Metabolism Clinical and Experimental 91 (2019) 53–60

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Central obesity transition increased urinary levels of 8-hydroxydeoxyguanosine in male adults: A 3-year follow up study

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ARTICLE INFO

Article history:
Received 1 October 2018
Accepted 27 November 2018

Keywords:
8-Hydroxydeoxyguanosine
Hip circumference
Central obesity

ABSTRACT

Objective: Association of oxidative DNA damage with gain in anthropometric indices has not been fully elucidated.
Methods: In this study, participants (n = 1151) were derived from the baseline visit of Wuhan residents in the Wuhan-Zhuhai Cohort Study. The participants finished the physical examinations at both baseline and 3-year follow up. Urinary levels of 8-hydroxydeoxyguanosine (8-OHdG) were measured by gradient-elution high performance liquid chromatography method and then calibrated by urinary creatinine (Cr) values.
Results: Generalized linear models showed that after adjusted for confounding factors, baseline central obesity individuals with a ≥2.5% hip circumference (HC) loss or >5% HC gain had a 0.290 μmol/mol Cr (95% confidence interval (CI): 0.108, 0.472) or 0.553 μmol/mol Cr (95% CI: 0.273, 0.833) increase in urinary 8-OHdG levels compared with those with a −2.5%–2.5% HC gain (both $P < 0.05$). Moreover, compared with non-central obesity at both baseline and 3-year follow-up, we observed that central obese men at both baseline and 3-year follow-up had a 0.46 μmol/mol Cr (95% CI: 0.16, 0.75) increased in urinary 8-OHdG levels.
Conclusions: HC gain showed dose-dependent associations with urinary 8-OHdG levels. Moreover, male central obesity at both baseline and 3-year follow-up had an increased risk for urinary 8-OHdG levels.

1. Introduction

Obesity is a growing health problem in China [1,2]. Data from the China Health and Nutrition Survey exhibited that the prevalence of central obesity increased from 8.5% in 1993 to 27.8% in 2009 for males and from 27.8 to 45.9% for females [3]. A recent study reported that the prevalence of central obesity increased to 10.2% (8.6% for males and 11.3% for females) among 14,964 participants in southern China [4]. Noteworthy, central obesity is found to be an independent risk factor for multiple chronic diseases, including hypertension, diabetes and coronary heart disease [5–7]. Nurdiantami et al. reported that the odds of hypertension risk increased by 150% among central obesity individuals (odds ratio = 1.50, 95% confidence interval (CI): 1.46–1.53) compared with normal-weight ones [8]. Moreover, Yoo et al. found a four-fold increased risk of diabetes in male central obesity rather than non-central obesity [9].

Nowadays, many adiposity indices have been used to reflect the distributions of body fat, including body mass index (BMI), waist circumference (WC), hip circumference (HC), waist-to-height ratio (WHtR) and waist-to-hip ratio (WHR). Whereas, the independent effects of abdominal adiposity rather than those of overall obesity need to be evaluated. Epidemiological studies indicated that HC and WHR not only are significant indices for central obesity but also are better predictors of risk for certain diseases (such as type 2 diabetes mellitus and coronary heart disease) rather than BMI and single general indicator of adiposity (such as body weight) [10,11]. The Iowa Women's Health Study indicated that WHR is a better anthropometric predictor of total mortality rather than BMI value or WC value [12]. Jayedi et al. reported that the odds of hypertension risk increased by 137% for each 0.1-unit increment in WHR value [13].

Accumulative evidences indicate that central obesity contribute to the development and progression of obesity-related diseases (such as diabetes mellitus and hypertension) along with excessive reactive oxygen species (ROS) generation, resulting from excess supply of energy substrates in relation to mitochondrial dysfunction and ROS

Abbreviations: BMI, body mass index; CI, confidence interval; Cr, creatinine; HC, hip circumference; IQR, interquartile range; ROS, reactive oxygen species; SD, standard deviation; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; 8-OHdG, 8-hydroxydeoxyguanosine.

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https://doi.org/10.1016/j.metabol.2018.11.015
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signaling [14,15]. Anderson et al. reported that H_2O_2-emitting potential of mitochondria was increased in rats fed high-fat diet, which attenuated ROS generation and shift the cellular redox environment to a more oxidized state by decline in the ratio of reduced glutathione (GSH) to oxidized glutathione (GSSG) [16]. Moreover, excessive supply of energy substrates (such as fatty acids) was found in obesity with higher lipid levels, which increased ROS generation. Several factors may contribute to inflammatory response and ROS generation in the body, including adipokines and proinflammatory cytokines, even adipose tissue macrophages [17,18]. 8-Hydroxydeoxyguanosine (8-OHdG) is the most sensitive marker for oxidative DNA damage, owing to its secretion by the oxidation of eoxyguanosine regarding DNA base modification [19]. Whereas, obese and overweight were risk factors for increased urinary 8-OHdG levels [20,21]. Animal studies showed that obese rats tended to have higher urinary 8-OHdG levels than lean ones [22].

Due to the limited data available concerning the relationship of changes in anthropometric indices with urinary 8-OHdG levels, the present study investigated effects of changes in anthropometric indices (including HC and WHR) on changes in urinary 8-OHdG levels among Chinese older adults during a 3-year follow-up.

