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Association of obesity severity and duration with incidence of chronic kidney disease

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Abstract

Introduction Obesity is a known risk factor for chronic kidney disease (CKD), but the impact of obesity severity and duration on CKD incidence is unclear.

Methods Cumulative Excess Weight (CEW) and Cumulative Excess Waist Circumference (CEWC) scores were calculated, which represent the accumulation of deviations from expected body mass index and waist circumference values over time until the development of CKD or the end of the follow-up period. Time-dependent Cox models were used to investigate the sex-stratified association of CEW and CEWC with CKD incidence while controlling for confounding variables.

Results Out of the 8697 participants who were evaluated in this study, 56% (4865) were women and the mean age was 40 ± 14. During the 15-year follow-up period, 41.7% (3629) of the participants developed CKD. Among the CKD patients, 65.4% (829) of men and 77.9% (1839) of women had a BMI higher than 25, and high WC was found to be 73.7% (934) and 55.3% (1306) for men and women, respectively. We found a significant association between one standard deviation change of CEW and the development of CKD in both sexes (fully adjusted hazard ratios and 95% CI of CEW in men and women were 1.155 [1.081–1.232) and 1.105 (1.047–1.167)]. However, the association between CEWC and CKD development was only significant among men participants [HR = 1.074 (1.006–1.147)].

Conclusion Over a 15-year follow-up, the accumulation of general and central obesity was associated with an increased incidence of CKD development.

Keywords Chronic kidney disease, General obesity, Central obesity, Cumulative excess weight, Cumulative excess waist circumference

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Introduction

Obesity, characterized by excessive accumulation of adiposity, is one of the most important medical concerns of our time and its incidence is estimated to increase by more than 30% by 2030 [1]. In 2020, approximately 2.6 billion people globally were classified as overweight or obese, representing around 38% of the world's population. This figure is projected to rise to over 4 billion people, or 51% of the global population, by 2035 [2]. Obesity has emerged as an independent risk factor for numerous chronic diseases, such as diabetes and kidney disease [3]. In a systematic review study, the prevalence of obesity among Iranian adults was 21.7%, with an increasing manner [4]. Some epidemiologic studies have revealed an association between high body mass index (BMI) and a wide range of chronic diseases including cardiovascular diseases and chronic kidney disease (CKD) [5, 6]. In a study by Wang et al. [7] it was shown that 24–33% of all patients diagnosed with kidney disease in the United States are associated with obesity.

Previous studies have shown that the severity of obesity and high BMI is associated with incident CKD [8, 9]. Additionally, obesity has been identified as a predictor of CKD in the general population [3]. It has also been shown that the duration of obesity affects the risk of CKD, with becoming overweight at younger ages being associated with a higher incidence of CKD in older ages [10]. The proposed mechanisms underlying this association include atherosclerosis, hypertension, and type 2 diabetes mellitus, which possess a causal relationship with CKD, as well as the detrimental effects exerted by adiposity itself [11].

While traditional measures of obesity, such as BMI, have been extensively studied, recent research has employed cumulative metrics like cumulative excess weight (CEW) and cumulative excess waist circumference (CEWC) to provide a more comprehensive assessment of obesity. These metrics account for both the severity and duration of exposure to excess BMI and WC over time, reflecting general and central adiposity, respectively. Prior studies have used CEW and CEWC to show associations with chronic diseases such as type 2 diabetes mellitus and cardiovascular diseases, offering deeper insights into how prolonged exposure to obesity impacts health outcomes [12, 13].

In this study, we aim to extend the understanding of the association between obesity and CKD by implementing cumulative metrics (CEW and CEWC) to evaluate the severity and duration of both central and general obesity. By leveraging data from the Tehran Lipid and Glucose Study (TLGS), a population-based cohort with more than 15 years of follow-up, we provide novel evidence on how cumulative exposure to excess weight and waist circumference contributes to the incidence of CKD. This approach offers additional insights beyond traditional measures, highlighting the importance of considering the temporal dynamics of obesity in assessing its impact on kidney health.

Methods

Study population

TLGS is an ongoing study designed to monitor risk factors related to chronic illness and cardiovascular diseases (CVD) in District 13, Tehran (the capital of Iran). Two recruitment phases were conducted: (I) 1999 to 2001 and (II) 2002 to 2005. In both phases, multistage cluster random sampling was used for selecting participants. Each participant has been followed up in four other subsequent examination cycles. In phases III to VI, which took about three years and a half (2006–2008), (2009–2011), (2012–2014), and (2015–2017), respectively, a similar process was applied. The average availability of participants during each phase was of 73%. Comprehensive details about the study protocol are reported elsewhere [14].

In this study, we included entries from phase 2 of the TLGS study with available data on weight, WC, and absence of CKD at baseline. Individuals who were under 18 years old, used corticosteroids, had cancer during the study, or had unavailable creatinine levels were excluded from this investigation. Finally, 8697 participants with complete profiles were eventually analyzed to determine the association between the severity and duration of obesity and the incidence of CKD until phase VI of the study (Fig. 1).

