ORIGINAL RESEARCH

Different Weight Histories and Risk of Incident Coronary Heart Disease and Stroke: Tehran Lipid and Glucose Study

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***Background*—**This study aimed to determine the association between different weight histories, including cumulative excess weight, cumulative excess waist circumference (WC), duration of general and central adiposity, current and maximum body mass index, and current and maximum WC, and incident coronary heart disease (CHD) and stroke.

***Methods and Results*—**The study population consisted of 4398 adults aged ≥40 years without CHD or stroke at baseline. Associations between different weight histories and CHD and stroke were determined by multivariable time-varying Cox regression models after adjustment for age, sex, and time-varying confounders. Further adjustment was also done for mediators (eg, diabetes mellitus, hypercholesterolemia, and hypertension). During median follow-up of 13.9 years, 718 incident CHD and 158 stroke events were documented. Multivariable adjusted hazard ratios (HRs) were calculated in the sex and confounder adjusted model for CHD per 1-SD increase in cumulative excess weight (HR: 1.02; 95% confidence interval [CI], 0.96–1.07), cumulative excess WC (HR: 1.14; 95% CI, 1.04–1.24), duration of general adiposity (HR: 1.00; 95% CI, 0.92–1.08), duration of central adiposity (HR: 1.01; 95% CI, 0.93–1.09), current body mass index (HR: 1.03; 95% CI, 0.99–1.07), current WC (HR: 1.21; 95% CI, 1.11–1.32), maximum body mass index (HR: 1.01; 95% CI, 0.95–1.07), and maximum WC (HR: 1.17; 95% CI, 1.07–1.28). After further adjustment for mediators, current and maximum WC still showed a significant risk (HR: 1.13 [95% CI, 1.03–1.23] and 1.09 [95% CI, 1.00–1.20], respectively). Moreover, in the sex and confounder adjusted model, cumulative excess WC and maximum WC were associated with higher risk of stroke (hazard ratio: 1.21 [95% CI, 0.99–1.48] and 1.25 [95% CI, 1.02–1.55], respectively).

***Conclusions*—**Exposure to cumulative excess weight and cumulative excess WC confers little additional risk beyond their current and maximum values. Even current and maximum WC were associated with incident CHD in the presence of obesity mediators, and the latter was a significant predictor of stroke in the presence of confounders. **(*J Am Heart Assoc*. 2018;7:e006924. DOI: 10.1161/JAHA.117.006924.)**

Key Words: body mass index • coronary heart disease • stroke • waist circumference

Obesity is reaching epidemic proportions in both developed and developing countries,[1] with a steep ascending trend for both central and general obesity among Iranian populations.[2] A recent systematic review indicated the prevalence of obesity in a Middle Eastern adult population to be >50%.[3] Overweight status and obesity are associated with increased risk of cardiovascular disease (CVD), especially coronary heart disease (CHD) and stroke, with the major effects through metabolic mediators such as hypertension, diabetes mellitus, and hypercholesterolemia.[4]

Most studies addressing the link between obesity and incident CHD and stroke are based on a 1-time point assessment of body mass index (BMI) and waist circumference (WC), and evidence of the cumulative effects of being overweight and obese during later stages of life on these outcomes remains scarce. BMI and WC above the normal

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Accompanying Tables S1 through S13 are available at http://jaha.ahajournals.org/content/7/4/e006924/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In this study, during 13.9 years of follow-up, exposure to cumulative excess weight or cumulative excess waist circumference (considering both duration and degree of adiposity) and duration of general and central adiposity (measures of the adiposity duration alone) conferred little additional risk beyond current and maximum values of body mass index and waist circumference for the development of coronary heart disease and stroke events.
- Current and maximum waist circumferences contribute independently to the development of incident coronary heart disease in the presence of time-varying obesity mediators including diabetes mellitus, hypercholesterolemia, and hypertension.
- Maximum waist circumference is a significant predictor of stroke in the presence of time-varying confounders including smoking status, education, and low physical activity.

What Are the Clinical Implications?

- We should pay more attention to weight loss strategies, especially focusing on central adiposity, at any time point to prevent or at least delay the development of coronary heart disease and stroke events.

range over time could be calculated to obtain cumulative excess weight (CEW) and cumulative excess WC (CEWC) scores, which show accumulation of weight and WC over years, respectively, and might have some effects, independent of their current values.[5] Some studies with different approaches—some considering only duration, others taking both degree and duration of overweight status or obesity into consideration—conducted in a US population show that the duration of abdominal and general adiposity are associated with increased likelihood of subclinical atherosclerosis, CVD, CHD, stroke, and mortality. Nevertheless, the extent to which their effects on cardiovascular outcomes are independent of baseline or current values and metabolic mediators is not yet clearly understood.[6–9] Moreover, the association between maximum BMI and mortality has been addressed in some prior studies, indicating that using maximum BMI might reverse the paradoxical association between being overweight or obese and mortality and is a better predictor of mortality than current BMI.[10–12] To the best of our knowledge, however, the association between maximum BMI or WC and CVD, especially CHD and stroke, has not previously examined.

Considering the high prevalence and incidence of obesity and CVD among Middle Eastern populations,[13,14] this study was conducted to investigate the effect of different weight histories—including current and maximum BMI, current and maximum WC, duration of general and central adiposity, and cumulative excess BMI and WC, considering both duration and degree of overweight status or obesity—on CHD and stroke events among Iranian adults in the population-based cohort of the TLGS (Tehran Lipid and Glucose Study).

Methods

Transparency and Reproducibility

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Participants

The TLGS is a prospective longitudinal population-based study being performed on a representative sample from Tehran, the capital city of Iran. The aim of the study was to determine the prevalence of noncommunicable disease risk factors. TLGS recruitment was conducted in 2 phases, the first from January 31, 1999, to July 3, 2001, and the second from October 20, 2002, to September 22, 2005. Data collection is ongoing and planned to continue for at least 20 years according to the triennial design (third phase, 2005–2008; fourth phase, 2009–2011; and fifth phase, 2012–2015, with an average of 73% of participants available during each phase). The design and enrollment of the TLGS cohort has been described previously.[15]

Of a total of 6308 participants aged ≥40 years (5303 individuals from phase 1 and 1005 new participants from phase 2), we excluded those who had prevalent CHD, congestive heart failure (CHF), and stroke (n=571); who did not have any follow-up (n=1024) or any BMI or WC measurements at baseline or during follow up (n=40); and those who had missing data on covariates including smoking, education, physical activity, systolic and diastolic blood pressure, fasting plasma glucose (FPG), 2-hour postchallenge plasma glucose (2 h-PCPG), and cholesterol at baseline and follow-up (n=275). Data for 4398 participants who were followed until March 20, 2014, remained for our analysis. The medical ethics committee of the Research Institute for Endocrine Sciences approved the study proposal, and written informed consent was obtained from all participants.

Anthropometrics and Laboratory Measurements

A trained nurse interviewed participants with a pretested questionnaire. Information on demographic data, personal and familial history of CHD and stroke, medical and drug history, level of education, physical activity, and smoking habits was obtained. Details of anthropometric measures including height, weight, and WC have been reported elsewhere.[15] BMI was measured as weight (kg) divided by the square of height (m^2).

Blood pressure was taken twice after a 15-minute rest in a sitting position, using a standardized mercury sphygmomanometer on the right arm; the mean of 2 measurements was considered to be each participant's blood pressure.

A venous blood sample was drawn from all study participants after 12 to 14 hours of overnight fasting. All blood samples were taken between 7 and 9 AM and analyzed at the TLGS research laboratory the same day; 2 h-PCPG with 75 g glucose was performed for all adult participants who were not on any glucose-lowering medication; FPG and 2 h-PCPG were measured by the enzymatic colorimetric method, using glucose oxidase, and their inter- and intra-assay coefficients of variation at baseline and follow-up phases were <2.3% and 2.3%, respectively. Total cholesterol was assayed using the enzymatic colorimetric method with cholesterol esterase and cholesterol oxidase, and both inter- and intra-assay coefficients of variation at baseline and follow-up phases were 1.9%. Analyses were carried out using related kits and a Selectra 2 autoanalyzer (Vital Scientific).

Physical activity level was assessed with the Lipid Research Clinics questionnaire in the first phase of the TLGS. Because of the inexactness of the questionnaire, it was replaced starting in the second phase by the Modifiable Activity Questionnaire, which measures all 3 forms of activities including leisure time, job, and household activities in the previous year.[15]

Definition of Terms

Participants were classified as having type 2 diabetes mellitus if they had one of the following criteria: FPG ≥7 mmol/L (126 mg/dL), 2 h-PCPG ≥11.1 mmol/L (200 mg/dL), or taking antidiabetic medications. High total cholesterol was defined as total cholesterol level ≥5.1 mmol/L (200 mg/dL) or using lipid-lowering drugs. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive drug treatment. Education status was stratified as *illiterate/primary school, below diploma/diploma*, and *higher than diploma*. Smoking status included current or occasional smokers, former smokers (those who used to smoke), and never smokers. Low physical activity was defined as individuals participating in physical activity <3 d/wk for participants recruited in first phase or <600 metabolic equivalent task–minutes per week[16] for those who entered in the second phase. Maximum BMI or WC was defined as the maximum value of BMI or WC measurements documented at examinations 1 through 5.

CEW and CEWC Calculation

We examined participants at 5 visits. Briefly, the differences between the BMI value and its normal reference (25 kg/m^2) and WC value from 95 cm[17] were calculated for all 5 visits until the incidence of CHD or stroke or the end of follow-up. For visits 2 through 5, we calculated time-weighted average of excess BMI or WC by averaging the differences obtained from the current and previous visits and subsequently multiplying the result by the time (years) between those visits. To calculate the CEW and CEWC scores for each visit, we summed all prior time-weighted averages of excess BMI or WC (Table S1). The CEW and CEWC scores represent the accumulation of BMI and WC deviations, respectively, from normal values during the follow-up period (kg/m^2×y and cm×y, respectively).