2. Materials and Methods

2.1. Study Population

Data used in this study were drawn from a prospective community-based cohort study: information on the baseline Wuhan residents (n = 3053) of the Wuhan-Zhuhai (WHZH) Cohort Study (established in 2011) were described in detail elsewhere [23]. Among them, 2283 (74.78%) participants finished the questionnaires and examinations during the 3-year follow-up visit. We excluded participants with missing data on anthropometric indices (n = 34) and urine samples (n = 206) at baseline, and further excluded participants those with missing data on anthropometric indices (n = 743) and urinary 8-OHdG levels (n = 149) at the 3-year follow-up visit. Finally, 1151 participants (407 males and 744 females) were included in the longitudinal analysis (Fig. 1). The sensitivity analysis revealed the differences in the distributions of age and passive smoking status between included and excluded participants (Table S1).

This research was approved by the Medical Research Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology. Each participant provided a written informed consent before starting the study.

2.2. Lifestyle Factors

Information from each individual were collected by face to face interviewer-administered questionnaires on demographic characteristics (such as age, gender and educational levels), occupational history, lifestyle (including active and passive smoking, leisure-time physical activity status, dietary intake and sleep habits) as well as personal medical histories. Non-smokers were defined as those who had smoked less than one cigarette per day in the past 6 months, otherwise, they were considered as smokers. Passive smokers were defined as those who exposed to tobacco smoke indoor environment at least once a week for at least 15 min each time. Non-drinkers were defined as those who had drunk alcohol less than once each week in the past six months; otherwise, they were considered as drinkers. Physical activity was defined as doing at least 20 min of regular exercise during leisure time within 6 months (yes or no). Furthermore, each participant was asked to provide information on the frequencies (daily, weekly, monthly, or never) and amount of food consumed as well as habitual sleep pattern in the last two weeks. Sleep pattern was assessed with a seven-day time-activity diary, regarding times of going to sleep and wake up during the time periods of daytime and night, sleep latency, self-reported sleep quality (good/general/poor) in addition to taking sleep aid medication.

2.3. Anthropometric Indices

Height (cm) and weight (kg) were measured with a stadiometer and two high-precision digital scales (range 0–150 kg × 0.1 kg) using the

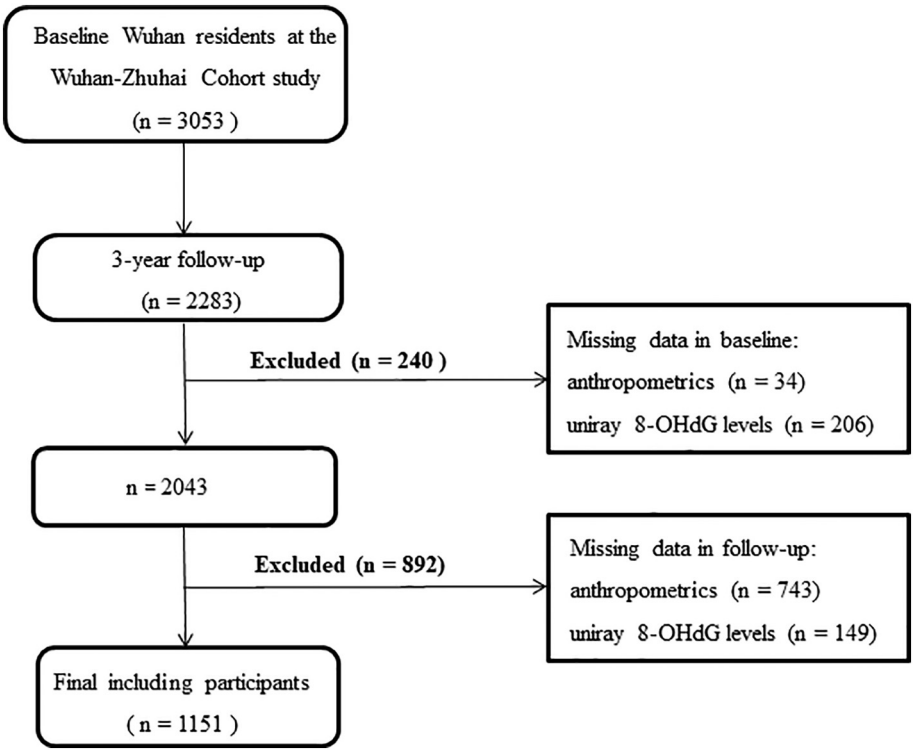

Fig. 1. Selection process for the study population. **Abbreviation**: 8-OHdG, 8-hydroxydeoxyguanosine.

standard methods, respectively. WC was done at a level midway between the lower rib margin and the iliac crest. Furthermore, hip circumference was determined at the point yielding the maximum circumference over the buttocks using a tape measurement to the nearest 1 cm. BMI was calculated as weight (kg) divided by the square of height (m^2). Participants were classified according to the BMI cut-off values recommended by the Working Group on Obesity in China (non-obese (<24 kg/m^2), overweight (24–28 kg/m^2) and obese (≥28 kg/m^2)) [24]. WHR was calculated as WC (cm) divided by HC (cm). Obesity individuals in both sexes were identified according to the WHR values recommended by the World Health Organization guideline (WHR ≥ 0.9 for male and WHR ≥ 0.85 for female) [25]. WHtR was calculated as WC (cm) divided by height (cm).

2.4. Blood Pressure and Blood Test Indicators

All participants took part in a physical examination and provided blood samples on the day of the physical examination. Systolic and diastolic blood pressures were measured using automated sphygmomanometers after the subject had rested for 15 min in a sitting position. Hypertension was defined as diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg or self-reported physician-diagnosed hypertension or taking antihypertensive drugs. Moreover, blood biochemical indicators (including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol) were determined by using a fully automatic biochemical analyzer (CS-400B, Dirui Industrial Co., Ltd., Changchun, China).