Definitions

Measurement of CEW and CEWC

General and central adiposity was defined as BMI ≥ 25 kg/m^2 and WC ≥ 91 cm for women and WC ≥ 89 for men. We calculated the CEW and CEWC scores as the sum of units of BMI and WC over or under the upper limit of the normal weight BMI category and WC [15], over each inter-cycle period until the reduction of eGFR to a level that we defined as CKD or the end of follow-up. Participants were examined at five visits. Except for the first visit, the differences obtained from the current and previous visits were averaged and multiplied by the time (years) between those visits. Then all prior time-weighted averages of excess BMI or WC were summed until the development of CKD or the end of follow-up to calculate the CEW and CEWC scores for each visit. This methodology allows for a comprehensive assessment of cumulative excess weight and waist circumference over time, accounting for variations between follow-up visits and providing a robust measure for analyzing their impact on health outcomes. Detailed explanations along with examples are presented in the supplementary Tables 1 and 2.

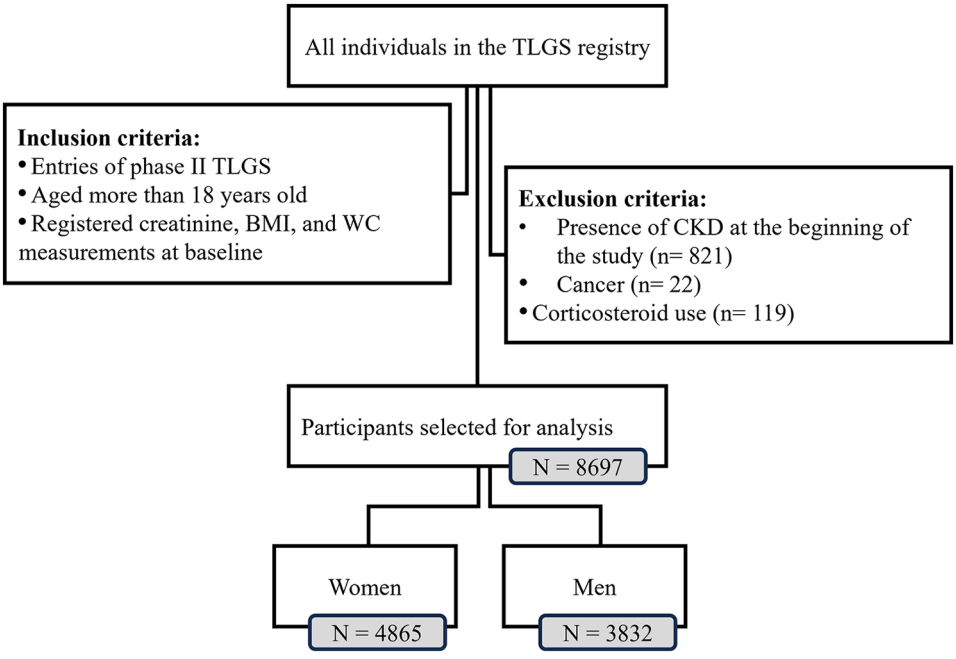

Fig. 1 Flowchart of the selection process of patients

Measurement of GFR

We used the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, as the most recommended creatinine-based alternative method for directly measured GFR [16] in this study to estimate eGFR and to diagnose CKD. CKD was defined as eGFR below 60 mL/min per 1.73 m^2 or alternatively more than 40% decline in eGFR during the follow-up. Using the CKD-EPI equation GFR is estimated as:

eGFR (mL/min per 1.73 m^2) = 141 × minimum (Scr/κ, 1) α × maximum (Scr/κ, 1) −1.209 × 0.993 Age × 1.018 [if female], where κ = 0.7 for females and 0.9 for males, α = -0.329 for females and −0.411 for males [17].

Anthropometrics and laboratories measurements

At first, all eligible participants were interviewed, and their age, sex, physical activity, smoking habits, educational level, consumption of medicines, and history of CVDs were collected. Measurements were performed by a trained staff based on the study protocol. Participants' weight was measured using a digital scale with shoes and clothes removed as much as possible. Values were rounded to the nearest 100 g. Height was measured with a tape meter while removing the shoes. BMI was calculated as the participant's weight divided by the square of height in meters. A Stretched tape meter was used to measure participants' WC at the level of the umbilicus without applying any pressure; measured values were rounded to the nearest 0.1 cm.

After about 15 min of rest, a general practitioner measured Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) twice, while participants were in a seated position. Blood pressure was considered the mean of the two measurements. The standard mercury sphygmomanometer was followed during all procedures. Blood samples, which were taken from participants with at least 12–14 h fasting were immediately sent for analysis in the TLGS laboratory; using the Selectra 2 auto-analyzer (Vital Scientific, Spankeren, Netherlands).

Serum creatinine values were quantified by the standard colorimetric Jaffe Kinetic reaction method (Pars Azmoun Inc., Iran). To determine Fasting Plasma Glucose (FPG), the enzymatic colorimetric method was used with glucose oxidation. Inter- and intra-assay coefficients of variations were both 2.2%. Enzymatic colorimetric assays using cholesterol esterase, cholesterol oxidase, and glycerol phosphate oxidase were performed. Total cholesterol (TC) and TG levels were measured using appropriate kits (Pars Azmoun, Tehran, Iran). Inter- and intra-assay coefficients of variation were 2 and 0.5% for TC and 1.6 and 0.6% for TG, respectively [14].

