0001
Current or former smoker	751 (19.96)	135 (14.36)	178 (18.92)	209 (22.23)	229 (24.34)	
Never smoker	3011 (80.04)	805 (85.64)	763 (81.08)	731 (77.77)	712 (75.66)	
Drinking status, n (%)						<0.0001
Current or former drinker	580 (15.42)	91 (9.68)	142 (15.09)	158 (16.81)	189 (20.09)	
Never drinker	3182 (84.58)	849 (90.32)	799 (84.91)	782 (83.19)	752 (79.91)	
Dietary intake frequency						
Meat (>4 times/week, n, %)	2487 (66.11)	651 (69.26)	643 (68.33)	614 (65.32)	579 (61.53)	0.0016
Fruit and vegetable (>4 times/week, n, %)	3547 (94.28)	874 (92.98)	875 (92.99)	897 (95.43)	901 (95.75)	0.0076
Smoked food (>1 time/week, n, %)	849 (22.57)	178 (18.94)	209 (22.21)	214 (22.77)	248 (26.35)	0.0019
Physical activity, n (%)	1843 (48.99)	511 (54.36)	483 (51.33)	433 (46.06)	416 (44.21)	<0.0001
Cooking meals at home, n (%)	2781 (73.92)	720 (76.60)	716 (76.09)	673 (71.60)	672 (71.41)	0.0094
Anthropometrics						
BMI (kg/m ² , mean±SD)	23.93±3.52	23.83±3.60	23.96±3.41	23.86±3.53	24.09±3.53	0.3625
WC (cm, mean±SD)	81.79±9.96	81.10±9.99	82.11±9.71	81.74±9.97	82.20±10.16	0.0668
WHR (% , mean±SD)	0.8678±0.0692	0.8608±0.0707	0.8719±0.0694	0.8689±0.0692	0.8696±0.0671	0.0030
WHtR (% , mean±SD)	0.5158±0.0630	0.5124±0.0641	0.5181±0.0611	0.5148±0.0630	0.5180±0.0635	0.1471
ABSI (m ^{7/6} /kg ^{2/3} , mean±SD)	0.0783±0.0049	0.0780±0.0050	0.0786±0.0047	0.0784±0.0049	0.0783±0.0050	0.0487
BAI (0.01m ^{-0.5} , mean±SD)	29.19±4.23	29.29±4.28	29.20±3.99	29.00±4.23	29.27±4.41	0.4330

Note: *P-values were estimated by one-way analysis of variance test for continuous variables and Chi-square test for categorical variables.

Abbreviations: WC, waist circumference; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height-ratio; BAI, body adiposity index; ABSI, a body shape index; SD, standard deviation; Cr, creatinine.

potential covariates, WHR, WHtR, and ABSI rather than BMI, WC, or BAI were significantly associated with 8-iso-PGF_{2α} in all participants (Table 2 and Figure 1). Each 1% increase in WHR, WHtR, and ABSI was significantly associated with a 0.007, 0.004, and 0.104 increase in log-transformed 8-iso-PGF_{2α} concentration, respectively (P<0.05). Additional subgroup analysis showed similar unanimous associations, and we found that the association of WHtR with 8-iso-PGF_{2α} is significant in the subgroup of non-overweight instead of overweight. The simple scatter plots with crude data between those relationships are shown in Supplementary Figure 1.

Longitudinal Associations of Gain in Weight-Related Anthropometric Indices with Altered Urinary 8-Iso-PGF_{2α}

As shown in Figure 2, the results of generalized linear models indicated positive dose–response relationships between increased 8-iso-PGF_{2α} and gain in BMI and BAI, after adjusting for potential confounders (all P_{trend}<0.05). Consistent with categorical analyses, continuous analyses exhibited that average increase in 8-iso-PGF_{2α} was 2.65% (95% CI=0.32–4.98%) with per 1-unit gain in BAI (P<0.05). Change in other weight-related anthropometric indices (BMI, WC, WHR, WHtR, and

Table 2 Associations Between Weight-Related Anthropometric Indices and Urinary 8-Iso-PGF_{2α} Levels at Baseline (N=3762)