2.5. Urinary 8-OHdG Levels

Baseline levels of urinary 8-OHdG in all individuals were measured according to the described method elsewhere [26]. To increase the number of measurable urinary samples daily, urinary 8-OHdG levels at the 3-year follow-up visit were measured by using high performance liquid chromatography (HPLC) method with a modification based on the reported method by Sun et al. [26]. Comparison of two analysis methods for urinary 8-OHdG levels showed no significant difference (Fig. S1). Briefly, a 2-mL urine sample was firstly centrifuged at 1500*g* for 10 min at 4 °C to remove the precipitates. Then 1.5 mL supernatant was adsorbed on a pretreated Bond Elut LRC C_{18}-OH cartridge (3 mL 500 mg; Waters incorporated company, Massachusetts, USA) with the solution consisting of 10-mL pure methanol, 5-mL deionized water, 10-mL 0.1 M potassium dihydrogen phosphate (KH_2PO4, pH = 6.0) and 3-mL deionized water. Afterwards, the obtained substances were absorbed on the column and then purified by 3-mL 0.1 M KH_2PO4 (pH = 6.0) and 3-mL 5% methanol. The adsorbed substances were eluted with 1-mL methanol and dried with a vacuum at 45 °C. The evaporated residue was dissolved in 1-mL KH_2PO4 (pH = 6.0) and then filtrated by using a micro injector (0.22 mm, Millipore Corp, CA) for further analysis. Finally, each sample (20 μL) was analyzed by a HPLC coupled with an electrochemical detector (Waters 2645, Waters Inc., USA). A gradient elution was performed at a flow rate of 1 mL/min with two mobile phases. Mobile phases A and B were made with water containing 1% (v/v) methanol or 20% (v/v) methanol, respectively. A gradient method starting with 70% of mobile phase A and 30% of mobile phase B was performed. Then, a liner gradient was employed by ramping 66% of mobile phase A and 34% of mobile phase B during the next 1 min and maintained at 7.46% (v/v) methanol for 15 min; subsequently, it was changed to 5% of A and 95% of B during the next 2 min and maintain at 19.05% (v/v) methanol for 8 min. Finally, the system was returned to the initial conditions during the next 2 min and maintained at 6.70% (v/v) methanol for 6 min (Table S2). The coefficient of variation for the duplicate analysis was <8%. The recoveries of spiked samples ranged from 85.7% to 103.7%. Urinary 8-OHdG value was adjusted by creatinine (Cr) value. Data were expressed as μmol/mol Cr.

2.6. Statistical Analysis

One-sample Kolmogorov-Smirnov test was performed to verify the normality of each continuous variable (such as weight, WC, HC or BMI). Student's *t*-test was used to compare means between two groups. Chi-square test was used to analyze differences in the distributions of categorical variables (such as education levels, smoking status and drinking status) between groups. Mann-Whitney *U* test was used to compare the difference in the distributions of non-normal variables (such as WHR and urinary 8-OHdG levels) between groups. Furthermore, urinary 8-OHdG values were adjusted using urinary creatinine levels and log-transformed prior to further analysis due to its skewed distribution. Restricted cubic splines (RCS) was used to assess possible dose-response relationships between gain in each anthropometric index (including weight, WC, HC, WHR or WHtR) and change in urinary 8-OHdG levels. We set the knots at the 25th, 50th and 75th percentiles of the distributions of anthropometric indices, as described elsewhere [27]. The corresponding median values were chosen as the reference values for anthropometric indices. Participants were classified into four groups of ≤−2.5%, −2.5%–2.5% (as reference group), 2.5%–5% and >5% according to the percent of HC change during a 3-year follow-up period [28]. Statistical differences in urinary 8-OHdG levels between the groups were determined by one-way analysis of variance (ANOVA), followed by Fisher's least significant difference test (LSD-*t*-test). The generalized linear models were used to estimate the relationships between changes in selected variables and change in urinary 8-OHdG levels during a 3-year follow-up period. Four models were conducted: **Model 1** was adjusted for sex and age; **Model 2** was adjusted for variables in Model 1 plus education levels, active smoking, passive smoking, alcohol consumption, physical activity; **Model 3** was adjusted for variables Model 2 plus intake frequency of each kind of food (meat, dairy and eggs, fishery products and smoked food), **Model 4** was adjusted for variables in Model 3 plus daytime nap duration, nocturnal sleep duration and self-reported sleep quality. A two-tailed *P* value of ≤0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics of Participants

Baseline characteristics in all participants (n = 1151) by sex were presented. As shown in Table 1, the baseline values of weight (68.01 ± 10.56 kg vs. 59.17 ± 18.19 kg, $P < 0.05$), WC (85.67 ± 9.15 cm vs. 80.69 ± 9.39 cm, $P < 0.05$) and WHR (0.90 (0.85, 0.93) vs. 0.85 (0.80, 0.89), $P < 0.05$) of men were higher than those of women. However, women had higher baseline levels of urinary 8-OHdG than men (median: 71.92 μmol/mol Cr vs. 48.85 μmol/mol Cr, $P < 0.05$).