Participants were divided into three educational level categories; "illiterate/primary school," "below high school diploma/diploma," and "above high school diploma." smoking status was also divided into three categories: "current or occasional smoker", "former smoker," and "never smoker." Lipid Research Clinic (LRC) questionnaire was used to collect data on physical activity at the initial step of the TLGS [18]. Since LRC is not accurate, the Modifiable Activity Questionnaire (MAQ) was used for the rest of the follow-up examinations to cover all

kinds of activity (i.e., leisure, occupation, and in-house) [19].

Statistical analysis

All normally-distributed continuous variables were expressed as mean ± standard deviation (SD). Otherwise, skewed-distributed continuous variables were shown as median and inter-quartile range (IQR) 25–75. Categorical variables of baseline characteristics were shown as frequency (percentages). Differences in characteristics of study participants based on gender or CKD were compared using an independent sample t-test, Mann-Whitney U test, and chi-square test for normal, skewed, and categorical variables, respectively. Moreover, time-varying Cox models (proportional hazards models) were used to evaluate associations between the obesity severity and duration and the incidence of CKD. The models were adjusted for age, smoking (non-smoker as reference), diabetes (non-DM as reference), hypertension (non-HTN as reference), and educational level (illiterate/primary school as reference) as time-dependent variables. The last observation carried forward (LOCF) method was used to handle the missing data of several variables, including smoking, family history of CVD, and educational status because of slight variation over time in these variables. Single imputations were performed for the missing data in each phase of the study for covariates or creatinine. To handle the missing values of covariates in a large dataset, including model covariates, the single imputation (M = 1) method was used, based on multiple imputations by chained equations (MICE). Simple random sampling with a replacement for the observed value was used to adjust for the missing values. In the current study, linear and logistic regression analyses were used for continuous and binary covariates, respectively. An analysis was performed on the imputed file with no missing values for BMI or other covariates. All analyses were performed in Stata version 14.0 (Stata Corp. LLC, TX, USA). P-values less than 0.05 were considered statistically significant (two-tailed test).

Sensitivity analysis

To assess the robustness of our findings, we conducted a sensitivity analysis by stratifying the study population into two age groups for both genders: <50 years and ≥50 years. The rationale for selecting 50 years as the cutoff point is based on the mean age at menopause in the total population of Iran, which is 50.4 years according to a national report [20]. Menopause is a significant biological milestone that can impact various health outcomes, including the risk of chronic diseases. By using this age threshold, we aimed to capture potential differences in CKD risk associated with hormonal changes and aging. We evaluated the HRs for the risk of CKD associated with one SD change in CEW and CEWC scores within these age categories. The analysis was further adjusted for potential confounders, including age, smoking status, diabetes, hypertension, and educational level.

Results

Of the 8,697 participants registered in this study, 4,865 (55.9%) were women and 3,832 were men. Out of the total participants, 3629 individuals were diagnosed with CKD. A breakdown of the CKD incidence by gender reveals that 1,267 (33%) of men and 2,362 (48.5%) women were affected by CKD. The mean age of the participants was 41.4 ± 15.5 for men and 38.9 ± 14.1 for women. Characteristics of participants at baseline and a comparison of the two sexes are described in Table 1. The mean BMI was 26.0 ± 4.3 and 27.6 ± 5.2 for men and women, respectively. BMI was significantly lower among men, and they were older than women. Central obesity according to WC was significantly higher in men with 92.4 ± 11.6 cm in comparison with mean WC of 88.0 ± 13.4 cm in women. Additionally, we observed a significant difference in CEW and CEWC scores, smoking status and education, family history of CVD, creatinine and eGFR measures, and metabolic profile including FPG, 2 h-PCPG (2-hour post-challenge plasma glucose), and TG level between men and women ($p<0.001$). Table 2 shows the baseline characteristics of the non-CKD and incident CKD participants for both sexes. During 15 years of follow-up, 3629 (41.7%) of the non-CKD patients developed CKD. Individuals who developed CKD were significantly older than participants who remained non-CKD. Anthropometric measures including BMI and WC were significantly higher in CKD patients for both sexes. High WC and overweight/obese was seen significantly more frequently among CKD patients. Systolic and Diastolic blood pressures were significantly higher in CKD patients. The mean estimated GFR was 75.3 ± 10.5 and 76.5 ± 12.1 for male and female CKD patients, respectively. Among both sexes, participants who developed CKD had an expressively more unfavorable metabolic profile, comprising FPG, TG, 2 h-PCPG, SBP, and DBP; and the frequency of comorbidities such as hypertension and diabetes were significantly higher among CKD patients ($p<0.001$).

The risk of incident CKD as one SD change in CEW and CEWC scores among both sexes are shown in three models in Table 3. The association between CEW score and incidence of CKD was significant in the unadjusted model for both sexes. After adjustment for time-dependent confounders, including age, smoking, family history of diabetes, family history of CVD, hypertension, and educational level, the hazard ratios (HRs) were 1.155 (95% Confidence Interval (CI), 1.081–1.232) and 1.105 (95% CI, 1.047–1.167) for men and women, respectively ($p<0.001$). HRs for incidence of CKD as one SD