Duration of General and Central Adiposity

As reported in the Framingham Heart Study,[18] we computed general adiposity duration using BMI values over ≈14-year follow-up from examinations 1 to 5. General adiposity was defined as being overweight or obese (BMI ≥25 kg/m^2). If someone had general adiposity based on assessment of at least 2 consecutive phases, the adiposity duration was the time from the first visit when BMI was ≥25 kg/m^2 to the last consecutive visit when BMI was ≥25 kg/m^2. Overall duration of general adiposity was the accumulation of the entire duration of having general adiposity between examinations 1 and 5 (Table S2). The same procedure was used to calculate central adiposity (WC ≥95 cm) duration.

Definition of Outcome

Cardiovascular outcomes have been published elsewhere in more detail.[19] In the current study, CHD was defined as cases of definite myocardial infarction diagnosed by ECG and biomarkers, probable myocardial infarction (positive ECG findings plus cardiac symptoms or signs but biomarkers showing negative or equivocal results), unstable angina pectoris (new cardiac symptoms or changing symptom patterns and positive ECG findings with normal biomarkers), angiographic-proven CHD, and CHD death.

The definition of CHF was based on echocardiographic findings among hospitalized patients because data regarding physical examination of patients were not completely mentioned in the hospital records. In our study, patients with systolic heart failure (left ventricular ejection fraction ≤40%)[20] were considered to have CHF. Moreover, definite stroke was defined using the World Health Organization's definition—"rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting >24 hours or leading to death with no apparent cause other than that of vascular origin"[21]—or imaging suggestive of stroke in cases of acute clinically relevant brain injuries accompanied by rapidly vanishing symptoms. A possible stroke was considered to be any acute neurologic deficit with no imaging assessment indicative of stroke or with data that were

not fully consistent with the World Health Organization's definition for definite stroke.[22] When symptoms resolved within 24 hours, cases were labeled *transient ischemic attack*. Stroke was defined as all cases of definite or possible stroke or transient ischemic attack.

Statistical Analyses

Mean (SD) and frequency (percentage) were presented for continuous and categorical variables, respectively, of baseline characteristics. Furthermore, the follow-up time for the study participants was presented as median and interquartile range. Baseline characteristics were compared between sexes using the Student *t* test and the χ^2 test for continuous and categorical variables, respectively.

Exposure information was updated about every 3 years, for which prospective time-varying multivariable Cox proportional hazards models were used to evaluate associations between one standard deviation (1-SD) change of CEW, CEWC, current and maximum BMI and WC levels as well as general and central adiposity duration and incident CHD, CHF and stroke events.

These associations were evaluated in 3 models. Model 1 included sex (for total sample) and age. Model 2 was further adjusted for potential time-varying confounders including smoking status (never smoker as reference), education (illiterate/primary school as reference), and low physical activity of each phase. The third model was additionally adjusted for time-varying obesity mediators including hypertension, diabetes mellitus, and hypercholesterolemia.

Follow-up duration for CHD participants were considered as the time between entrance to the study and the end of follow-up. Censored data were defined as subjects with loss to follow-up, death due to non-CHD cause, or not having a CHD event until March 20, 2014 (end of study), whichever occurred earlier; a similar approach was applied for incident stroke and CHF events.

Interactions between sex and main exposures were checked by the log–likelihood ratio test in multivariate analysis; generally, no significant interactions were found (all $P>0.1$); therefore, analysis was performed in a pooled sample. However, to compare our findings with those of other studies in this field, we also performed a sex-stratified analysis of CHD and stroke events. Considering the limited number of CHF events, the analysis was performed only in the age-, sex-, and confounder-adjusted model to increase the study power. Moreover, CEW, CEWC, current BMI, and current WC were categorized into quartiles, and association of different quartiles with CHD and stroke were examined.

Sensitivity Analysis

A sensitivity analysis was performed to examine whether the association between current BMI, current WC, CEW, or CEWC and the risk of CHD and stroke might be influenced by missing data at baseline and follow-up measurements. Considering missing covariate features in the long data set (numbers of person-observations for CHD and stroke events were 11 278 and 13 787, respectively, in the complete data set and 14 687 and 17 234, respectively, in the imputed data set) including model-based covariates, we used multivariate imputation (M=30) based on the MICE (multiple imputation by chained equations) method to handle missing values based on a collection of imputation models, at least 1 for each missing variable.[23] Simple random sampling with replacement from the observed value was used to fill all missing values. The important feature of using MICE for our imputation was its ability to handle different types of variables simultaneously. Linear regression for continuous covariates, logistic regression for binary covariates, and multivariate logistic regression for ordinal or uncorrelated categorical variables were chosen for this study. All M estimation coefficients were combined into 1 overall estimation using Rubin's Rule.[24] Because our analyses were based on proportional hazards regression models, in addition to using the relevant covariates in multiple imputation processing, we also considered CHD and stroke events, time, and logarithm of time with an appropriate functional form of cumulative hazards function. For those participants for whom the event had occurred, the imputation was done until the time of the event; therefore, an analysis was performed on an imputed file with no missing values for BMI, WC, or other covariates in any examinations. Statistical analyses were performed using Stata version 12.0 (StataCorp).

Results

Baseline characteristics of participants by sex are shown in Table 1. Mean age at baseline was 54.6 years (SD: 10.2) for men and 52.5 years (SD: 8.8) for women. There were significant differences in baseline characteristics between men and women, except for low physical activity level and diabetes mellitus status. Compared with men, women had higher values for BMI, WC, systolic and diastolic blood pressure, FPG, 2 h-PCPG, and total cholesterol but had lower rates of smoking and were less educated.

During the median follow-up time of 13.9 years (interquartile range: 9.78–14.47 years), CHD was observed in 410 men and 308 women; the corresponding incidence rates were 16.8 (95% confidence interval [CI], 15.2–18.4) and 9.8 (95% CI, 8.7–10.9) per 1000 person-years, respectively. Moreover, during follow-up, 90 men and 68 women had stroke events; the corresponding incidence rates were 3.4 (95% CI, 2.7–4.2) and 2.0 (95% CI, 1.6–2.6) per 1000 person-years. We also found 50 CHF events among

Table 1. Baseline Characteristics of the Study Population: TLGS, 1999–2014

	Men (n=1978)	Women (n=2420)	Total (N=4398)	*P* Value
Age, y	54.6±10.2	52.5±8.8	53.5±9.5	<0.001
BMI, kg/m^2	26.3±3.9	29.2±4.4	27.8±4.4	<0.001
WC, cm	91.8±10.7	93.3±11.3	92.6±11.1	<0.001
SBP, mm Hg	124.8±19.9	126.6±21.0	125.8±20.5	0.003
DBP, mm Hg	79.3±11.5	80.7±11.0	80.1±11.3	<0.001
FPG, mmol/L	5.7±2.0	5.9±2.3	5.9±2.2	0.008
2 h-PCPG, mmol/L	7.0±3.7	7.4±3.3	7.2±3.5	<0.001
Total cholesterol, mmol/L	5.36±1.0	5.9±1.2	5.6±1.2	<0.001
Smoking status, n (%)				<0.001
Never	1067 (53.9)	2248 (92.9)	3315 (75.4)	
Former	354 (17.9)	72 (2.98)	426 (9.7)	
Current	557 (28.2)	100 (4.1)	657 (14.9)	
Education, n (%)				
Illiterate/primary school	842 (42.6)	1603 (66.2)	2445 (55.6)	<0.001
Below diploma/diploma	821 (41.5)	708 (29.3)	1529 (34.8)	
Higher than diploma	315 (15.9)	109 (4.5)	424 (9.6)	
Low physical activity, n (%)	1414 (71.5)	1706 (70.5)	3120 (70.9)	0.54
Hypertension, n (%)	585 (29.6)	885 (36.6)	1470 (33.4)	<0.001
Diabetes mellitus, n (%)	389 (19.7)	541 (22.4)	930 (21.1)	0.10
Hypercholesterolemia, n (%)	1184 (59.9)	1807 (74.7)	2991 (68.0)	<0.001

Values are shown as mean±SD and number (percentage) for continuous and categorical variables, respectively. 2 h-PCPG indicates 2-h postchallenge plasma glucose; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; SBP, systolic blood pressure; TLGS, Tehran Lipid and Glucose Study; WC, waist circumference.

the total sample, with an incidence rate of 0.83 (95% CI, 0.63–1.1) per 1000 person-years.

Table 2 shows the adjusted hazard ratios (HRs) and 95% CIs in 3 models for CHD based on CEW, CEWC, and general and central adiposity durations. Throughout the study, following adjustment for age (model 1), the HR for every 1-SD increase in CEW among men was 1.20 (95% CI, 1.03–1.41). After further adjustment for time-varying confounders and mediators, the risk reached null. Moreover, we found no significant association between CEW and CHD among women or the total sample. In addition, HRs for CHD by CEWC among men in models 1 and 2 were 1.19 (95% CI, 1.07–1.33) and 1.17 (95% CI, 1.05–1.32), respectively; similar significant risks were found for these models among the total sample, whereas no significant risk was seen in the mediator-adjusted model. We also found no significant association between CEWC and CHD among women. According to our data analysis, no association was found between duration of general or central adiposity and CHD events in any of the models.