3.2. Associations of Dynamic Changes in HC with Urinary 8-OHdG Levels

As shown in Fig. 2, results from restricted cubic splines model indicated no significant dose-dependent association between WC values and urinary 8-OHdG levels (P for overall association = 0.1927). However, non-linear relationship was found between change in HC and change in urinary 8-OHdG levels (P for overall association <0.05) after adjusted for age, gender, educational levels, active and passive smoking, alcohol use, physical activity and intake frequency of each kind of food, daytime nap duration, nocturnal sleep duration and self-reported sleep quality. To examine the association between dynamic changes in HC and changes in urinary 8-OHdG levels, individuals were classified into four subgroups according to the range of HC percent gain. Table 2 shows the baseline characteristics of participants in each subgroup by percent change in HC. Differences in age, physical activity, napping time, sleep duration, self-reported sleep quality and urinary 8-OHdG levels were observed between the four subgroups (all $P < 0.05$). Individuals with >5% HC gain had longer night sleep period

Table 1
Baseline characteristics of Wuhan residents between male and female (n = 1151).

Variables	Male (n = 407)	Female (n = 744)	P
Age (years, mean ± SD)	54.06 ± 11.95	54.04 ± 11.95	0.985[a]
Educational levels (<9/9–12/≥13, years, n, %)	202/143/62 (49.6/35.2/15.2)	440/240/64 (59.1/32.3/8.6)	0.000[b]
Smoking status			
Active smoking (yes/no, n, %)	100/307 (24.6/75.4)	126/618 (16.9/83.1)	0.002[b]
Passive smoking (yes/no, n, %)	191/216 (46.9/53.1)	400/344 (53.8/46.2)	0.027[b]
Alcohol drinking (yes/no, n, %)	89/318 (21.9/78.1)	116/628 (15.6/84.4)	0.008[b]
Physical activity (yes/no, n, %)	249/158 (61.2/38.8)	433/311 (58.2/41.8)	0.325[b]
Dietary intake frequency			
Coarse grain (≤1/>1 time/week, n, %)	340/67 (83.5/16.5)	563/181 (75.7/24.3)	0.002[b]
Meet (≤1/>1 time/day, n, %)	156/251 (38.3/61.7)	327/417 (44.0/56.0)	0.065[b]
Fishery products (≤1/>1 time/week, n, %)	252/155 (61.9/38.1)	521/223 (70.0/30.0)	0.005[b]
Dairy and eggs (≤1/>1 time/week, n, %)	187/220 (45.9/54.1)	330/414 (44.4/55.6)	0.604[b]
Smoked food (≤1/>1 time/week, n, %)	316/91 (77.6/22.4)	528/216 (71.0/29.0)	0.014[b]
Sleep habits			
Daytime nap duration (minutes/day, median, IQR)	30.0 (0.0, 60.0)	0.0 (0.0, 45.0)	0.000[c]
Nocturnal sleep duration (hours/day, mean ± SD)	8.0 ± 1.4	8.1 ± 1.4	0.211[b]
Anthropometrics			
Weight (kg, mean ± SD)	68.01 ± 10.56	59.17 ± 18.19	0.000[a]
WC (cm, mean ± SD)	85.67 ± 9.15	80.69 ± 9.39	0.000[a]
HC (cm, mean ± SD)	95.03 ± 8.58	95.35 ± 8.04	0.836[a]
Body shape indices			
BMI (kg/m^2, mean ± SD)	24.53 ± 3.36	24.48 ± 7.28	0.902[a]
WHR (%, median, IQR)	0.90 (0.85, 0.93)	0.85 (0.80, 0.89)	0.000[c]
8-OHdG (μmol/mol Cr, median, IQR)	48.85 (20.38, 100.40)	71.92 (29.18, 151.17)	0.000[c]

Abbreviations: WC, waist circumference; HC, hip circumference; BMI, body mass index; WHR, waist-to-hip ratio; SD, standard deviation; IQR, interquartile range; 8-OHdG, 8-hydroxydeoxyguanosine; Cr, creatinine.
[a] Student's *t*-test was used to compare means of the continuous variables between males and females.
[b] Chi-square test was used to compare distributions of category variables between males and females.
[c] Mann-Whitney test was used to compare differences in non-normal variable distributions between males and females.

(8.28 ± 1.24 h), however, the least individuals did exercise (40.2%) compared with the other three subgroups. Individuals in the subgroups of ≥2.5% HC loss (−0.08 ± 1.05 μmol/mol Cr) and >5% HC gain (0.21 ± 1.06 μmol/mol Cr) exhibited a greater change in urinary 8-OHdG compared with ones in the subgroup of −2.5% to 2.5% change in HC (−0.37 ± 1.10 μmol/mol Cr) (both $P < 0.05$).

3.3. Associations of Central Obesity Transition with Urinary 8-OHdG Levels

As shown in Fig. 3, the fitted models revealed that among baseline individuals with normal weight (BMI < 24 kg/m^2), overweight (BMI ≥ 24 kg/m^2) or central obesity (males: WHR ≥ 0.90, females: WHR ≥ 0.85), there was a dose-response relationship between percent