Variables	All (N=3762)		BMI<24 (n=2003)		BMI≥24 (n=1759)	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
BMI	-0.0010 (-0.0084–0.0063)	0.7796	0.0018 (-0.0177–0.0213)	0.8569	-0.0024 (-0.0168–0.0121)	0.7474
WC	0.0018 (-0.0009–0.0045)	0.1987	0.0049 (-0.0005–0.0103)	0.0732	0.0028 (-0.0023–0.0080)	0.2817
WHR	0.6805 (0.2739–1.0872)	0.0010	0.9256 (0.3152–1.5360)	0.0030	0.8427 (0.1594–1.5261)	0.0157
WHtR	0.4384 (0.0052–0.8717)	0.0473	1.1828 (0.3157–2.0498)	0.0075	0.6027 (-0.2002–1.4056)	0.1411
ABSI	10.3966 (4.7817–16.0115)	0.0003	11.0364 (3.6652–18.4076)	0.0034	10.1115 (1.3540–18.8691)	0.0237
BAI	0.0012 (-0.0057–0.0082)	0.7246	0.0076 (-0.0062–0.0214)	0.2797	-0.0013 (-0.0123–0.0097)	0.8179

Notes: All models were adjusted for age, gender (male/female), city (Wuhan/Zhuhai), education (middle school or below/high/university or beyond), smoking status (current or former smoker/never smoker), alcohol status (current or former drinker/never drinker), exercise (time for physical activity), intake frequency of each food type (fruit (≤4/>4 times/week), meat (≤4/>4 times/week), smoked food (≤1/>1 time/week)), cooking (yes/no), history of hypertension (yes/no), diabetes (yes/no), coronary heart disease (yes/no).

Abbreviations: WC, waist circumference; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height-ratio; BAI, body adiposity index; ABSI, a body shape index.

ABSI) were positively associated with an increase in 8-iso-PGF_{2α} without statistical significance ([Supplementary Table 1](#)). When contrasting with those overweight at baseline but non-overweight at follow-up, females who were non-overweight at baseline but overweight at follow-up showed a 42.15% (95% CI=8.62–75.68%) increase in urinary 8-iso-PGF_{2α} levels ([Table 3](#)).

Stratification analyses of selected characteristics are presented in [Table 4](#). Gender and smoking status were potential effect modifiers of the association between BMI gain and altered urinary 8-iso-PGF_{2α} levels ($P_{\text{for interaction}} < 0.05$), and no statistical significance was noted in other interaction terms. The relationships between BMI, as well as BAI gain and increased urinary 8-iso-PGF_{2α}, were more remarkable among females and nonsmokers. Thus, we then examined such associations in subgroups of different genders and smoking status. Among females or nonsmokers, but not males or smokers, significant dose–response relationships between anthropometric indices (BMI and BAI) gain and increased urinary 8-iso-PGF_{2α} still existed. In addition, individuals who cooked at home exhibited more pronounced associations compared with those did not cook ([Supplementary Tables 2](#) and [3](#)).

Discussion

In this study, we explored the cross-sectional and longitudinal associations of various weight-related anthropometric indices with urinary 8-iso-PGF_{2α}, a biomarker of lipid peroxidation. We observed that urinary 8-iso-PGF_{2α} concentrations were increased along with elevated WHR, WHtR, and ABSI (an indicator reflecting body fat distributions) among all participants in the cross-sectional analysis. After follow-up of 3 years, we found significant

dose–response relationships between gain in BMI and BAI and increased urinary 8-iso-PGF_{2α} in longitudinal analysis. And such a relationship was more obvious in females and non-smokers than in males and smokers.