Table 1 Characteristics of participants at baseline

	Total	Men	Women	*p*-value
Number	8697	3832	4865	-
Age, years	40.0 ± 14.8	41.4 ± 15.5	38.9 ± 14.1	< 0.001
Age ≥ 50 years	2354 (27.1)	1168 (30.5)	1186 (24.4)	< 0.001
BMI, kg/m^2	26.97 ± 4.94	26.0 ± 4.3	27.6 ± 5.2	< 0.001
Overweight/obese, BMI ≥ 25 kg/m^2	5573 (64.1)	2267 (59.2)	3306 (68.0)	< 0.001
WC, cm	89.9 ± 12.9	92.4 ± 11.6	88.0 ± 13.4	< 0.001
High WC (> 89 cm for men and > 91 cm for women)	4504 (51.8)	2459 (64.2)	2045 (42.0)	< 0.001
SBP, mmHg	114.8 ± 17.6	117.5 ± 16.7	112.6 ± 17.9	< 0.001
DBP, mmHg	74.2 ± 10.5	75.1 ± 10.7	73.4 ± 10.3	< 0.001
FPG, mg/dL	96.3 ± 29.3	96.9 ± 27.7	95.7 ± 30.5	0.057
2 h-PCPG, mg/dL *	124.8 ± 78.4	120.4 ± 74.8	128.2 ± 80.8	< 0.001
TG, mg/dL †	129.0 (88.0–191.0)	140.0 (96.0–208.0)	120.0 (83.0–179.0)	< 0.001
HDL-C, mg/dL	39.1 ± 10.6	35.6 ± 9.1	41.7 ± 10.8	< 0.001
Total cholesterol, mg/dL	188.16 ± 41.4	185.9 ± 39.6	189.9 ± 42.8	< 0.001
LDL-C, mg/dL	118.2 ± 35.6	116.8 ± 34.7	119.4 ± 36.2	0.001
Hypertension, n (%)	1334 (15.3%)	592 (15.4)	742 (15.3)	0.800
Diabetes, n (%)	887 (10.2)	379 (9.9)	508 (10.4)	0.339
Dyslipidemia, n (%)	7114 (81.8)	2992 (78.1)	4122 (84.7)	< 0.001
CVD events, n (%)	337 (3.9%)	198 (5.2)	139 (2.9)	< 0.001
Current smoking status, n (%)	1131 (13.0%)	966 (25.2)	165 (3.4)	< 0.001
Education, n (%) < 12 years	7345 (84.5)	3102 (80.9)	4243 (87.2)	< 0.001
Low physical activity, n (%)	3320 (38.2)	1674 (34.4)	1646 (43.0)	< 0.001
CEW score	1.9 ± 4.9	1.1 ± 4.4	2.7 ± 5.2	< 0.001
CEWC score	-0.15 ± 13.1	3.5 ± 11.6	-3.0 ± 13.5	< 0.001
Family history of CVD, n (%)	891 (10.2%)	491 (12.8%)	400 (8.2%)	< 0.001
Creatinine, mg/dL	1.0 ± 0.1	1.1 ± 0.1	0.9 ± 0.1	< 0.001
eGFR, mL/min per 1.73 m^2	84.8 ± 14.6	86.2 ± 14.7	83.6 ± 14.5	< 0.001

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high-density lipoprotein- cholesterol; CVD, cardiovascular disease; CEW, cumulative excess weight; CEWC, cumulative excess waist circumference

Data represented as mean ± SD or n (%).

*2 h-PCPG, 2-hour post challenge plasma glucose

† Data represented as median IQ (25–75)

change in CEWC score were 1.074 (95% CI, 1.006–1.147, $p=0.033$) for men in a fully adjusted model. Moreover, we found no significant association between CEWC score and incidence of CKD among women in the fully adjusted model, with HR of 0.941 (95% CI, 0.884–1.002, $p=0.057$) as shown in Table 4.

In the sensitivity analysis, the HRs for CKD associated with CEW were significant for both sexes across all age groups in the unadjusted model. However, in the fully adjusted model, significant associations were observed only in participants aged ≥ 50 years, suggesting an increased risk of CKD with higher CEW in the older population (Supplementary Table 3). For CEWC the unadjusted model indicated significant HRs for CKD in both sexes across all age groups. In the fully adjusted model, significant associations persisted only in participants aged ≥ 50 years, indicating a pronounced risk of CKD associated with higher CEWC in the older age group (Supplementary Table 4).

Discussion

This population-based study indicated that the higher duration and severity of excess BMI and WC, as demonstrated by CEW and CEWC, were associated with the increased incidence of CKD among patients involved in the cohort during 15 years of follow-up. We found significant HRs of incident CKD in one SD change of CEW score for men and women in the fully adjusted model that HRs were 1.155 (1.081–1.232) and 1.105 (1.047–1.167), respectively. We also found significant HR of incident CKD in one SD change of CEWC score for men with HR of 1.074 (1.006–1.147) in a fully adjusted model. No significant association was found between central obesity duration and severity according to CEWC scores among women. However, the sensitivity analysis indicates that the risk of CKD associated with CEW and CEWC is significantly higher in individuals aged 50 and above, particularly in women.