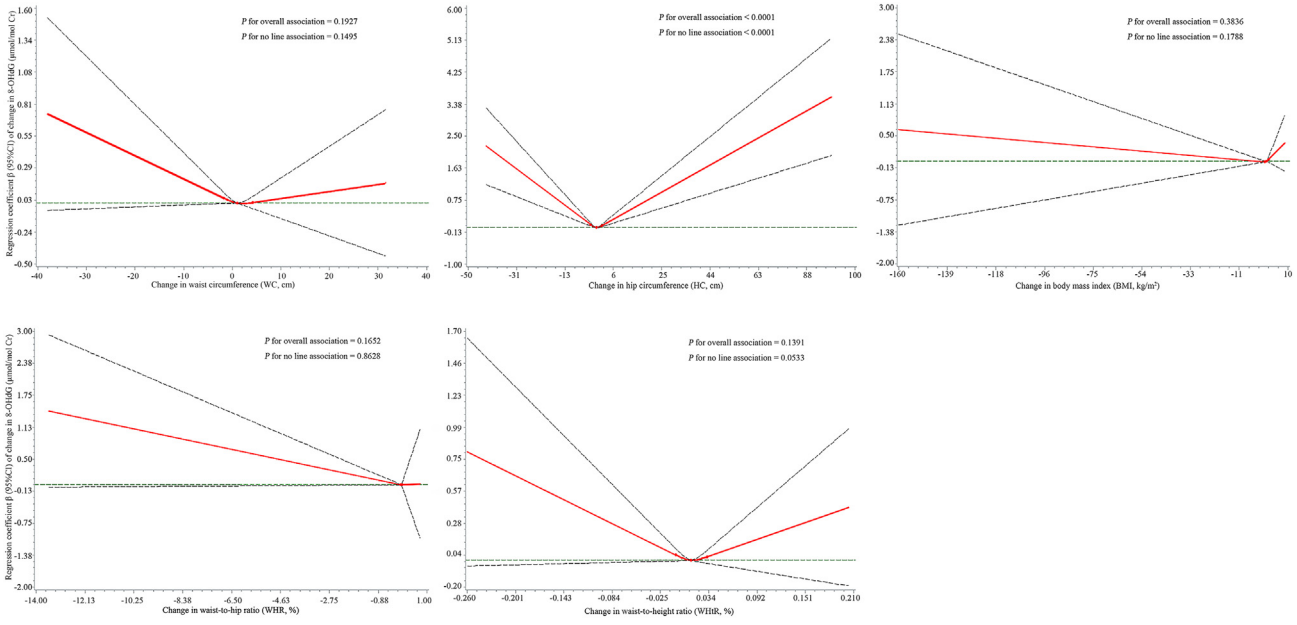

Fig. 2. Association between anthropometric indices and urinary 8-OHdG levels in all participants (n = 1151) based on restricted cubic spline models. All models were constructed after adjusted for age, sex, education level, active smoking, passive smoking, alcohol consumption, physical activity, intake frequency of each kind of food (meat, dairy and eggs, fishery product and smoked food), napping time, sleeping quality and sleep duration. **Abbreviations**: HC, hip circumference; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; 8-OHdG, 8-hydroxydeoxyguanosine.

Table 2
Baseline characteristics and changes in anthropometrics of participants by percent hip circumference (HC) gain during a 3-year follow-up period.

Characteristics	Percent HC gain (%)				P
	≤−2.5	−2.5 to 2.5	2.5 to 5	>5	
Age (years, mean ± SD)	56.45 ± 12.18	53.31 ± 11.68	52.56 ± 12.19	53.92 ± 11.77	0.00[a]
Sex (male/female, n, %)	102/185 (35.5/64.5)	232/414 (35.9/64.1)	49/87 (36.0/64.0)	24/58 (29.3/70.7)	0.66[b]
Educational levels (years, n, %)					0.16[b]
<9	145 (50.5)	361 (55.9)	81 (59.6)	55 (67.1)	
9–	105 (36.6)	215 (33.3)	44 (32.4)	19 (23.2)	
≥13	37 (12.9)	70 (10.8)	11 (8.1)	8 (9.8)	
Smoking status					
Active smoking (yes/no, n, %)	51/236 (17.8/82.2)	132/514 (20.4/79.6)	27/109 (19.9/80.1)	16/66 (19.5/80.5)	0.83[b]
Passive smoking (yes/no, n, %)	141/146 (49.1/50.8)	338/308 (52.3/47.7)	73/63 (53.7/46.3)	39/43 (47.6/52.4)	0.66[b]
Alcohol drinking (yes/no, n, %)	49/238 (17.1/82.9)	110/536 (17.0/83.0)	29/107 (21.3/78.7)	17/65 (20.7/79.3)	0.57[b]
Physical activity (yes/no, n, %)	154/133 (53.7/46.3)	289/357 (44.7/55.3)	59/77 (43.4/56.6)	34/49 (40.2/59.8)	0.04[b]
Dietary intake frequency					
Coarse grain (≤1/>1 time/week, n, %)	212/75 (73.9/26.1)	513/133 (79.4/20.6)	114/22 (83.8/16.2)	64/18 (78.0/22.0)	0.10[b]
Meat (≤1/>1 time/day, n, %)	118/169 (41.1/58.9)	260/386 (40.2/59.8)	63/73 (46.3/53.7)	42/40 (51.2/48.8)	0.18[b]
Fishery products (≤1/>1 time/day, n, %)	207/80 (72.1/27.9)	418/228 (64.7/35.3)	96/40 (70.6/29.4)	52/30 (63.4/36.6)	0.10[b]
Dairy and eggs (≤1/>1 time/day, n, %)	124/163 (43.2/56.8)	285/361 (44.1/55.9)	66/70 (48.5/51.5)	42/40 (51.2/48.8)	0.47[b]
Smoked food (≤1/>1 time/week, n, %)	203/84 (70.7/29.3)	470/176 (72.8/27.2)	108/28 (79.4/20.6)	63/19 (76.8/23.2)	0.24[b]
Daytime nap duration (min/day, median, IQR)	30 (0, 60)	0 (0, 60)	0 (0, 30)	0 (0, 30)	0.00[c]
Nocturnal sleep duration (hours/day, n, %)	7.91 ± 1.25	8.11 ± 1.23	8.12 ± 1.12	8.28 ± 1.24	0.04[b]
Changes in anthropometrics					
ΔWeight (kg, mean ± SD)	−0.15 ± 3.64	−0.23 ± 1.81	2.71 ± 2.68	4.21 ± 3.61	0.00[a]
ΔWC (cm, mean ± SD)	−1.99 ± 5.05	1.27 ± 4.54	3.82 ± 5.04	6.54 ± 6.46	0.00[a]
ΔHC (cm, mean ± SD)	−4.98 ± 3.34	−0.13 ± 1.34	3.30 ± 0.69	9.81 ± 5.68	0.00[a]
Change in body shape indices					
ΔBMI (kg/m^2, mean ± SD)	−0.14 ± 1.35	0.37 ± 7.25	1.53 ± 1.23	2.20 ± 1.42	0.00[a]
ΔWHR (median, IQR)	0.024 (−0.008, 0.058)	0.017 (−0.010, 0.419)	0.006 (−0.027, 0.043)	0.002 (−0.042, 0.049)	0.00[c]
Δ8-OHdG (μmol/mol Cr, mean ± SD)	−0.08 ± 1.05	−0.37 ± 1.10	−0.25 ± 1.08	0.21 ± 1.06	0.00[a]