Table 3 illustrates the adjusted HRs (95% CIs) of every 1-SD increase in current and maximum BMI and WC for CHD events in the 3 models. The association of current BMI with CHD was stronger among men, and each 1-SD increase was associated with 20% and 19% higher risk of CHD after adjustment for age and confounders, respectively. Furthermore, after considering mediators, the risk decreased to 11% (HR: 1.11; 95% CI, 0.99–1.24; *P*=0.062), whereas no association was seen among women. In addition, among the total sample, each 1-SD increase in current BMI was associated with a 3% higher risk of CHD in model 1. Considering current WC, each 1-SD increase resulted in 28%, 28%, and 19% greater risk of CHD among men after adjusting for covariates in models 1, 2, and 3, respectively; the corresponding risk among total sample was 23%, 21%, and 13%, respectively (all *P*<0.05). Among women, each 1-SD increase in current WC was associated with 16% greater risk only in the age-adjusted model (HR: 1.16, 95% CI, 1.03–1.30). Moreover, as shown in Table 3, regarding maximum BMI, among men, HRs for each 1-SD increase after adjustment for age (model 1) and time-varying confounders (model 2) were 1.16 (95% CI, 1.06–1.28) and 1.15 (95% CI, 1.04–1.28), respectively; we found no significant association between maximum BMI and CHD among women and total sample. Focusing on maximum WC,

Table 2. Risk of CHD Based on 1-SD Change of CEW, CEWC, and General and Central Adiposity Duration: TLGS, 1999–2014*

	Men (Person-Observations=4791)		Women (Person-Observations=6487)		Total sample (Person-Observations=11 278)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
CEW						
Model I†	1.20 (1.03–1.41)	0.02	0.99 (0.92–1.08)	0.90	1.02 (0.97–1.07)	0.33
Model 2‡	1.18 (0.99–1.40)	0.06	0.99 (0.90–1.08)	0.80	1.02 (0.96–1.07)	0.50
Model 3§	1.09 (0.91–1.30)	0.37	0.98 (0.87–1.10)	0.71	1.00 (0.92–1.08)	0.92
CEWC						
Model 1†	1.19 (1.07–1.33)	0.001	1.09 (0.97–1.22)	0.13	1.15 (1.06–1.24)	<0.001
Model 2‡	1.17 (1.05–1.32)	0.007	1.07 (0.94–1.22)	0.28	1.14 (1.04–1.24)	0.003
Model 3§	1.11 (0.98–1.25)	0.096	1.00 (0.87–1.15)	0.98	1.06 (0.97–1.16)	0.21
General adiposity duration						
Model 1†	1.00 (0.90–1.1)	0.98	0.94 (0.85–1.06)	0.27	0.98 (0.91–1.05)	0.52
Model 2‡	1.00 (0.89–1.12)	0.96	0.96 (0.86–1.08)	0.55	1.00 (0.92–1.08)	0.87
Model 3§	0.97 (0.87–1.09)	0.61	0.97 (0.87–1.09)	0.65	0.97 (0.90–1.05)	0.49
Central adiposity duration						
Model 1†	1.01 (0.92–1.11)	0.76	0.97 (0.87–1.07)	0.52	1.00 (0.93–1.07)	0.91
Model 2‡	1.02 (0.92–1.13)	0.73	0.98 (0.87–1.10)	0.72	1.01 (0.93–1.09)	0.85
Model 3§	0.98 (0.90–1.09)	0.78	0.95 (0.85–1.07)	0.44	0.97 (0.90–1.05)	0.48

General and central adiposity are defined as BMI ≥25 kg/m^2 and WC ≥95 cm, respectively. BMI indicates body mass index; CEW, cumulative excess weight; CEWC, cumulative excess waist circumference; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; TLGS, Tehran Lipid and Glucose Study; WC, waist circumference.

*1-SD changes among men, women, and total sample, respectively: CEW: 11.1, 20.2, and 17.4 kg/m^2×y; CEWC: 29.0, 30.9, and 30.1 cm×y (eg, comparing 2 men with 10 years of follow-up, the one who lived with a mean BMI of 1.1 higher and WC 2.9 cm greater during this time period would have 18% and 17% higher hazard, respectively, for CHD); duration of general adiposity: 4.0, 3.7, and 4.1 y; duration of central adiposity: 3.32, 3.3, and 3.34 y.

†Model 1: Age, sex (for total sample).

‡Model 2: model 1 plus smoking, education, and low physical activity at each phase.

§Model 3: model 2 plus hypertension, diabetes mellitus, and hypercholesterolemia at each phase.

each 1-SD increase among men, resulted in 23% and 15% greater risk of CHD after adjusting for covariates in models 2 and 3, respectively; the corresponding risks among total sample were 17% and 9%, respectively (the latter risk being marginally significant; *P*=0.06).

Adjusted HRs (95% CIs) of stroke events for every 1-SD increase in CEW, CEWC, general and central adiposity duration, and current and maximum BMI and WC in the 3 models for men, for women, and total sample are shown in Tables 4 and 5. Among all exposures, after considering time-varying confounders in the sex-adjusted model, CEWC and maximum WC were associated with stroke events (HR: 1.21 [95% CI, 0.99–1.48] and 1.25 [95% CI, 1.02–1.55], respectively), whereas after stratifying the results by sex, no significant association in the confounder-adjusted model was seen for any exposure in either sex.

Regarding incident CHF, no significant associations were found between main exposures and events, considering the limited number of events in our study period (Table S3).

The associations between quartiles of CEW, CEWC, current BMI, and current WC and CHD events are presented in Tables S4 through S7. In the presence of confounders generally, all mentioned exposures in this categorical analysis showed a significant trend among men and total sample. Moreover, in the presence of mediators, this trend among men remained statistically significant for quartiles of CEWC and current WC and marginally significant for CEW and current BMI. In this categorical analysis among men, the HRs for the last quartile of CEW, CEWC, current BMI, and current WC compared with the first quartile in the mediator-adjusted model were 1.50 (95% CI, 1.04–2.16), 1.68 (95% CI, 1.15–2.46), 1.41 (95% CI, 0.99–2.01), and 1.46 (95% CI, 1.02–2.08), respectively. In contrast, no significant trend was seen among exposures in the categorical analysis and stroke events in either sex (Tables S8 through S11).

Results of the sensitivity analysis of imputed files for CHD, based on CEW and CEWC, current BMI, and current WC, are presented in Table S12. Results were generally in line with the complete data set except for the absence of any association between CEW and CHD among men and a significant risk of 9% and 8% for a 1-SD increase in CEWC in models 1 and 2, respectively, among women. Considering stroke events, in the

Table 3. Risk of CHD Based on 1-SD Change of Current and Maximum BMI and WC: TLGS, 1999–2014*

	Men (Person-Observations=4791)		Women (Person-Observations=6487)		Total sample (Person-Observations=11 278)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Current BMI						
Model 1†	1.20 (1.08–1.32)	<0.001	1.01 (0.94–1.09)	0.69	1.03 (1.00–1.07)	0.034
Model 2‡	1.19 (1.07–1.32)	0.001	1.00 (0.88–1.12)	0.96	1.03 (0.99–1.07)	0.11
Model 3§	1.11 (0.99–1.24)	0.062	0.96 (0.80–1.15)	0.64	1.01 (0.95–1.08)	0.67
Current WC						
Model 1†	1.28 (1.15–1.44)	<0.001	1.16 (1.03–1.30)	0.01	1.23 (1.13–1.33)	<0.001
Model 2‡	1.28 (1.14–1.44)	<0.001	1.12 (0.99–1.28)	0.08	1.21 (1.11–1.32)	<0.001
Model 3§	1.19 (1.05–1.35)	0.005	1.06 (0.92–1.21)	0.42	1.13 (1.03–1.23)	0.01
Maximum BMI						
Model 1†	1.16 (1.06–1.28)	0.002	0.98 (0.86–1.11)	0.76	1.01 (0.96–1.07)	0.56
Model 2‡	1.15 (1.04–1.28)	0.009	0.95 (0.76–1.18)	0.63	1.01 (0.95–1.07)	0.83
Model 3§	1.08 (0.96–1.21)	0.19	0.89 (0.64–1.26)	0.52	0.98 (0.88–1.09)	0.75
Maximum WC						
Model 1†	1.24 (1.12–1.38)	<0.001	1.12 (0.99–1.26)	0.06	1.19 (1.10–1.29)	<0.001
Model 2‡	1.23 (1.10–1.38)	<0.001	1.07 (0.94–1.23)	0.30	1.17 (1.07–1.28)	<0.001
Model 3§	1.15 (1.02–1.29)	0.021	1.02 (0.90–1.18)	0.575	1.09 (1.00–1.20)	0.06

BMI indicates body mass index; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; TLGS, Tehran Lipid and Glucose Study; WC, waist circumference.
*1-SD changes in men, women, and total sample, respectively: current BMI for each visit as time-varying exposure: 4.0, 7.4, and 6.4 kg/m^2; current WC for each visit as time-varying exposure: 10.7, 11.5, and 11.2 cm; maximum BMI: 9.9, 4.2, and 12.5 kg/m^2; maximum WC: 10.8, 10.4, and 10.9 cm (eg, comparing 2 men, the one who recently has BMI 4 higher and WC 10.7 cm greater would have 19% and 28% higher hazard, respectively, for CHD, or the one has maximum BMI 9.9 higher and WC 10.8 cm greater would have 15% and 23% higher hazard, respectively, for CHD).
†Model 1: age, sex (for total sample).
‡Model 2: model 1 plus smoking, education, and low physical activity at each phase.
§Model 3: model 2 plus hypertension, diabetes mellitus, and hypercholesterolemia at each phase.

imputed data set, a significant association of CEWC and current WC was found after adjustment for sex and time-varying confounders (HR: 1.19 [95% CI, 1.06–1.35] and 1.24 [95% CI, 1.06–1.45], respectively; Table S13).