The association between obesity and chronic renal failure has been outlined in several studies. Some studies establish that patients with overweight and obesity are at a higher risk of CKD, in contrast to individuals with a normal BMI, this is also compatible with "metabolically healthy" obese patients [21]. A systematic review and meta-analysis pointed out that approximately 14% and 25% of males and females of industrialized populations respectively, develop CKD as a clinical sequela of obesity [7]. Obesity is a potent risk factor for kidney disease. A cohort study of more than 320,000 participants, revealed a graded increase in the risk of ESRD with an increase in BMI classes [11]. Higher baseline BMI continued to be an independent predictor for ESRD after further adjustments for blood pressure and status of diabetes mellitus [11]. In the present study, 65.4% (829) of men and 77.9%

Table 2 Baseline characteristics of CKD and non-CKD participants after follow-up

	Men			Women		
	non-CKD	CKD	*p*-value	non-CKD	CKD	*p*-value
Number	2565	1267	-	2503	2362	-
Age, years	35.1 ± 12.2	54.4 ± 13.5	< 0.001	31.9 ± 10.5	46.2 ± 13.7	< 0.001
Age ≥ 50 years	337 (13.1)	831 (65.6)	< 0.001	150 (6.0)	1036 (43.9)	< 0.001
BMI, kg/m^2	25.8 ± 4.5	26.6 ± 4.1	< 0.001	26.5 ± 5.0	28.9 ± 5.1	< 0.001
Overweight/Obese, BMI ≥ 25 kg/m^2	1438 (56.1)	829 (65.4)	< 0.001	1467 (58.6)	1839 (77.9)	< 0.001
WC, cm	91.1 ± 11.9	95.0 ± 10.7	< 0.001	84.1 ± 12.6	92.1 ± 13.1	< 0.001
High WC (> 89 cm for men and > 91 cm for women)	1525 (59.5)	934 (73.7)	< 0.001	739 (29.5)	1306 (55.3)	< 0.001
SBP, mmHg	114.3 ± 13.9	124.2 ± 19.7	< 0.001	107.1 ± 13.4	118.1 ± 20.1	< 0.001
DBP, mmHg	74.2 ± 10.1	77.0 ± 11.7	< 0.001	71.1 ± 9.4	76.0 ± 10.6	< 0.001
FPG, mg/dL	93.4 ± 22.4	104.1 ± 35.2	< 0.001	89.9 ± 20.8	101.9 ± 37.2	< 0.001
2 h-PCPG, mg/dL *	109.7 ± 61.3	142.2 ± 92.9	< 0.001	111.9 ± 56.4	145.7 ± 97.5	< 0.001
TG, mg/dL †	135.0 (91.0–203.7)	151.0 (107.0–217.0)	< 0.001	104.0 (73.0–153.0)	140.0 (97.0–202.0)	< 0.001
HDL-C, mg/dL	35.7 ± 9.0	35.5 ± 9.4	0.383	41.9 ± 10.7	41.6 ± 10.9	0.273
Total cholesterol, mg/dL	182.4 ± 40.1	193.3 ± 37.4	< 0.001	179.1 ± 37.9	201.3 ± 44.6	< 0.001
LDL-C, mg/dL	114.1 ± 34.6	122.3 ± 34.1	< 0.001	112.2 ± 32.6	127.0 ± 38.3	< 0.001
Hypertension, n (%)	247 (9.6)	345 (27.2)	< 0.001	159 (6.4)	583 (24.7)	< 0.001
Diabetes, n (%)	157 (6.1)	222 (17.5)	< 0.001	135 (5.4)	373 (15.8)	< 0.001
Dyslipidemia, n (%)	1987 (77.5)	1005 (79.3)	0.192	2065 (82.5)	2057 (87.1)	< 0.001
CVD events, n (%)	67 (2.6)	131 (10.3)	< 0.001	18 (0.7)	121 (5.1)	< 0.001
Current smoking status, n (%)	685 (26.7)	281 (22.2)	0.002	65 (2.6)	100 (4.2)	0.002
Education, n (%) < 12 years	2022 (79.7)	1058 (83.5)	0.004	2110 (84.3)	2133 (90.3)	< 0.001
Low physical activity, n (%)	1095 (42.7)	551 (43.5)	0.652	909 (36.3)	765 (32.4)	0.004
CEW score	0.8 ± 4.5	1.6 ± 4.2	< 0.001	1.5 ± 5.0	3.9 ± 5.2	< 0.001
CEWC score	2.2 ± 11.9	6.1 ± 10.7	< 0.001	-6.9 ± 12.6	1.1 ± 13.3	< 0.001
Family history of CVD, n (%)	330 (12.9)	161 (12.7)	0.918	202 (8.1%)	198 (8.4%)	0.715
Creatinine, mg/dL	1.1 ± 0.1	1.1 ± 0.1	< 0.001	0.9 ± 0.1	0.9 ± 1	< 0.001
eGFR, mL/min per 1.73 m^2	91.6 ± 13.4	75.3 ± 10.49	< 0.001	90.4 ± 13.3	76.5 ± 12.1	< 0.001

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triglyceride; HDL-C, high-density lipoprotein- cholesterol; CVD, cardiovascular disease; CEW, cumulative excess weight; CEWC, cumulative excess waist circumference

Data represented as mean ± SD

*2 h-PCPG, 2-hour post challenge plasma glucose

† Data represented as median IQ (25–75)

Table 3 Risk CKD determined by one standard deviation change of CEW score

CEW	Men (Person observation = 11118)		Women (Person observation = 11464)	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Unadjusted	1.329 (1.253–1.408)	**< 0.001**	1.503 (1.439–1.569)	**< 0.001**
Adjusted model[a]	1.190 (1.118–1.268)	**< 0.001**	1.167 (1.107–1.230)	**< 0.001**
Adjustedmodel[b]	1.155 (1.081–1.232)	**< 0.001**	1.105 (1.047–1.167)	**< 0.001**

CKD, chronic kidney disease; CEW, cumulative excess weight; HR, hazard ratio; CI, confidence interval, cardiovascular disease

model [a] Adjusted for age

model [b] Adjusted for age, smoking, diabetes, hypertension, and educational level

(1839) of women with CKD had a BMI higher than 25, and high WC (>89 cm for men and >91 cm for women) was found to be 73.7% (934) and 55.3% (1306) for men and women, respectively.