Data from a Framingham Heart Study involving 1250 adults showed that subcutaneous adipose tissue and visceral adipose tissue were related to higher urinary 8-iso-PGF_{2α}, which indicated a direct cross-sectional association of visceral adiposity and oxidative stress.²¹ In line with that, subsequent studies implied both general adiposity (accessed by BMI) and central adiposity (measured by WC and WHtR) were positively and similarly associated with lipid peroxidation.^{22–25} Besides, evidence from Japanese scholars found that the relationship between urinary F₂-isoprostane (a lipid peroxidation marker) excretion and BMI showed a U-shaped curve with the lowest F₂-isoprostane level at BMI 23 among 15 subjects.²⁶ Indeed, our research also showed positive relationships between weight-related anthropometric indices (WHR, WHtR, ABSI) and urinary 8-iso-PGF_{2α} concentrations (a stable biomarker of lipid peroxidation), which indicated central obesity may contribute to lipid peroxidation by examining a large population in China. However, with respect to BMI, we did not find its effect on urinary 8-iso-PGF_{2α} at baseline, though this result was in accordance with a Japanese study conducted on 677 healthy adults.¹⁵ The possible explanations for the discrepancy between our findings and previously published data might be the differences in biological specimens and detection method of lipid peroxides. Blood specimens and mass spectrometric methods were applied in some prior research. While considering the short half-life of plasma F₂-isoP and large sample size,^{15,27} immunoassays in urine may be a more suitable method.