Discussion

In the presence of confounders in this long-term population-based cohort of Middle Eastern adults, we found that each 1-SD increase in CEW and CEWC (as a measure of both duration and degree of general and central adiposity, respectively) was associated with 18% and 17% higher risk of CHD events, respectively, only among men; however, no association was found for duration of general and central adiposity per se. In addition, among men, the current and maximum values for both BMI and WC showed significant risk of incident CHD events in the presence of confounders; moreover, for current and maximum WC, each 1-SD increase was associated with 19% and 15% greater risk, respectively, even in the presence of important mediators (ie, hypertension, diabetes mellitus, and hypercholesterolemia). For stroke events in the total sample, CEWC and maximum WC showed 21% and 25% risk, respectively, in the confounder-adjusted model, with the risk being marginally significant for CEWC.

Effects of obesity on CHD and stroke are well known, and most evidence supporting this issue is based on baseline measurement of general or central adiposity in longitudinal studies.[4,25] However, some investigators emphasize not only the importance of excess body weight but also focus on duration of obesity (eg, analogous to the concept of pack-year for smoking versus current smoking status).[26]

To our knowledge, only 4 longitudinal studies, conducted with US populations and differing designs, have investigated the effects of cumulative excess adiposity on incident CVD.[6–9] However, comparing our findings with other studies might be difficult, considering the different designs and definitions of both degree and duration of obesity. The study conducted by Abdullah et al[8] using data from the Framingham cohort study showed that for every 2 additional years lived with obesity, a 4% higher risk of CVD mortality was seen in the fully adjusted model; this risk increased from 4% to 7% after adjustment for current BMI, a finding based on the fact that current BMI was

Table 4. Risk of Stroke Based on 1-SD Change of CEW, CEWC, and General and Central Adiposity Duration: TLGS, 1999–2014*

	Men (Person-Observations=6073)		Women (Person-Observations=7714)		Total sample (Person-Observations=13 787)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
CEW						
Model 1†	1.17 (0.94–1.46)	0.15	1.03 (0.96–1.10)	0.37	1.04 (0.98–1.10)	0.16
Model 2‡	1.09 (0.84–1.42)	0.50	1.02 (0.93–1.12)	0.69	1.03 (0.95–1.11)	0.51
Model 3§	0.94 (0.71–1.24)	0.67	1.03 (0.94–1.13)	0.54	1.03 (0.93–1.13)	0.60
CEWC						
Model 1†	1.23 (0.98–1.54)	0.07	1.38 (1.09–1.76)	0.008	1.31 (1.10–1.54)	0.002
Model 2‡	1.14 (0.88–1.49)	0.31	1.27 (0.95–1.70)	0.11	1.21 (0.99–1.48)	0.06
Model 3§	0.97 (0.74–1.30)	0.84	1.31 (0.96–1.78)	0.08	1.12 (0.91–1.39)	0.28
General adiposity duration						
Model 1†	0.90 (0.73–1.11)	0.34	1.13 (0.90–1.42)	0.29	1.00 (0.86–1.16)	0.99
Model 2‡	0.86 (0.66–1.11)	0.24	1.09 (0.84–1.40)	0.54	0.96 (0.80–1.16)	0.70
Model 3§	0.77 (0.59–1.01)	0.06	1.13 (0.86–1.48)	0.38	0.94 (0.78–1.13)	0.52
Central adiposity duration						
Model 1†	0.93 (0.77–1.14)	0.51	1.24 (1.03–1.51)	0.02	1.07 (0.94–1.23)	0.31
Model 2‡	0.87 (0.67–1.12)	0.28	1.20 (0.96–1.50)	0.11	1.02 (0.87–1.03)	0.77
Model 3§	0.78 (0.60–1.01)	0.06	1.23 (0.98–1.54)	0.08	0.98 (0.83–1.16)	0.85

General and central adiposity are defined as body mass index ≥25 kg/m^2 and waist circumference ≥95 cm, respectively. CEW indicates cumulative excess weight; CEWC, cumulative excess waist circumference; CI confidence interval; HR, hazard ratio; TLGS, Tehran Lipid and Glucose Study.

*1-SD change in men, women, and total sample, respectively: CEW: 11.1, 20.1, and 17.3 kg/m^2×y; CEWC: 29.0, 31.2, and 30.3 cm×y; duration of general adiposity: 4.0, 3.8, and 4.1 y; duration of central adiposity: 3.4, 3.4, and 3.4 y.

†Model 1: age, sex (for total sample).

‡Model 2: model 1 plus smoking, education, and low physical activity at each phase.

§Model 3: model 2 plus hypertension, diabetes mellitus, and hypercholesterolemia at each phase.

associated with lower risk of CVD mortality in their study (HR: 0.96; 95% CI, 0.95–0.98). In contrast, in our study, we found a significant positive association among men between current BMI (but not for duration of general adiposity) and incident CHD in the confounder-adjusted model. In another study,[7] Abdullah et al demonstrated that the level and number of years lived with general obesity (BMI ≥30) was associated with greater risk of CHD, stroke, and CHF. Each additional 10 "obese-years" for men and women was associated with 4% and 3%, respectively, higher risk of incident CHD; 6% and 2% greater risk of stroke; and 6% and 4% higher risk of CHF, after adjustment for potential confounders. Comparing goodness of fit of models containing current BMI versus duration of obesity or obese-years, Abdullah et al showed generally better model fitness for obese-years than other measurements for CVD outcome; however, the results were not consistent in the subgroups of CVD including CHD, stroke, and CHF events. Furthermore, in their study, they found a more significant association of obese-years in men compared with women. In the current study, regarding CHD events, both CEW and current BMI showed significant risk among men but not in women. Furthermore, after adjusting for time-varying mediators, each 1-SD increase in current BMI (≈4) showed a marginally significant risk of 11% among men. Considering stroke and CHF events, we did not show an association between CEW and current BMI overall.

Recent results from the CARDIA (Coronary Artery Risk Development in Young Adults) study[6] indicated that each additional year of overall and abdominal obesity was associated with 2% and 3%, respectively, higher risk of the presence of subclinical CHD, as measured by coronary artery calcification; risk was independent of the degree of adiposity. Furthermore, the authors emphasized that time-varying BMI and WC were associated with increased risk of coronary artery calcification even after adjustment for duration of overall and abdominal obesity. In our analysis, among the total sample in the confounder model, current WC and CEWC but not duration of central adiposity were associated with significant risk for CHD. Moreover, increasing levels of current WC in our study were associated with CHD events among men and total sample, even in the presence of obesity mediators. In another study, Reis et al,[9] using a different approach

Table 5. Risk of Stroke Based on 1-SD Change of Current and Maximum BMI and WC: TLGS, 1999–2014*

	Men (Person-Observations=6073)		Women (Person-Observations=7714)		Total sample (Person-Observations=13 787)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Current BMI						
Model 1†	1.13 (0.90–1.42)	0.29	1.04 (0.96–1.14)	0.32	1.03 (0.97–1.10)	0.25
Model 2‡	1.15 (0.88–1.49)	0.30	1.03 (0.87–1.22)	0.74	1.03 (0.94–1.12)	0.56
Model 3§	0.97 (0.74–1.29)	0.85	1.03 (0.90–1.21)	0.68	1.01 (0.87–1.18)	0.90
Current WC						
Model 1†	1.20 (0.94–1.52)	0.14	1.24 (0.94–1.64)	0.12	1.22 (1.02–1.46)	0.03
Model 2‡	1.21 (0.92–1.58)	0.17	1.08 (0.78–1.50)	0.62	1.15 (0.93–1.42)	0.19
Model 3§	1.01 (0.77–1.34)	0.92	1.07 (0.77–1.50)	0.68	1.04 (0.84–1.30)	0.69
Maximum BMI						
Model 1†	1.22 (0.99–1.50)	0.06	1.01 (0.92–1.11)	0.84	1.02 (0.95–1.10)	0.52
Model 2‡	1.17 (0.91–1.51)	0.22	1.00 (0.87–1.14)	0.95	1.01 (0.91–1.12)	0.83
Model 3§	1.01 (0.76–1.33)	0.97	1.00 (0.88–1.14)	0.99	1.00 (0.88–1.14)	0.95
Maximum WC						
Model 1†	1.30 (1.03–1.65)	0.02	1.30 (1.00–1.71)	0.05	1.30 (1.09–1.56)	0.003
Model 2‡	1.29 (0.97–1.70)	0.08	1.23 (0.90–1.70)	0.19	1.25 (1.02–1.55)	0.03
Model 3§	1.08 (0.81–1.44)	0.61	1.24 (0.90–1.71)	0.18	1.16 (0.94–1.44)	0.17

BMI indicates body mass index; CI, confidence interval; HR, hazard ratio; TLGS, Tehran Lipid and Glucose Study; WC, waist circumference.
*1-SD changes in men, women, and total sample, respectively: current BMI for each visit as time-varying exposure: 3.9, 7.3, and 6.3 kg/m^2; current WC for each visit as time-varying exposure: 11.2, 10.6, and 11.5 cm; maximum BMI: 9.7, 4.2, and 12.2 kg/m^2; maximum WC: 10.8, 10.3, and 11.0 cm.
†Model 1: age, sex (for total sample).
‡Model 2: model 1 plus smoking, education, and low physical activity at each phase.
§Model 3: model 2 plus hypertension, diabetes mellitus, and hypercholesterolemia at each phase.

considering degree and duration of overall and central adiposity, showed a significant trend for both excess BMI and WC years with risk of CHD and CHF events after adjustment for time-varying confounders. Similarly, in the sample from the TLGS population, a significant trend was found for both CEW and CEWC and CHD events. These trends remained significant among men, even after adjustment for time-varying mediators.