Some studies outlined the association between obesity severity and duration on different clinical outcomes in the general population. In a nationwide cohort study among Korean patients, Park et al. [22]. investigated the association between cumulative obesity exposure (COE) and the risk of kidney cancer. They defined COE as the number of years since obesity diagnosis during the exposure period; It was shown that the HRs for kidney cancer

Table 4 Risk CKD determined by one standard deviation (SD) change of CEWC score

CEWC	Men (Person observation = 11118)		Women (Person observation = 11464)	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Unadjusted	1.355 (1.281–1.434)	**< 0.001**	1.401 (1.329–1.478)	**< 0.001**
Adjusted model[a]	1.110 (1.041–1.183)	**0.001**	0.991 (0.932–1.053)	0.763
Adjustedmodel[b]	1.074 (1.006–1.147)	**0.033**	0.941 (0.884–1.002)	0.057

CKD, chronic kidney disease; CEWC, cumulative excess waist circumference; HR, hazard ratio; CI, confidence interval, cardiovascular disease

model [a] Adjusted for age

model [b] Adjusted for age, smoking, diabetes, hypertension, and educational level

increased significantly alongside BMI and WC. Silverwood et al. [10] outlined a higher risk of CKD with onset of overweight and obesity in earlier ages, the strength of the association decreases significantly with increases in the age of first-onset obesity. In a longitudinal study by Mongraw-Chaffin et al. [22], it was pointed out that higher time-varying obesity severity and duration were both associated with increased odds of incident metabolic syndrome. Several studies have shown that CEW and CEWC scores, as described previously, are associated with the incidence of type 2 diabetes, coronary heart disease, and are predictive factors for stroke [12, 23, 24]. All the studies highlighted the link between the duration and severity of obesity and negative clinical outcomes, using varying evaluation methods. To the best of our knowledge, no study has investigated the association of cumulative obesity with CKD development.

In the present study, obesity severity and duration were associated with significantly higher HRs for incident CKD with a one SD change in CEW and CEWC scores. Our findings indicated that the accumulation of central obesity during follow-up, as reflected by the CEWC score, is associated with the incidence of CKD only among men. The observed sex-specific differences in the association between CEWC and CKD incidence may be attributed to a combination of biological, hormonal, and lifestyle factors [25, 26]. Biologically, men and women exhibit different patterns of fat distribution, with men typically accumulating more visceral fat, which has a stronger correlation with metabolic disturbances and CKD than subcutaneous fat [27, 28]. Hormonal differences also play a significant role; premenopausal women have protective effects from estrogen, which promotes a more favorable fat distribution and metabolic profile [29, 30]. However, postmenopausal women experience a shift towards central adiposity, increasing their risk of CKD [31]. This is supported by evidence indicating that menopause is associated with an increase in visceral fat and a consequent higher risk of metabolic syndrome and CKD.

In our study, 75% of female participants were under 50 at baseline, with a mean age of 38.9 years. During the 15-year follow-up, many had not yet transitioned to menopause, reflected by the mean ages of non-CKD (31.9 years) and CKD-affected women (46.2 years). For women over 50, the HR for CKD risk associated with a one SD change in CEWC score was 1.160, more pronounced than in men over 50. A recent study showed that women experiencing early menopause (before age 45) had a higher CKD risk (OR: 1.26) than those reaching menopause later [31]. This suggests that the menopausal transition, with its hormonal changes leading to central fat distribution, increases CKD risk in older women. Studies confirm that menopause increases visceral fat, contributing to metabolic syndrome and CKD [30, 32].

Obesity leads to CKD directly through obesity-related glomerulopathy and indirectly through associated conditions like hypertension, atherosclerosis, and type 2 diabetes. Prolonged obesity causes sodium retention, sympathetic activation, and elevated leptin levels which increase blood pressure [33, 34]. Hemodynamic changes like afferent arteriole dilation and increased sodium reabsorption lead to hyperfiltration and proteinuria [35]. Obese patients have increased GFR, renal plasma flow, and filtration fraction compared to lean patients, resulting in tubule-glomerular feedback that causes vasodilation, hypertension, and further kidney damage [36, 37]. Insulin resistance and hyperinsulinemia also play a key role in increasing oxidative stress, endothelial dysfunction, and release of TGF-β and IGF-1 [38, 39]. Resulting dyslipidemia, characterized by high triglycerides and LDL along with low HDL, as well as increased renal sinus fat deposits and adipokine/cytokine production, may further contribute to CKD progression in obesity [40–43].