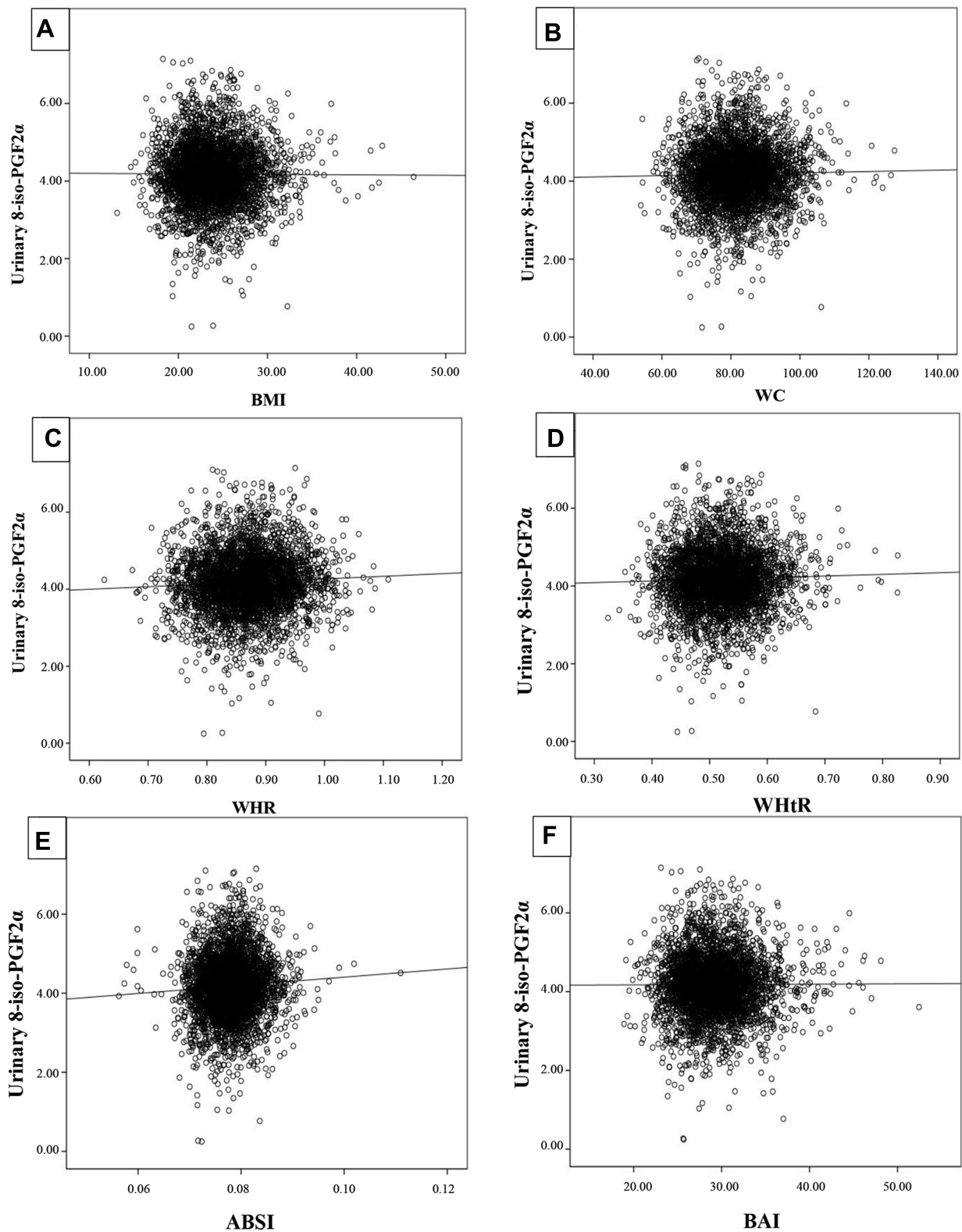


Figure 1 Associations between different weight-related anthropometric indices and urinary 8-iso-PGF_{2α} in baseline, adjusted for potential confounders (N=3762). Figures A to F represent the scatter plots of BMI (kg/m²) (A), WC (cm) (B), WHR (%) (C), WHtR (%) (D), ABSI (m^{7/6}/kg^{2/3}) (E), BAI (0.01 m^{-0.5}) (F), and urinary 8-iso-PGF_{2α} concentrations, respectively. All models were adjusted for age, gender (male/female), city (Wuhan/Zhuhai), education (middle school or below/high/university or beyond), smoking status (current or former smoker/never smoker), alcohol status (current or former drinker/never drinker), exercise (time for physical activity), intake frequency of each food type (fruit (≤4/>4 times/week), meat (≤4/>4 times/week), smoked food (≤1/>1 time/week), cooking (yes/no), history of hypertension (yes/no), diabetes (yes/no), coronary heart disease (yes/no).

Abbreviations: WC, waist circumference; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height-ratio; BAI, body adiposity index; ABSI, a body shape index.