Regarding the importance of lifetime weight dynamics and mortality events, Mehta et al[27] showed that Finnish adults with a peak BMI in the obese category experienced higher mortality than those with peak BMI <25. Yu et al[10] also reported the importance of maximum BMI rather than its baseline value in prediction of mortality events in the pooled data of 3 prospective cohort studies. They found the paradoxical association between overweight and mortality events (HR: 0.96; 95% CI, 0.94–0.99) was reversed when maximum BMI was applied in this BMI category (HR: 1.06; 95% CI, 1.03–1.08); therefore, they concluded that the measurement of maximum BMI might be a useful tool to minimize reverse association bias applying a single BMI measurement. To the best of our knowledge, our study is the first to examine the impact of maximum BMI and WC on incident CHD and stroke. In contrast to the cited studies, we did not find any superiority of maximum BMI and WC over their current values in prediction of CHD; however, for stroke events, only the maximum level of WC—not its current value or central adiposity duration—showed significant risk in the confounder-adjusted model.

As for the strengths of our study, it is the first to be conducted among a non-US population with a high CVD burden.[28] Other strengths are the large sample size, direct measurement of different variables and outcomes other than self-reported data, repeated assessments of BMI and WC as well as potential confounding and intermediate factors, and verification and adjudication of CHD, stroke and CHF events. Nevertheless, there are some important limitations. First, the anthropometric measurements were assessed every 3 years, and it is possible that more frequent assessments could have yielded more accurate estimations. Second, the measurements of BMI and WC as well as other confounder and mediator variables were not complete for all study

participants; however, our results in the multiple imputed data set were generally in line with the complete data file. Third, our study was conducted on a sample of an Iranian population; further studies should be conducted to assess the applicability of our findings to other populations.

In conclusion, the current findings suggest that over 14 years of follow-up, with respect to CHD events, the exposure to cumulative excess general and central adiposity confers little additional risk beyond the current and maximum levels of general and abdominal adiposity. Even current and maximum WC values were associated with incident CHD in the presence of obesity mediators. Regarding stroke events, among different weight histories, we found that maximum WC and CEWC were predictors in the presence of important obesity confounders. Our findings suggest that public health interventions for CHD and stroke prevention should focus on weight-loss strategies at any time point to prevent or at least delay the development of events.

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Disclosures

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References

1. Lau DC, Douketis JD, Morrison KM, Hramiak IM, Sharma AM, Ur E. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. *CMAJ*. 2007;176:S1–S13.
2. Azizi F, Azadbakht L, Mirmiran P. Trends in overweight, obesity and central fat accumulation among Tehranian adults between 1998–1999 and 2001–2002: Tehran Lipid and Glucose Study. *Ann Nutr Metab*. 2005;49:3–8.
3. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384:766–781.
4. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants. *Lancet*. 2014;383:970–983.
5. Ortega FB, Lavie CJ, Blair SN. Obesity and cardiovascular disease. *Circ Res*. 2016;118:1752–1770.
6. Reis JP, Loria CM, Lewis CE, Powell-Wiley TM, Wei GS, Carr JJ, Terry JG, Liu K. Association between duration of overall and abdominal obesity beginning in young adulthood and coronary artery calcification in middle age. *JAMA*. 2013;310:280–288.
7. Abdullah A, Amin FA, Stoelwinder J, Tanamas SK, Wolfe R, Barendregt J, Peeters A. Estimating the risk of cardiovascular disease using an obese-years metric. *BMJ Open*. 2014;4:e005629.
8. Abdullah A, Wolfe R, Stoelwinder JU, de Courten M, Stevenson C, Walls HL, Peeters A. The number of years lived with obesity and the risk of all-cause and cause-specific mortality. *Int J Epidemiol*. 2011;40:985–996.
9. Reis JP, Allen N, Gunderson EP, Lee JM, Lewis CE, Loria CM, Powell-Wiley TM, Rana JS, Sidney S, Wei G, Yano Y, Liu K. Excess body mass index- and waist circumference-years and incident cardiovascular disease: the CARDIA study. *Obesity (Silver Spring)*. 2015;23:879–885.
10. Yu E, Ley SH, Manson JE, Willett W, Satija A, Hu FB, Stokes A. Weight history and all-cause and cause-specific mortality in three prospective cohort studies weight history and mortality in three prospective cohort studies. *Ann Intern Med*. 2017;166:613–620.
11. Stokes A, Preston SH. Revealing the burden of obesity using weight histories. *Proc Natl Acad Sci USA*. 2016;113:572–577.
12. Stokes A. Using maximum weight to redefine body mass index categories in studies of the mortality risks of obesity. *Popul Health Metr*. 2014;12:6.
13. Khalili D, Sheikholeslami FH, Bakhtiyari M, Azizi F, Momenan AA, Hadaegh F. The incidence of coronary heart disease and the population attributable fraction of its risk factors in Tehran: a 10-year population-based cohort study. *PLoS One*. 2014;9:e105804.
14. Hosseinpanah F, Mirbolouk M, Mossadeghkhah A, Barzin M, Serahati S, Delshad H, Azizi F. Incidence and potential risk factors of obesity among Tehranian adults. *Prev Med*. 2016;82:99–104.
15. Azizi F, Ghanbarian A, Momenan AA, Hadaegh F, Mirmiran P, Hedayati M, Mehrabi Y, Zahedi-Asl S, Tehran L; Glucose Study G. Prevention of non-communicable disease in a population in nutrition transition: Tehran Lipid and Glucose Study phase II. *Trials*. 2009;10:5.
16. Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ)—Short and Long Forms. Available at: https://www.researchgate.net/file.PostFileLoader.html?id=5641f4c36143250eac8b45b7&assetKey=AS%3A294237418606593%401447163075131. Published November 2005. Accessed January 28, 2018.
17. Hadaegh F, Zabetian A, Sarbakhsh P, Khalili D, James WP, Azizi F. Appropriate cutoff values of anthropometric variables to predict cardiovascular outcomes: 7.6 years follow-up in an Iranian population. *Int J Obes (Lond)*. 2009;33:1437–1445.
18. Abdullah A, Stoelwinder J, Shortreed S, Wolfe R, Stevenson C, Walls H, De Courten M, Peeters A. The duration of obesity and the risk of type 2 diabetes. *Public Health Nutr*. 2011;14:119–126.
19. Hadaegh F, Harati H, Ghanbarian A, Azizi F. Association of total cholesterol versus other serum lipid parameters with the short-term prediction of cardiovascular outcomes: Tehran Lipid and Glucose Study. *Eur J Cardiovasc Prev Rehabil*. 2006;13:571–577.
20. Fonarow GC, Abraham WT, Albert NM, Gattis WA, Gheorghiade M, Greenberg B, O'Connor CM, Yancy CW, Young J. Organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF): rationale and design. *Am Heart J*. 2004;148:43–51.
21. Goldstein M, Bolis C. *Cerebrovascular Disorders: A Clinical and Research Classification*. Geneva: World Health Organization; 1978.
22. Azarpazhooh M, Etemadi M, Donnan G, Mokhber N, Majdi M, Ghayour-mobarhan M, Ghandehary K, Farzadfard M, Kiani R, Panahandeh M. Excessive incidence of stroke in Iran: evidence from the Mashhad Stroke Incidence Study (MSIS), a population-based study of stroke. *Int J Stroke*. 2010;5:207.
23. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377–399.
24. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New Jersey: John Wiley & Sons; 2004.
25. Boloukat RR, Ramezankhani A, Hasheminia M, Tasdighi E, Azizi F, Hadaegh F. Impact of blood pressure, cholesterol and glucose in the association between

adiposity measures and coronary heart disease and stroke among Iranian population. *Clin Nutr*. 2017. Available at: http://www.clinicalnutritionjournal.com/article/S0261-5614(17)31355-9/fulltext. Accessed January 31, 2018.

26. Bouchard DR, Porneala B, Janssen I, Langlois MF, Baillargeon JP, Fox CS, Meigs JB, D'Agostino RB Sr, Pencina M, Hivert MF. Risk of type 2 diabetes and cumulative excess weight exposure in the Framingham Offspring Study. *J Diabetes Complications*. 2013;27:214–218.
27. Mehta NK, Stenholm S, Elo I, Aromaa A, Heliövaara M, Koskinen S. Weight histories and mortality among Finnish adults: the role of duration and peak BMI. *Epidemiology*. 2014;25:707.
28. Eslami A, Mozaffary A, Derakhshan A, Azizi F, Khalili D, Hadaegh F. Sex-specific incidence rates and risk factors of premature cardiovascular disease. A long term follow up of the Tehran Lipid and Glucose Study. *Int J Cardiol*. 2017;227:826–832.

SUPPLEMENTAL MATERIAL

Table S1. An example of Cumulative Excess Weight (CEW) and cumulative excess waist circumference (CEWC) calculation*

ID	visit	Time (y)	WC (cm)	BMI (kg/m^2)	1st CVD event	Time between visits T and T-1 (y)	Time-weighted average of excess BMI for visit T and T-1*	CEW (kg/m^2×years)	Time-weighted average of excess WC for visit T and T-1	CEWC (cm×years)
1	1	0	98	27	0	0	2	2	3	3
1	2	3.5	96	26	0	3.5	5.25	7.25	7	10
1	3	6	96	26	0	2.5	2.5	9.75	2.5	12.5
1	4	9	97.5	24.5	0	3	0.75	10.5	5.25	17.75
1	5	12	98	26	1	3	0.75	11.25	6.75	24.5

WC indicates waist circumference; BMI, body mass index; CEW, cumulative excess weight; CEWC, cumulative excess waist circumference.