Abbreviations: WC, waist circumference; HC, hip circumference; BMI, body mass index; WHR, waist-to-hip ratio; SD, standard deviation; IQR, interquartile range; 8-OHdG, 8-hydroxydeoxyguanosine; Cr, creatinine.
[a] One-way analysis of variance test was used to compare means of the continuous variables.
[b] Chi-square test was used to compare distributions of category variables.
[c] Kruskal-Wallis test was used to compare non-normally distributed variables.

change in HC value and change in urinary 8-OHdG levels (P for trend <0.05). The estimated results are consistent with the results obtained from individuals at different groups classified by the BMI cut-off values recommended by the WHO, NIH or NHS (Table S3). Generalized linear models revealed that after adjusted for age, gender, educational levels, active and passive smoking, alcohol consumption, physical activity, dietary intake frequency, daytime nap duration, nocturnal sleep duration and self-reported sleep quality, baseline central obesity with a ≥2.5% HC loss or >5% HC gain had a 0.290 μmol/mol Cr (95% CI: 0.108, 0.472) or 0.553 μmol/mol Cr (95% CI: 0.273, 0.833) increased in urinary 8-OHdG levels (both $P < 0.05$) as compared with the referent (−2.5%–2.5% HC gain). However, we found that only baseline non-central obesity with a ≥2.5% HC loss had a 0.361 μmol/mol Cr (95% CI: 0.096, 0.625) increased in urinary 8-OHdG levels.

As shown in Table 3, compared with non-central obesity at both baseline and 3-year follow-up, males with non-central obesity at baseline and central obesity during 3-year follow-up exhibited a 0.30 μmol/mol Cr (95% CI: 0.06, 0.55) increase in urinary 8-OHdG levels, moreover, central obesity men at baseline and at 3-year follow-up visits had a 0.46 μmol/mol Cr (95% CI: 0.16, 0.75) increase in urinary 8-OHdG levels.

4. Discussion

We observed the dose-response relationship of HC gain with increased urinary 8-OHdG levels in all participants regardless of central obesity status at baseline, after adjusting for sex, age, educational levels, active and passive smoking, physical activity status, dietary intake and sleep habits at baseline. Moreover, compared with non-central obese at baseline and a 3-year follow-up period, central obese men at the 3-year follow-up visit exhibited increased urinary 8-OHdG levels regardless of the status of central obesity at baseline. In this study, no significant dose-dependent association was found between BMI values and urinary 8-OHdG levels (P for overall association = 0.3836). However, contradictory results were obtained regarding the linkage between BMI and plasma or urinary 8-OHdG levels. For instance, Donmez-Altuntas H et al. found that obese had slightly lower plasma 8-OHdG concentrations than those with normal-weight (0.54 ± 0.33 vs. 0.58 ± 0.12, $P < 0.05$) [21]. Nevertheless, another research reported that no association was found between BMI and plasma 8-OHdG [29]. The reason for the difference in the relations needs to be further elucidated.

The mechanisms underlying the association between HC gain and higher risk for urinary 8-OHdG were reported. On the one hand, adipose tissue may enhance expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and decrease expression of antioxidative enzymes (such as superoxide dismutase (SOD), glutathione peroxidase and catalase) along with excessive ROS generation, which consequently lead to the increase of 8-OHdG levels. Steinbeck et al. reported that increased fatty acid levels in obese individuals may promote the up-regulation of NADPH oxidase expression [30]. Furthermore, Furukawa et al. observed increased mRNA levels of NADPH oxidase subunits (including gp91phox, p22phox, p47phox, p67phox and p40phox) in white adipose tissue in relation to increasing transcriptional levels of NOX4 [31]. NOX4 as one of the NOX family members can generate H_2O_2 [32]. A study reported that compared with that of normal mice, transcriptional factor PU.1 in adipose tissue of obese mice was up-regulated, which subsequently triggered the transcription of NADPH oxidase gene [33]. On the other hand, obesity is also characterized by chronic or low-grade systemic inflammation regarding excessive accumulation of ROS in adipose tissue, which leads to increase in urinary 8-OHdG excretion [17,34]. Weisberg et al. found that 30% of the 100 most significantly encoded genes for proteins, exhibited characteristics of macrophages and positively related to body mass [35]. Accumulative evidence indicates that inflammatory cells (such as macrophages and lymphocytes) not only catalyze the production of nitric oxide from