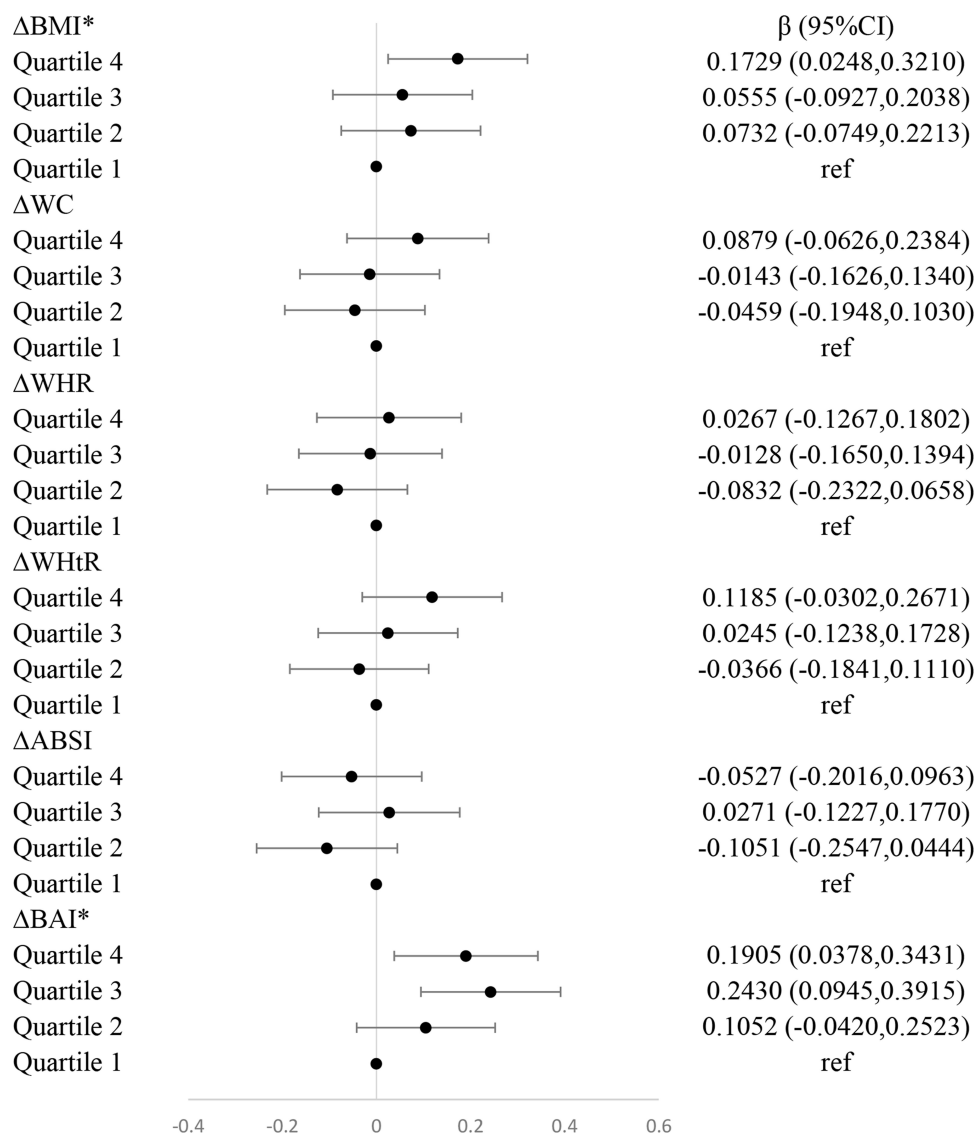


Figure 2 Associations between gain in weight-related anthropometric indices and change of urinary 8-iso-PGF_{2 α} levels during 3-year follow-up (N=1386). All models were adjusted for age, gender (male/female), city (Wuhan/Zhuhai), education (middle school or below/high/university or beyond), smoking status (current or former smoker/never smoker), alcohol status (current or former drinker/never drinker), exercise (time for physical activity), intake frequency of each food type (fruit (≤ 4 / > 4 times/week), meat (≤ 4 / > 4 times/week), smoked (≤ 1 / > 1 times/week), cooking (yes/no), history of hypertension (yes/no), diabetes (yes/no), coronary heart disease (yes/no). * $P_{\text{trend}} < 0.05$. **Abbreviations:** WC, waist circumference; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height-ratio; BAI, body adiposity index; ABSI, a body shape index.

To our knowledge, our present results provided vital insight into altered urinary 8-iso-PGF_{2 α} (a biomarker used to reflect the degree of lipid peroxidation) influenced by gain in weight-related anthropometric indices, which were largely unknown before. In the present study, as BMI or BAI levels keep increasing after 3 years, urinary 8-iso-PGF_{2 α} concentrations were gradually increased. Furthermore, compared with the female who lost weight during 3-year follow-up, those with gained weight had increased urinary 8-iso-PGF_{2 α} , suggesting that the levels of lipid peroxidation may strengthen with growing fat accumulation over time, especially in women. A study

by Chae et al²⁸ found that 122 overweight/obese participants exhibited decreased urinary 8-iso-PGF_{2 α} after 3-year-long intervention involving daily 100-kcal calorie deficits. Il'yasova et al²⁹ discovered that 2-year calorie restriction in healthy volunteers caused a statistical reduction in F₂-isoP at both time points. Nevertheless, in the Insulin Resistance Atherosclerosis Study (IRAs) Cohort followed by 5 years, increased urinary F₂-isoP levels predicted lower weight gain using the data from 299 individuals,³⁰ which showed incongruity with our results. The heterogeneity may be owing to the discrepancy of subject characteristics and sample size.