*Time-weighted average of excess BMI (WC) was calculated as: [(BMI at visit X−25) + (BMI at visit Y−25)] / 2 × (years between visits) and [(WC at cycle X−95) + (WC at cycle Y−95)] / 2 × (years between visits), respectively. CEW and CEWC score for each visit T>1 was calculated by summing the prior Time-weighted average of excess BMI (WC) scores, e.g. for the last visit of one subject: CEW=[(27-25) ×1]+ [(26-25.0) + (27–25.0)] / 2 × 3.5 + [(26–25.0) + (26–25.0)] / 2 × 2.5 + [(24.5-25.0) + (26–25.0)] / 2 × 3 + [(26–25.0) + (24.5– 25.0)] / 2 × 3 = 11.25 kg/m^2 × years.

Table S2. An example of general adiposity duration calculation.

ID	Visit	Time (year)	BMI (kg/m^2)	1st CHD event	Time between visits T and T-1 (year)	BMI score*	Time weighted general adiposity duration (year)	Overall adiposity duration†
1	1	0	24	0	0	0	0	0
1	2	3.5	23.5	0	3.5	0	0	0
1	3	6	26	0	2.5	1	0	0
1	4	9	28	0	3	1	3	3
1	5	12	26	1	3	1	3	6

BMI indicates body mass index.

*BMI scores were designated as 1 if BMI≥25 kg/m^2 and as 0 if BMI<25 kg/m^2.

†Overall general adiposity duration was accumulation of time weighted general adiposity duration based on two consecutive phases.

Table S3. Risk of congestive heart failure according to 1-SD change in CEW/CEWC, current and maximum BMI/WC as well as general and central adiposity duration: Tehran Lipid and Glucose Study (1999-2014)[*,†]

	Model 1[‡]		Model 2[§]	
	HR(95%CI)	P-value	HR(95%CI)	P-value
(Person observation=13881)				
CEW	0.82(0.50-1.34)	0.44	1.03(0.85-1.25)	0.73
CEWC	0.85(0.61-1.18)	0.34	1.02(0.69-1.49)	0.93
General adiposity duration	1.04(0.77-1.42)	0.78	1.17(0.81-1.67)	0.40
Central adiposity duration	1.10(0.84-1.45)	0.48	1.11(0.79-1.54)	0.55
Current BMI	0.79(0.46-1.38)	0.41	1.04(0.86-1.22)	0.64
Current WC	0.79(0.55-1.14)	0.20	1.00(0.66-1.52)	0.99
Maximum BMI	0.98(0.68-1.41)	0.92	1.03(0.84-1.25)	0.79
Maximum WC	0.98(0.69-1.39)	0.90	1.16(0.76-1.76)	0.48

SD indicates standard deviation; CEW, cumulative excess weight; CEWC, cumulative excess waist circumference BMI, body mass index; WC, waist circumference.

[*]Current BMI /WC for each visit as time-varying exposures, General and central adiposity were defined as BMI≥25kg/m^2 and WC≥95cm, respectively.

[†]1-SD change in CEW, CEWC, general and central adiposity duration, current BMI/WC, maximum BMI/WC are 17.4 kg/m^2×years, 30.1 cm×years, 3.9 years, 3.3 years, 6.4 kg/m^2, 11.2 cm, 9.9 kg/m^2 and 10.8 cm, respectively.

[‡]Model 1: Age and sex.

[§]Model 2: Model 1+ smoking, education and low physical activity at each phase.

Table S4. Adjusted hazard ratios (95%Confidence Interval) for coronary heart disease by CEW quartiles.

	CEW quartiles				
	Q1(<-1.76)	**Q2(-1.76 to 2.81)**	**Q3(2.82 to 9.24)**	**Q4(≥9.25)**	**P for trend**
Men					
Events (n):Person-observation	142(869):1864	206(921):1266	49(180):1044	2(8):617	
Model 1 HR(95%CI)*	Ref	1.53(1.08-2.18)	1.66(1.18-2.34)	1.68(1.21-2.34)	0.003
Model 2 HR(95%CI)†	Ref	1.60(1.09-2.35)	1.65(1.13-2.41)	1.74(1.21-2.50)	0.005
Model 3 HR(95%CI)‡	Ref	1.44(0.97-2.11)	1.41(0.96-2.07)	1.50(1.04-2.16)	0.054
	Q1<3.06	**Q2 (3.06 to 9.43)**	**Q3(9.44 to 20.26)**	**Q4 (≥20.27)**	
Women					
Events (n): Person-observation	50(517):921	153(1166):1336	93(711):1846	5(26):2384	
Model 1 HR(95%CI)*	Ref	1.29(0.88-1.87)	1.19(0.83-1.72)	1.22(0.85-1.76)	0.38
Model 2 HR(95%CI)†	Ref	1.19(0.79-1.77)	1.04(0.70-1.55)	1.15(0.77-1.68)	0.68
Model 3 HR(95%CI)‡	Ref	1.13(0.75-1.69)	1.00(0.68-1.49)	1.04(0.70-1.55)	0.99
	Q1(<0.57)	**Q2(0.57 to 6.21)**	**Q3(6.22 to 15.5)**	**Q4(≥15.6)**	
Total population					
Events (n): Person-observation	192(1386):2785	359(2087):2602	142(891):2890	7(34):3001	
Model 1 HR(95%CI)*	Ref	1.69(1.33-1.76)	1.69(1.33-1.76)	1.40(1.07-1.80)	0.003
Model 2 HR(95%CI)†	Ref	1.32(1.00-1.74)	1.60(1.24-2.08)	1.33(1.01-1.76)	0.014
Model 3 HR(95%CI)‡	Ref	1.14(0.87-1.51)	1.41(1.09-1.84)	1.10(0.83-1.47)	0.25

CEW indicates cumulative excess weight (kg/m^2×year); n, number; HR, hazard ratio; CI, confidence interval; Q, quartile

*Model 1: Age, sex (for total population).

†Model 2: Model 1+ smoking, education and low physical activity at each phase.

‡Model 3: Model 2+ hypertension, diabetes and hypercholesterolemia at each phase.

Table S5. Adjusted hazard ratios (95%Confidence Interval) for coronary heart disease by CEWC quartiles.

	CEWC quartiles				
	Q1(<-13.7)	**Q2(-13.7 to 0.82)**	**Q3(0.83 to 14.9)**	**Q4(≥14.9)**	**P for trend**
Men					
Events (n): Person-observation	39(338):1864	190(998):1266	161(601):1044	9(51):617	
Model 1 HR(95%CI)*	Ref	1.62(1.12-2.33)	1.90(1.33-2.70)	1.89(1.34-2.65)	<0.001
Model 2 HR(95%CI)†	Ref	1.66(1.12-2.48)	1.91(1.30-2.81)	1.94(1.34-2.80)	0.001
Model 3 HR(95%CI) ‡	Ref	1.54(1.03-2.31)	1.70(1.14-2.52)	1.68(1.15-2.46)	0.012
	Q1<-13.0	**Q2(-13.0 to 1.84)**	**Q3(1.84 to 18.5)**	**Q4 (≥18.5)**	
Women					
Events (n): Person-observation	30(373):921	130(1083):1336	123(872):1846	18(92):2384	
Model 1 HR(95%CI)*	Ref	1.19(0.81-1.76)	1.05(0.72-1.54)	1.38(0.97-1.96)	0.11
Model 2 HR(95%CI)†	Ref	1.21(0.80-1.84)	1.01(0.66-1.54)	1.26(0.85-1.86)	0.38
Model 3 HR(95%CI)‡	Ref	1.08(0.71-1.64)	0.87(0.57-1.34)	1.03(0.70-1.54)	0.93
	Q1(<-13.08)	**Q2(-13.08 to 1.0)**	**Q3(1.0 to 17.0)**	**Q4(≥17.0)**	
Total population					
Events (n): Person-observation	69(711):2785	320(2071):2602	284(1473):2890	27(143):3001	
Model 1 HR(95%CI)*	Ref	1.41(1.08-1.83)	1.49(1.15-1.92)	1.63(1.27-2.07)	<0.001
Model 2 HR(95%CI)†	Ref	1.44(1.08-1.92)	1.51(1.14-2.00)	1.60(1.22-2.09)	0.001
Model 3 HR(95%CI)‡	Ref	1.31(0.98-1.75)	1.29(0.97-1.72)	1.33(1.00-1.75)	0.08

CEWC indicates cumulative excess waist circumference (cm×year); n, number; HR, hazard ratio; CI, confidence interval; Q, Quartile.

*Model 1: Age, sex (for total population).

†Model 2: Model 1+ smoking, education and low physical activity at each phase.

‡Model 3: Model 2+ hypertension, diabetes and hypercholesterolemia at each phase.

Table S6. Adjusted hazard ratios (95%Confidence Interval) for coronary heart disease by current body mass index (BMI) quartiles.