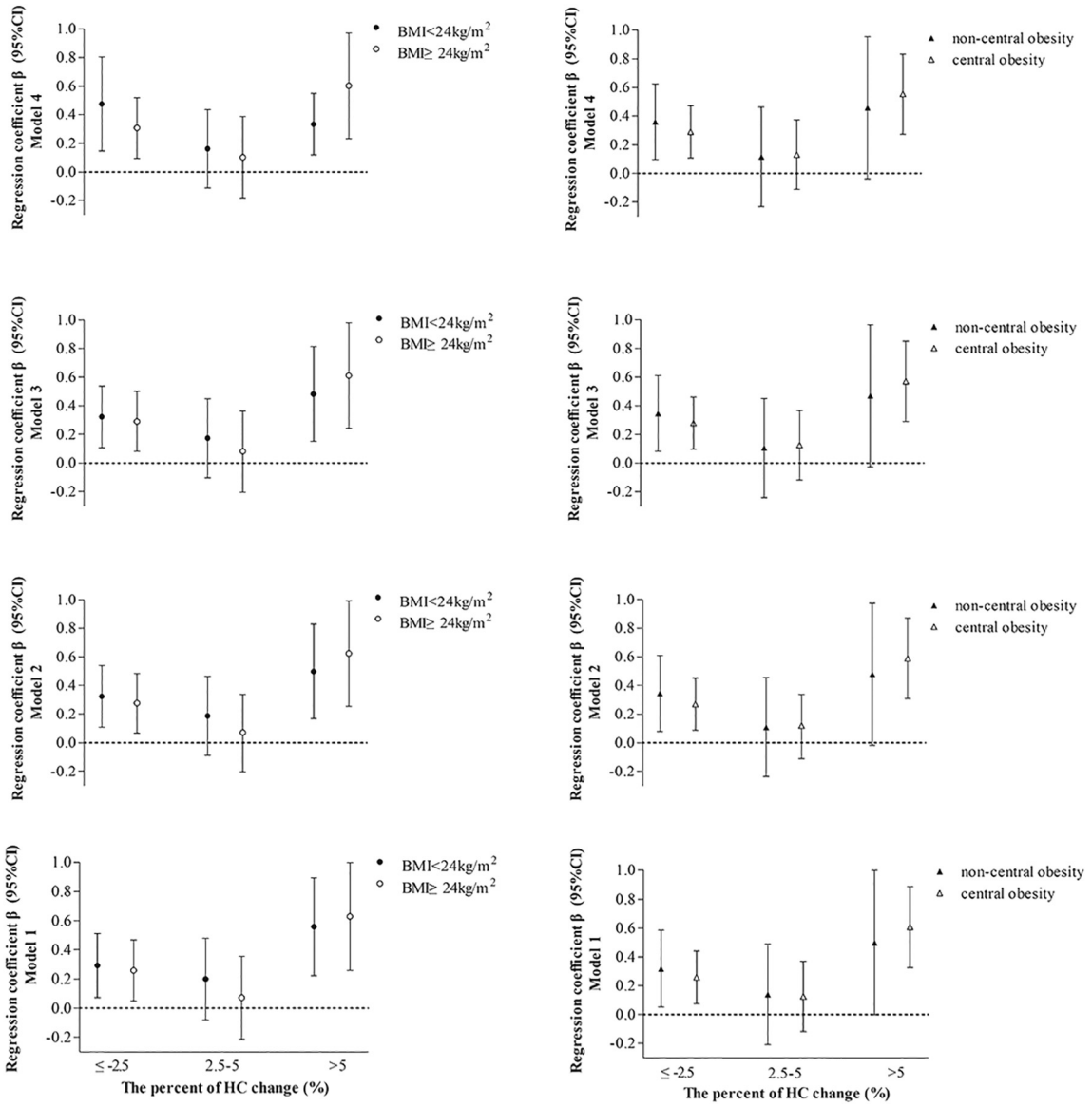

Fig. 3. Regression coefficients of change in urinary 8-OHdG by percent hip circumference (HC) gain from baseline to 3-year follow-up. Generalized linear models were used to evaluate the association of change in HC with higher risk of urinary 8-OHdG levels. The percent (−2.5 to 2.5%) of change in HC was chosen as a referent. Model 1: Adjusted for age and gender at baseline. Model 2: Adjusted for variables in model 1 plus education level, active smoking, passive smoking, alcohol consumption, physical activity. Model 3: Adjusted for variables in model 2 + intake frequency of each food type (meat, dairy and eggs, fishery product and smoked food). Model 4: Adjusted for variables in model 3 + daytime nap duration, nocturnal sleep duration, sleep quality. **Abbreviations:** BMI, body mass index; WHR, waist-to-hip ratio; CI, confidence interval; 8-OHdG, 8-hydroxydeoxyguanosine.

L-arginine but also induce NADPH oxidase and release xanthine oxidase to produce more superoxides, leading to increased urinary 8-OHdG levels. Additionally, adipose tissue may up-regulate expression of pro-inflammatory proteins, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP), and may be followed by the stimulated aggregation and proliferation of cells and ROS generation [36–39].

Interestingly, we observed a link between loss in HC value and increased urinary 8-OHdG levels. A longitudinal study also reported the association of leanness with increased urinary 8-OHdG levels among 677 subjects aged 20–67 years, which is supported by the reports on the negative association between urinary 8-OHdG levels and body weight [40,41]. Oxidative DNA damage may link to weight loss, which may relate to ROS production. Moreover, weight loss may be induced by an increase in energy expenditure or metabolic rate, which may promote ROS production in the mitochondrial cells [42]. Mizoue et al. found that leanness among the smokers had increased urinary 8-OHdG levels, indicating that body leanness may be involved in the association between smoking exposure and urinary 8-OHdG levels, which may be a marker of host susceptibility to smoking-related diseases [38]. However, the mechanisms underlying the association of HC loss and higher risk of urinary 8-OHdG levels need to be further investigated.