Table 3 Regression Coefficients of Change in Urinary 8-Iso-PGF_{2α} by Overweight at Baseline and 3-Year Follow-Up

Overweight at Baseline	Overweight at Follow-Up	N	β (95% CI)	
			Crude [†]	Adjusted [‡]
All participants				
Yes	No	57	ref	ref
No	No	530	0.2163 (−0.0682–0.5008)	0.1785 (−0.0939–0.4508)
Yes	Yes	618	0.1531 (−0.1294–0.4357)	0.1380 (−0.1323–0.4083)
No	Yes	181	0.2997 (−0.0103–0.6097)	0.2804 (−0.0153–0.5761)
Females				
Yes	No	46	ref	ref
No	No	384	0.2243 (−0.0945–0.5431)	0.2180 (−0.0890–0.5249)
Yes	Yes	410	0.2183 (−0.0994–0.5360)	0.2183 (−0.0856–0.5222)
No	Yes	131	0.4132 (0.0631–0.7634)	0.4215 (0.0862–0.7568)

Notes: [†]Single factor for generalized linear regression. [‡]Adjusted for age, gender (male/female), city (Wuhan/Zhuhai), education (middle school or below/high/university or beyond), smoking status (current or former smoker/never smoker), alcohol status (current or former drinker/never drinker), exercise (time for physical activity), intake frequency of each food type (fruit (≤4/>4 times/week), meat (≤4/>4 times/week), smoked food (≤1/>1 time/week)), cooking (yes/no), history of hypertension (yes/no), diabetes (yes/no), coronary heart disease (yes/no).

The explicit mechanism underlying the associations between weight-related anthropometric indices gain and higher level of lipid peroxidation over time remain not elucidated. The following pathways were likely to be involved. Enlarged white adipose tissue lead to the synthesis of various adipokines, which facilitate the generation of lipid peroxides in turn.³¹ Among adipokines, leptin serves as a crucial regulator for energy expenditure and food intake, and plays an important role in the formation of lipid peroxides; so as inflammatory cytokines from macrophages and monocytes, like TNF-α, IL-1, and IL-6.^{23,32} Experimental models have observed that the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathway (NOX) is another major source of ROS.³³ NOX, particularly NOX4, shares the capacity to transfer electrons and convey various cellular signals.³⁴ Marchesi et al³⁵ found that vascular superoxide and NADPH oxidase activity was aroused in perivascular adipose tissue of New Zealand obese mice. In addition, susceptibility to lipid peroxidative injury is aggravating in obese individuals because of reduced antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX).³¹ Compared to those with a BMI of more than 40 kg/m², subjects with healthy BMI had significant higher SOD and GPX.³⁶ And it has been proved that supplementation with antioxidants decreased systemic oxidative stress and plasma 8-iso-PGF_{2α} concentrations among those of overweight or obese.³⁷ Finally, visceral fat accumulation triggers increased lipid peroxidation through excess free fatty acids.⁵ As Randle et al³⁸ identified that mitochondrial NADH/NAD⁺ ratio rose with high levels of fatty acid oxidation.

Interestingly, the females were more likely to have stronger associations between anthropometric indices (BMI and BAI) gain and 8-iso-PGF_{2α} increment, supporting the hypothesis that significant sex interactions were found between plasma 8-iso-PGF_{2α} levels and most measures of adiposity.²³ The prior literatures have indicated that a higher adipose tissue volume in women than men may be responsible for the gender differences.²³ Another possible interpretation was menopausal status. Most researches have shown increased lipid peroxidation levels and decreased antioxidant status were discovered in postmenopausal women,^{39,40} and women over 50 years old took up a large percentage in our study. The concrete reasons for the gender difference in the relationships need to be investigated in the future.

There are several strengths in our study. First and foremost, we clarified the relationships of weight-related anthropometric indices and urinary 8-iso-PGF_{2α} via both cross-sectional and longitudinal analyses in a relatively large population. Besides, several weight-related anthropometric indices which could evaluate the fat accumulation from different dimensions were applied to offer a better understanding of the associations. Third, we adjusted for potential confounders such as cigarette smoking and drinking. As for our limitations, participants involved in this study were followed with a short interval, as such, the indices of anthropometry and lipid peroxidation may not reflect a long-term change. Further studies are needed to explore their associations for a long period in a larger population. Another limitation is that information about dietary intake habits,

Table 4 Associations Between Gain in Weight-Related Anthropometric Indices and Change in Urinary 8-Iso-PGF_{2α} Levels During 3-Year Follow-Up, Stratified by Selected Characteristics