	Current BMI				
	Q1(<24.0)	**Q2(24.0 to 26.5)**	**Q3(26.5 to 29.0)**	**Q4(≥29)**	**P for trend**
Men					
Events (n): Person-observation	129(813):1864	136(598):1266	85(388):1044	49(179):617	
Model 1 HR(95%CI)*	Ref	1.42(1.02-1.97)	1.64(1.19-2.25)	1.72(1.25-2.35)	0.001
Model 2 HR(95%CI)†	Ref	1.44(1.00-2.07)	1.68(1.19-2.38)	1.75(1.24-2.46)	0.001
Model 3 HR(95%CI) ‡	Ref	1.32(0.91-1.90)	1.48(1.04-2.10)	1.41(0.99-2.01)	0.053
	Q1(<26.7)	**Q2(26.7 to 29.6)**	**Q3(29.6 to 32.9)**	**Q4(≥32.9)**	
Women					
Events (n): Person-observation	43(468):921	81(554):1336	82(680):1846	95(718):2384	
Model 1 HR(95%CI)*	Ref	1.14(0.80-1.61)	1.26(0.90-1.76)	1.04(0.73-1.48)	0.67
Model 2 HR(95%CI)†	Ref	1.19(0.82-1.73)	1.18(0.81-1.72)	1.00(0.68-1.50)	0.96
Model 3 HR(95%CI)‡	Ref	1.08(0.74-1.57)	1.10(0.76-1.61)	0.87(0.58-1.30)	0.55
	Q1(<25.3)	**Q2(25.3 to 28.1)**	**Q3(28.1 to 31.2)**	**Q4(≥31.2)**	
Total population					
Events (n):Person-observation	172(1281):2785	217(1152):2602	167(1068):2890	144(897):3001	
Model 1 HR(95%CI)*	Ref	1.44(1.15-1.81)	1.54(1.22-1.94)	1.33(1.03-1.71)	0.016
Model 2 HR(95%CI)†	Ref	1.42(1.11-1.82)	1.52(1.18-1.95)	1.24(0.94-1.63)	0.07
Model 3 HR(95%CI)‡	Ref	1.29(1.00-1.65)	1.29(1.00-1.67)	1.00(0.75-1.33)	0.92

BMI indicates body mass index (kg/m^2); n, number; HR, hazard ratio; CI, confidence interval; Q, quartile.

*Model 1: Age, sex (for total population).

†Model 2: Model 1+ smoking, education and low physical activity at each phase.

‡Model 3: Model 2+ hypertension, diabetes and hypercholesterolemia at each phase.

Table S7. Adjusted hazard ratios (95%Confidence Interval) for coronary heart disease by current waist circumference (WC) quartiles.

	Current WC quartiles				
	Q1(<90)	**Q2(90 to 97)**	**Q3(97 to 103)**	**Q4(≥103)**	**P for trend**
Men					
Events (n): Person-observation	130(828):1864	99(518):1266	101(381):1044	69 (251):617	
Model 1 HR(95%CI)*	Ref	1.27(0.91-1.78)	1.91(1.39-2.63)	1.73(1.26-2.37)	<0.001
Model 2 HR(95%CI)†	Ref	1.28(0.89-1.85)	2.01(1.43-2.84)	1.71(1.22-2.41)	<0.001
Model 3 HR(95%CI)‡	Ref	1.24(0.85-1.80)	1.78(1.26-2.53)	1.46(1.02-2.08)	0.013
	Q1(<89)	**Q2(90 to 97)**	**Q3(97 to 104)**	**Q4(≥105**	
Women					
Events (n): Person-observation	80(871):921	80(588):1336	66(516):1846	75(445):2384	
Model 1 HR(95%CI)*	Ref	1.19(0.81-1.73)	1.36(0.96-1.94)	1.37(0.96-1.96)	0.18
Model 2 HR(95%CI)†	Ref	1.12(0.74-1.69)	1.36(0.93-1.98)	1.24(0.84-1.84)	0.18
Model 3 HR(95%CI)‡	Ref	1.02(0.68-1.54)	1.23(0.84-1.80)	1.02(0.69-1.53)	0.70
	Q1(<90)	**Q2(90 to 96)**	**Q3(97 to 104)**	**Q4 (≥105)**	
Total population					
Events (n): Person-observation	172(1699):2785	217(1106):2602	167(897):2890	144(696):3001	
Model 1 HR(95%CI)*	Ref	1.25(0.97-1.60)	1.71(1.35-2.16)	1.54(1.21-1.95)	<0.001
Model 2 HR(95%CI)†	Ref	1.23(0.94-1.62)	1.78(1.39-2.29)	1.47(1.13-1.90)	<0.001
Model 3 HR(95%CI)‡	Ref	1.16(0.88-1.53)	1.56(1.21-2.01)	1.22(0.94-1.59)	0.05

WC indicates waist circumference (cm); n, number; HR, hazard ratio; CI, confidence interval; Q, quartile

*Model 1: Age, sex (for total population).

†Model 2: Model 1+ smoking, education and low physical activity at each phase.

‡Model 3: Model 2+ hypertension, diabetes and hypercholesterolemia at each phase.

Table S8. Adjusted hazard ratios (95%Confidence Interval) for stroke by cumulative excess weight (CEW) quartiles.

	CEW quartiles				
	Q1(<-1.7)	**Q2(-1.7 to 3.0)**	**Q3(3.0 to 9.5)**	**Q4(≥9.5)**	**P for trend**
Men					
Events (n): Person-observation	14(433):1545	41(934):1454	29(558):1498	6(53):1576	
Model 1 HR(95%CI)*	1.00(ref)	1.07(0.53-2.17)	0.80(0.38-1.70)	1.05(0.54-2.07)	0.93
Model 2 HR(95%CI)†	1.00(ref)	1.23(0.56-2.72)	0.80(0.33-1.95)	1.06(0.49-2.29)	0.89
Model 3 HR(95%CI)‡	1.00(ref)	1.11(0.50-2.49)	0.64(0.26-1.58)	0.69(0.31-1.56)	0.22
	Q1(<3.13)	**Q2(3.13 to 9.6)**	**Q3(9.6 to 20.5)**	**Q4(≥20.5)**	
Women					
Events (n): Person-observation	25(1030):1952	35(1117):1930	6(269):1881	2(4):1951	
Model 1 HR(95%CI)*	1.00(ref)	1.55(0.52-4.62)	2.45(0.95-6.35)	2.79(1.08-7.24)	0.02
Model 2 HR(95%CI)†	1.00(ref)	1.33(0.43-4.14)	1.71(0.61-4.75)	1.87(0.66-5.28)	0.20
Model 3 HR(95%CI)‡	1.00(ref)	1.59(0.48-5.24)	2.09(0.70-6.23)	2.14(0.76-7.06)	0.12
	Q1(<0.6)	**Q2(0.6 to 6.35)**	**Q3(6.35 to 15.78)**	**Q4(≥15.78)**	
Total population					
Events (n): Person-observation	39(1463):3497	76(2051):3384	35(827):3379	8(57):3527	
Model 1 HR(95%CI)*	1.00(ref)	1.02(0.56-1.86)	1.43(0.83-2.45)	1.61(0.93-2.79)	0.054
Model 2 HR(95%CI)†	1.00(ref)	1.34(0.69-2.59)	1.39(0.74-2.63)	1.50(0.78-2.86)	0.22
Model 3 HR(95%CI)‡	1.00(ref)	1.16(0.59-2.28)	1.26(0.66-2.39)	1.23(0.63-2.37)	0.66

CEW indicates cumulative excess weight ($kg/m^2 \times year$); n, number; HR, hazard ratio; CI, confidence interval; Q, quartile.

*Model 1: Age, sex (for total population).

†Model 2: Model 1+ smoking, education and low physical activity at each phase.

‡Model 3: Model 2+ hypertension, diabetes and hypercholesterolemia at each phase.

Table S9. Adjusted hazard ratios (95%Confidence Interval) for stroke by cumulative excess waist circumference (CEWC) quartiles.

	CEWC quartiles				
	Q1(<-13)	**Q2(-13 to 0.83)**	**Q3(0.83 to 16)**	**Q4(≥16)**	**P for trend**
Men					
Events (n): Person-observation	10(385):1545	35(885):1454	33(636):1498	12(72):1576	
Model 1 HR(95%CI)*	Ref	1.07(0.50-2.30)	0.80(0.36-1.79)	1.43(0.74-2.74)	0.35
Model 2 HR(95%CI)†	Ref	1.27(0.54-3.01)	0.98(0.40-2.38)	1.37(0.63-2.96)	0.53
Model 3 HR(95%CI)‡	Ref	1.11(0.46-2.66)	0.72(0.29-1.77)	0.87(0.39-1.94)	0.57
	Q1(<-12.9)	**Q2(-12.9 to 2)**	**Q3(2 to 19.3)**	**Q4(≥19.3)**	
Women					
Events (n): Person-observation	8(424):1952	24(1125):1930	31(798):1881	5(73):1951	
Model 1 HR(95%CI)*	Ref	0.86(0.27-2.73)	0.94(0.32-2.65)	2.49(1.07-5.75)	0.01
Model 2 HR(95%CI)†	Ref	0.63(0.18-2.15)	0.66(0.21-2.09)	1.56(0.63-3.85)	0.21
Model 3 HR(95%CI)‡	Ref	0.49(0.13-1.87)	0.67(0.21-2.14)	1.57(0.63-4.00)	0.17
	Q1(<-13)	**Q2(-13 to 1.34)**	**Q3(1.34 to 17.7)**	**Q4(≥17.7)**	
Total population					
Events (n): Person-observation	18(809):3497	59(2010):3384	64(1434):3379	17(145):3527	
Model 1 HR(95%CI)*	1.00(ref)	1.06(0.57-1.98)	0.78(0.41-1.48)	1.88(1.13-3.12)	0.01
Model 2 HR(95%CI)†	1.00(ref)	1.06(0.53-2.10)	0.76(0.37-1.56)	1.52(0.85-2.72)	0.20
Model 3 HR(95%CI)‡	1.00(ref)	0.92(0.45-1.87)	0.65(0.31-1.34)	1.20(0.66-2.19)	0.58

CEWC indicates body cumulative excess waist circumference (cm×year); n, number; HR, hazard ratio, CI, confidence interval.

*Model 1: Age, sex (for total population).

†Model 2: Model 1+ smoking, education and low physical activity at each phase.

‡Model 3: Model 2+ hypertension, diabetes and hypercholesterolemia at each phase.

Table S10. Adjusted hazard ratios (95%Confidence Interval) for stroke by current body mass index (BMI) quartiles.