It is the first to examine the link between cumulative obesity metrics and the development of CKD, utilizing a long follow-up period and objective measures instead of self-reported data. Additionally, the study comprehensively accounted for important confounders such as physical activity, smoking, educational level, and metabolic variables. However, there are limitations to consider. We did not account for socioeconomic and nutritional status, nor did we include variables such as proteinuria frequency and inflammatory mediator levels, which could provide a more comprehensive assessment of obesity's role in CKD. Potential confounders like dietary habits, socioeconomic status, and genetic predispositions were

also not considered, which can significantly influence both obesity and CKD outcomes. Dietary patterns and physical activity are closely related to obesity and metabolic health, and their omission could lead to residual confounding. Socioeconomic status affects access to healthcare, education, and lifestyle choices, while genetic predispositions may modify the observed associations. Additionally, the generalizability of the findings should be interpreted with caution, as our study sample was drawn from Tehran, a metropolitan area. Further investigation is needed to determine if these results apply to the broader population and different racial and socioeconomic groups.

The accumulation of general and central obesity, as measured by CEW and CEWC, was associated with an increased incidence of CKD over the 15-year follow-up period in the TLGS. The results demonstrated that both men and women with higher CEW scores had a higher risk of developing CKD, while men also showed a significant association with CEWC scores. Although no significant association was found between central obesity and CKD in women based on CEWC scores, sensitivity analysis indicated that the risk of CKD was significantly higher in individuals aged 50 and above, especially in women. These findings highlight the importance of considering both the duration and severity of obesity in CKD risk assessments. Healthcare providers may incorporate cumulative metrics like CEW and CEWC into routine evaluations to better identify high-risk individuals and implement targeted interventions. Further studies evaluating different races, as well as other potential confounders such as diet, genetics, and physical activity, are needed to generalize these findings and provide a comprehensive understanding of the factors influencing the association between cumulative obesity and CKD.

Supplementary Information

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Supplementary Material 1

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Author contributions
FG: Conceptualization, Data curation, Writing - Original draft preparation. NE: Data curation, Writing - Original draft preparation. AE: Methodology, Writing - Review & Editing. MM: Software, Formal analysis. MB: Validation, Writing - Review & Editing. MV: Validation, Writing - Review & Editing. FA: Resources, Supervision. FH: Conceptualization, Methodology, Supervision.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests
The authors declare no competing interests.

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References

1. Hawkesworth S, Obesity. Definition, Etiology, and Assessment. In: Caballero B, editor. Encyclopedia of Human Nutrition (Third Edition). Waltham: Academic Press; 2013. pp. 350-3.
2. Federation T. World obesity Atlas 2023. World Obesity Federation; 2022.
3. Garofalo C, Borrelli S, Minutolo R, Chiodini P, De Nicola L, Conte G. A systematic review and meta-analysis suggests obesity predicts onset of chronic kidney disease in the general population. Kidney Int. 2017;91(5):1224–35.
4. Rahmani A, Sayehmiri K, Asadollahi K, Sarokhani D, Islami F, Sarokhani M. Investigation of the prevalence of obesity in Iran: a systematic review and Meta-analysis study. Acta Med Iran. 2015;53(10):596–607.
5. Singh GM, Danaei G, Farzadfar F, Stevens GA, Woodward M, Wormser D, et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. PLoS ONE. 2013;8(7):e65174.
6. Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet. 2011;377(9771):1085–95.
7. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ. Association between obesity and kidney disease: a systematic review and meta-analysis. Kidney Int. 2008;73(1):19–33.
8. Foster MC, Hwang SJ, Larson MG, Lichtman JH, Parikh NI, Vasan RS, et al. Overweight, obesity, and the development of stage 3 CKD: the Framingham Heart Study. Am J Kidney Dis. 2008;52(1):39–48.
9. Xu H, Kuja-Halkola R, Chen X, Magnusson PKE, Svensson P, Carrero JJ. Higher body mass index is associated with incident diabetes and chronic kidney disease independent of genetic confounding. Kidney Int. 2019;95(5):1225–33.
10. Silverwood RJ, Pierce M, Thomas C, Hardy R, Ferro C, Sattar N, et al. Association between younger age when first overweight and increased risk for CKD. J Am Soc Nephrol. 2013;24(5):813–21.
11. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006;144(1):21–8.
12. Zameni F, Bakhtiyari M, Mansournia MA, Ramezankhani A, Azizi F, Hadaegh F. Is incident type 2 diabetes associated with cumulative excess weight and abdominal adiposity? Tehran lipid and glucose study. Diabetes Res Clin Pract. 2018;136:134–42.
13. Kabootari M, Asgari S, Mansournia MA, Khalili D, Valizadeh M, Azizi F, et al. Different weight histories and risk of incident coronary heart disease and stroke: tehran lipid and glucose study. J Am Heart Assoc. 2018;7(4):e006924. https://doi.org/10.1161/JAHA.117.006924. PMID: 29440011; PMCID: PMC5850180.
14. Azizi F, Ghanbarian A, Momenan AA, Hadaegh F, Mirmiran P, Hedayati M, et al. Prevention of non-communicable disease in a population in nutrition transition: Tehran lipid and glucose study phase II. Trials. 2009;10:5.
15. Delavari A, Forouzanfar MH, Alikhani S, Sharifian A, Kelishadi R. First nationwide study of the prevalence of the metabolic syndrome and optimal cutoff points of waist circumference in the Middle East: the national survey of risk factors for noncommunicable diseases of Iran. Diabetes Care. 2009;32(6):1092–7.
16. Kilbride HS, Stevens PE, Eaglestone G, Knight S, Carter JL, Delaney MP, et al. Accuracy of the MDRD (modification of Diet in Renal Disease) study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. Am J Kidney Dis. 2013;61(1):57–66.
17. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.