Group	N (%)	ΔBMI			ΔBAI		
		β (95% CI)	P	P for Interaction	β (95% CI)	P	P for Interaction
Gender							
Male	415 (29.94)	-0.0377 (-0.1102-0.0348)	0.3078	0.0368	0.0251 (-0.0234-0.0736)	0.3096	0.9347
Female	971 (70.06)	0.0482 (0.0105-0.0859)	0.0123		0.0285 (0.0015-0.0555)	0.0385	
Age, years							
<45	290 (20.92)	0.0606 (-0.0084-0.1295)	0.0847	0.2574	0.0486 (-0.0064-0.1037)	0.0832	0.2596
45-59	656 (47.33)	0.0334 (-0.0221-0.0890)	0.2379		0.0409 (0.0057-0.0760)	0.0229	
≥59	440 (31.75)	-0.0026 (-0.0553-0.0502)	0.9244		0.0078 (-0.0307-0.0464)	0.6906	
Smoking status							
Current or former	266 (19.19)	-0.0540 (-0.1449-0.0369)	0.2429	0.0471	-0.014 (-0.0804-0.0520)	0.6723	0.2135
Never	1120 (80.81)	0.0434 (0.0077-0.0792)	0.0174		0.0336 (0.0086-0.0587)	0.0086	
Alcohol consumption							
Current or former	231 (16.67)	-0.0098 (-0.1094-0.0898)	0.8461	0.4640	0.0024 (-0.0693-0.0742)	0.9471	0.8011
Never	1155 (83.33)	0.0331 (-0.0022-0.0684)	0.0664		0.0286 (0.0038-0.0534)	0.0238	
Cooking							
Yes	1068 (77.06)	0.0458 (0.0087-0.0829)	0.0155	0.0591	0.0294 (0.0041-0.0547)	0.0226	0.9475
No	318 (22.94)	-0.0220 (-0.0968-0.0527)	0.5622		0.0282 (-0.0331-0.0896)	0.3659	

Notes: All models were adjusted for age, gender (male/female), city (Wuhan/Zhuhai), education (middle school or below/high/university or beyond), smoking status (current or former smoker/never smoker), alcohol status (current or former drinker/never drinker), exercise (time for physical activity), intake frequency of each food type (fruit (≤4/>4 times/week), meat (≤4/>4 times/week), smoked food (≤1/>1 times/week)), cooking (yes/no), history of hypertension (yes/no), diabetes (yes/no), coronary heart disease (yes/no).

Abbreviations: BMI, body mass index; BAI, body adiposity index.

smoking, and drinking status were obtained through questionnaires, and possible bias in recall may exist. In addition, although all persons participating in physical examination were trained by professionals on the basis of the same standard, there is also the chance for bias in anthropometric measurement. Further studies are needed to confirm our results.

Conclusions

In summary, we found that WHR, WHtR, and ABSI are powerful predictors of lipid peroxidation that was reflected by urinary 8-iso-PGF_{2α} levels and associated closely with obesity-related health risks. Among females, pronounced dose-dependent relationships were reported between gain in BMI, BAI, and increased urinary 8-iso-PGF_{2α}. The study highlights that BAI and BMI may also be suitable indicators of dynamic response to lipid peroxidation.

Abbreviations

WC, waist circumference; BMI, body mass index; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; ABSI, a body shape index; BAI, body adiposity index; HC, hip

circumference; 8-iso-PGF_{2α}, 8-iso-prostaglandin-F_{2α}; Cr, creatinine; ROS, reactive oxygen species; RNS, reactive nitrogen species; F₂-isoP, F₂-isoprostanes; NADPH, nicotinamide adenine dinucleotide phosphate; NOX, nicotinamide adenine dinucleotide phosphate oxidase pathway; SOD, superoxide dismutase; CAT, catalase; GPX, glutathione peroxidase; SD, standard deviation.

Data Sharing Statement

The datasets used and analyzed in this study are available from the corresponding author with reasonable request.

Ethics Approval and Informed Consent

The study was approval by the Ethics and Human Subject Committee of Tongji Medical College, Huazhong University of Science and Technology. Written informed consent was gained from residents before participation.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest for this work.

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