	Current BMI quartiles				
	<24.06	**Q2(24.06 to 26.5)**	**Q3(26.5 to 29.05)**	**Q4(≥29.5)**	**P for trend**
Men					
Events (n): Person-observation	19(565):1545	22(508):1454	18(475):1498	31(430):1576	
Model 1 HR(95%CI)*	1.00(ref)	1.49(0.78-2.86)	0.82(0.38-1.77)	1.42(0.73-2.78)	0.62
Model 2 HR(95%CI)†	1.00(ref)	1.55(0.73-3.27)	0.88(0.37-2.08)	1.40(0.65-3.00)	0.68
Model 3 HR(95%CI)‡	1.00(ref)	1.35(0.64-2.88)	0.70(0.29-1.67)	0.87(0.39-1.93)	0.43
	Q1(<26.7)	**Q2(26.7 to 29.6)**	**Q3(29.6 to 32.9)**	**Q4(≥32.9)**	
Women					
Events (n): Person-observation	17(744):1952	16(619):1930	25(586):1881	10(471):1951	
Model 1 HR(95%CI)*	1.00(ref)	1.14(0.48-2.70)	1.43(0.62-3.27)	2.19(1.00-4.80)	0.04
Model 2 HR(95%CI)†	1.00(ref)	1.24(0.51-3.00)	0.81(0.29-2.28)	1.62(0.66-3.94)	0.44
Model 3 HR(95%CI)‡	1.00(ref)	1.34(0.53-3.38)	0.93(0.32-2.69)	1.78(0.69-4.56)	0.35
	Q1(<25.3)	**Q2(25.3 to 28.1)**	**Q3(28.1 to 31.2)**	**Q4(≥31.2)**	
Total population					
Events (n): Person-observation	36(1309):3497	38(1127):3384	43(1061):3379	41(901):3527	
Model 1 HR(95%CI)*	1.00(ref)	1.31(0.79-2.19)	1.30(0.73-2.19)	1.79(1.04-3.08)	0.05
Model 2 HR(95%CI)†	1.00(ref)	1.38(0.78-2.43)	1.13(0.60-2.12)	1.50(0.80-2.82)	0.30
Model 3 HR(95%CI)‡	1.00(ref)	1.18(0.67-2.11)	0.94(0.50-1.77)	1.19(0.62-2.26)	0.79

BMI indicates body mass index (kg/m^2); n, number; HR, hazard ratio; CI, confidence interval.

*Model 1: Age, sex (for total population).

†Model 2: Model 1+ smoking, education and low physical activity at each phase.

‡Model 3: Model 2+ hypertension, diabetes and hypercholesterolemia at each phase.

Table S11. Adjusted hazard ratios (95%Confidence Interval) for stroke by current waist circumference (WC) quartiles.

	Current WC quartiles				
	Q1(<90)	**Q2(90 to 97)**	**Q3(97 to 103)**	**Q4(≥103)**	**P for trend**
Men					
Events (n): Person-observation	27(828):1545	20(519):1454	18(345):1498	25(286):1576	
Model 1 HR(95%CI)*	1.00(ref)	0.79(0.40-1.58)	0.63(0.29-1.37)	1.25(0.68-2.30)	0.53
Model 2 HR(95%CI)†	1.00(ref)	0.84(0.39-1.84)	0.57(0.23-1.41)	1.24(0.62-2.46)	0.67
Model 3 HR(95%CI)‡	1.00(ref)	0.78(0.36-1.72)	0.41(0.17-1.03)	0.80(0.39-1.63)	0.42
	Q1(<90)	**Q2(90 to 98)**	**Q3(98 to 105)**	**Q4(≥105)**	
Women					
Events (n): Person-observation	18(868):1952	14(683):1930	17(472):1881	19(397):1951	
Model 1 HR(95%CI)*	1.00(ref)	0.42(0.14-1.22)	1.76(0.82-3.79)	1.36(0.62-3.00)	0.08
Model 2 HR(95%CI)†	1.00(ref)	0.46(0.16-1.34)	1.26(0.54-2.93)	0.94(0.39-2.29)	0.64
Model 3 HR(95%CI)‡	1.00(ref)	0.36(0.11-1.14)	1.27(0.54-3.00)	0.91(0.37-2.24)	0.64
	Q1(<90)	**Q2(90 to 96)**	**Q3(96 to 104)**	**Q4(≥104)**	
Total population					
Events (n): Person-observation	45(1694):3497	34(1202):3384	35(817):3379	44(683):3527	
Model 1 HR(95%CI)*	1.00(ref)	0.65(0.36-1.17)	1.00(0.60-1.68)	1.35(0.83-2.18)	0.09
Model 2 HR(95%CI)†	1.00(ref)	0.68(0.36-1.28)	0.83(0.46-1.50)	1.12(0.65-1.93)	0.57
Model 3 HR(95%CI)‡	1.00(ref)	0.64(0.34-1.27)	0.67(0.37-1.23)	0.90(0.50-1.52)	0.70

WC indicates waist circumference (cm); n, number; HR, hazard ratio; CI, confidence interval.

*Model 1: Age, sex (for total population).

†Model 2: Model 1+ smoking, education and low physical activity at each phase.

‡Model 3: Model 2+ hypertension, diabetes and hypercholesterolemia at each phase.

Table S12. Risk of coronary heart disease(CHD) based on one standard deviation (SD) change of CEW, CEWC and current BMI/WC in the imputed file: Tehran Lipid and Glucose Study (1999-2014)[*,†,‡,§]

	Men (Person observation=6506)		Women (Person observation=8181)		Total population (Person observation=14687)	
	HR(95%CI)	P-value	HR(95%CI)	P-value	HR(95%CI)	P-value
CEW						
Model 1[||]	1.07(0.97-1.17)	0.20	0.95(0.86-1.05)	0.31	1.01(0.93-1.06)	0.96
Model 2[#]	1.06(0.98-1.16)	0.18	0.95(0.86-1.05)	0.34	1.00(0.95-1.06)	0.90
Model 3[**]	0.99(0.91-1.07)	0.82	0.99(0.91-1.05)	0.82	0.95(0.88-1.01)	0.14
CEWC						
Model 1[||]	1.11(1.03-1.19)	0.01	1.09(1.02-1.19)	0.01	1.11(1.03-1.17)	<0.001
Model 2[#]	1.10(1.02-1.21)	0.01	1.08(1.02-1.19)	0.01	1.10(1.03-1.17)	0.001
Model 3[**]	1.03(0.96-1.12)	0.32	1.03(0.96-1.12)	0.32	1.03(0.97-1.09)	0.24
Current BMI						
Model 1[||]	1.14(1.04-1.25)	0.003	1.00(0.99-1.01)	0.78	1.03(1.00-1.06)	0.05
Model 2[#]	1.14(1.05-1.25)	0.002	1.00(0.99-1.01)	0.88	1.03(1.00-1.06)	0.05
Model 3[**]	1.06(0.97-1.16)	0.2	0.99(0.97-1.02)	0.63	1.01(0.95-1.07)	0.70
Current WC						
Model 1[||]	1.24(1.05-1.31)	<0.001	1.12(1.01-1.25)	0.03	1.18(1.10-1.26)	0.001
Model 2[#]	1.20(1.09-1.31)	<0.001	1.10(0.99-1.23)	0.06	1.17(1.09-1.25)	0.001
Model 3[**]	1.11(1.01-1.21)	0.03	1.03(0.92-1.15)	0.53	1.08 (1.00-1.16)	0.03

BMI indicates body mass index; WC, waist circumference; CEW, cumulative excess weight; CEWC, cumulative excess waist circumference.

[*]1-SD change in CEW in the total population, men and women are 42.5 and 31.2 and 47.2 kg/m^2×years, respectively.

[†]1-SD change in CEWC in the total population, men and women are 82.7 and 79.7 and 84.8 cm×years, respectively.

[‡]1-SD change in current BMI in total population, men and women are 6.2, 4.0 and 7.2 kg/m^2, respectively.

[§]1-SD change in current WC in total population, men and women are 11.3, 10.8 and 11.6 cm, respectively.

[||]Model 1: Age, sex (for total population).

[#]Model 2: Model 1+ smoking, education and low physical activity at each phase.

[**]Model 3: Model 2+ hypertension, diabetes and hypercholesterolemia at each phase.

Table S13. Risk of stroke based on one standard deviation (SD) change of CEW/CEWC and current BMI/WC in imputed file: Tehran Lipid and Glucose Study (1999-2014)[*, †]

	Model 1[‡]		Model 2[§]		Model 3[‖]	
	HR(95%CI)	P-value	HR(95%CI)	P-value	HR(95%CI)	P-value
(Person observation=17234)						
CEW	1.04(0.97-1.12)	0.20	1.04(0.98-1.12)	0.19	1.02(0.92-1.13)	0.73
CEWC	1.20(1.07-1.36)	0.002	1.19(1.06-1.35)	0.004	1.10(0.97-1.24)	0.13
Current BMI	1.04(0.99-1.08)	0.10	1.04(0.99-1.08)	0.12	1.03(0.95-1.10)	0.44
Current WC	1.26(1.07-1.47)	0.004	1.24(1.06-1.45)	0.006	1.12(0.96-1.32)	0.15

CEW indicates cumulative excess weight; CEWC, cumulative excess waist circumference; BMI, body mass index; WC, waist circumference; HR, hazard ratio; CI, confidence interval.

[*]Current BMI /WC for each visit as time-varying exposures.

[†]1-SD change in CEW, CEWC and current BMI/ WC are 43.1 kg/m^2×years, 84.4 cm×years, 6.2 kg/m^2 and 11.1 cm, respectively.

[‡]Model 1: Age, sex (for total population).

[§]Model 2: Model 1+ smoking, education and low physical activity at each phase.

[‖]Model 3: Model 2+ hypertension, diabetes and hypercholesterolemia at each phase.