Long nocturnal sleep duration and physical inactivity may be risk factors for central obesity, due to their effects on increased urinary 8-OHdG levels. Because exercise can reduce size of adipocytes, attenuate the up-regulation of NADPH oxidase and down-regulation of Mn-SOD proteins [43]. Moreover, the down-regulations of inflammation-related adipokines (such as plasminogen activator inhibitor 1) are found to be related to the reduction of oxidative stress. Roberto et al. reported that physically active adults had lower sNox2-dp levels, one of the most important enzymes for ROS production [44]. Animal studies showed that rats in the exercise train group had lower TNF-α and MCP-1 levels [45]. Moreover, long nocturnal sleep duration showed a link to increased ROS, which may enhance inflammatory response in the body. The Clevel and Family Study revealed that nocturnal

Table 3
Regression coefficients of change in urinary 8-OHdG by central obesity at baseline and 3-year follow-up.

Central obesity at baseline	Central obesity at follow-up	Regression coefficient β (95% CI)			
		Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
All					
No	No	Ref	Ref	Ref	Ref
Yes	No	0.12 (−0.09, 0.33)	0.13 (−0.08, 0.34)	0.14 (−0.07, 0.35)	0.13 (−0.01, 0.34)
No	Yes	0.22 (0.00, 0.45)	0.23 (0.00, 0.45)	0.23 (0.004, 0.46)*	0.17 (0.01, 0.33)*
Yes	Yes	0.18 (0.02, 0.45)*	0.16 (0.00, 0.32)	0.16 (0.00, 0.32)	0.23 (0.01, 0.46)*
Male					
No	No	Ref	Ref	Ref	Ref
Yes	No	0.18 (−0.24, 0.62)	0.16 (−0.27, 0.59)	0.16 (−0.27, 0.59)	0.26 (−0.04, 0.56)
No	Yes	0.23 (−0.07, 0.54)	0.25 (−0.05, 0.56)	0.26 (−0.04, 0.57)	0.30 (0.06, 0.55)*
Yes	Yes	0.28 (0.03, 0.54)*	0.27 (0.02, 0.53)*	0.27 (0.02, 0.53)*	0.46 (0.16, 0.75)*
Female					
No	No	Ref	Ref	Ref	Ref
Yes	No	0.07 (−0.18, 0.32)	0.08 (−0.17, 0.33)	0.09 (−0.16, 0.35)	0.09 (−0.12, 0.27)
No	Yes	0.22 (−0.13, 0.56)	0.20 (−0.15, 0.55)	0.21 (−0.14, 0.56)	0.09 (−0.16, 0.34)
Yes	Yes	0.10 (−0.11, 0.31)	0.08 (−0.14, 0.29)	0.08 (−0.13, 0.30)	0.21 (−0.14, 0.56)

Abbreviations: 8-OHdG, 8-hydroxydeoxyguanosine; CI, confidence interval.
[a] Adjusted for age and sex at baseline.
[b] Adjusted for variables in model 1 plus education level, active smoking, passive smoking, alcohol consumption, physical activity.
[c] Adjusted for variables in model 2 plus intake frequency of each food type (meat, dairy and eggs, fishery product and smoked food).
[d] Adjusted for variables in model 3 plus daytime nap duration, nocturnal sleep duration, sleep quality.
* $P < 0.05$.

sleep duration increased serum CRP and IL-6 levels, individuals with long nocturnal sleep duration were engaged in less physical activity or reduced energy expenditure, which may increase risk for central obesity and followed by ROS generation [46]. In additional, individuals with too long nocturnal sleep duration may have potential health problems without other symptoms.

This study had several limitations. First, the participants from a country may not be a representative sample of the multiethnic. Second, self-reported smoking and drinking status may lead to inevitable of measurement errors. Third, information obtained through questionnaires on dietary intake habits and physical activity may be bias (like recall bias). Fourth, as several factors (including ethnic differences, blood biochemical indicators and blood pressure and measuring methods of 8-OHdG levels) affecting 8-OHdG levels, the results need to be further confirmed in a larger population.

5. Conclusions

We found a significant dose-dependent association of HC gain with urinary 8-OHdG levels, and central obese men at both baseline and 3-year follow-up had increased urinary 8-OHdG levels, indicating that HC gain might serve as a marker for the development of obesity-related health risk in relation to the consequence of excessive ROS generation. Measures of adiposity indices should be regularly taken to maintain a healthy HC size and reduce the risk of obesity-related diseases.

Author Contributions

Jing Yuan and Chen Hu designed the experiments and contributed to revisions of the manuscript; Chen Hu and Guiyang Wang measured urinary 8-OHdG levels; Chen Hu and Yun Zhou collected data; Wenjun Yin, Jian Hou and Xian Wang contributed to data analysis and interpreted data; Chen Hu prepared the manuscript draft; Jing Yuan and Weihong Chen supervised the project. All authors meticulously reviewed the final version of manuscript.

Conflicts of Interest

We declare that we have no conflicts of interest.

Funding

This work was supported by funds from the Public Sector Program of National Environmental Protection of the People's Republic of China (No. 201409081), the Key Project of the National Natural Science Foundation of China (No.91543207) and the National Key Research and Development Plan of China (No.2016YFC1303903).

Acknowledgements

The authors are grateful to all subjects in the study.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2018.11.015.

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