18. Ainsworth BE, Jacobs DR Jr., Leon AS. Validity and reliability of self-reported physical activity status: the Lipid Research Clinics questionnaire. Med Sci Sports Exerc. 1993;25(1):92–8.
19. Kriska AM, Knowler WC, LaPorte RE, Drash AL, Wing RR, Blair SN, et al. Development of questionnaire to examine relationship of physical activity and diabetes in Pima indians. Diabetes Care. 1990;13(4):401–11.
20. Mohammad K, Sadat Hashemi SM, Farahani FK. Age at natural menopause in Iran. Maturitas. 2004;49(4):321–6.
21. Chang Y, Ryu S, Choi Y, Zhang Y, Cho J, Kwon MJ, et al. Metabolically healthy obesity and development of chronic kidney disease: a Cohort Study. Ann Intern Med. 2016;164(5):305–12.
22. Park YH, Moon HW, Cho HJ, Ha US, Hong SH, Lee JY, et al. Cumulative obesity exposure increases the risk of kidney cancer: a longitudinal nationwide cohort study. Am J Cancer Res. 2021;11(10):5016–26.
23. Kabootari M, Asgari S, Mansournia MA, Khalili D, Valizadeh M, Azizi F, et al. Different weight histories and risk of Incident Coronary Heart Disease and Stroke: Tehran lipid and glucose study. J Am Heart Association. 2018;7(4):e006924.
24. Bouchard DR, Porneala B, Janssen I, Langlois MF, Baillargeon JP, Fox CS, et al. Risk of type 2 diabetes and cumulative excess weight exposure in the Framingham offspring study. J Diabetes Complications. 2013;27(3):214–8.
25. Yau K, Kuah R, Cherney DZI, Lam TKT. Obesity and the kidney: mechanistic links and therapeutic advances. Nat Rev Endocrinol. 2024;20(6):321–35.
26. Goossens GH, Jocken JWE, Blaak EE. Sexual dimorphism in cardiometabolic health: the role of adipose tissue, muscle and liver. Nat Rev Endocrinol. 2021;17(1):47–66.
27. Pou KM, Massaro JM, Hoffmann U, Lieb K, Vasan RS, O'Donnell CJ, et al. Patterns of abdominal fat distribution: the Framingham Heart Study. Diabetes Care. 2009;32(3):481–5.
28. Kotronen A, Westerbacka J, Bergholm R, Pietiläinen KH, Yki-Järvinen H. Liver fat in the metabolic syndrome. J Clin Endocrinol Metab. 2007;92(9):3490–7.
29. Garaulet M, Pérez-Llamas F, Baraza JC, Garcia-Prieto MD, Fardy PS, Tébar FJ, et al. Body fat distribution in pre-and post-menopausal women: metabolic and anthropometric variables. J Nutr Health Aging. 2002;6(2):123–6.
30. Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond). 2008;32(6):949–58.
31. Qian D, Wang ZF, Cheng YC, Luo R, Ge SW, Xu G. Early menopause may associate with a higher risk of CKD and all-cause mortality in postmenopausal women: an analysis of NHANES, 1999–2014. Front Med (Lausanne). 2022;9:823835. https://doi.org/10.3389/fmed.2022.823835. PMID: 35372385; PMCID: PMC8971204.
32. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Menopause-related changes in body fat distribution. Ann N Y Acad Sci. 2000;904:502–6.
33. Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: interaction of neurohumoral and renal mechanisms. Circ Res. 2015;116(6):991–1006.
34. Nawaz S, Chinnadurai R, Al-Chalabi S, Evans P, Kalra PA, Syed AA, et al. Obesity and chronic kidney disease: a current review. Obes Sci Pract. 2023;9(2):61–74.
35. D'Agati VD, Chagnac A, de Vries AP, Levi M, Porrini E, Herman-Edelstein M, et al. Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. Nat Rev Nephrol. 2016;12(8):453–71.
36. Chagnac A, Herman M, Zingerman B, Erman A, Rozen-Zvi B, Hirsh J, et al. Obesity-induced glomerular hyperfiltration: its involvement in the pathogenesis of tubular sodium reabsorption. Nephrol Dial Transpl. 2008;23(12):3946–52.
37. Bosma RJ, Krikken JA, van der Homan JJ, de Jong PE, Navis GJ. Obesity and renal hemodynamics. Contrib Nephrol. 2006;151:184–202.
38. Sarafidis PA, Ruilope LM. Insulin resistance, hyperinsulinemia, and renal injury: mechanisms and implications. Am J Nephrol. 2006;26(3):232–44.
39. De Cosmo S, Menzaghi C, Prudente S, Trischitta V. Role of insulin resistance in kidney dysfunction: insights into the mechanism and epidemiological evidence. Nephrol Dial Transpl. 2013;28(1):29–36.
40. Wagner R, Machann J, Lehmann R, Rittig K, Schick F, Lenhart J, et al. Exercise-induced albuminuria is associated with perivascular renal sinus fat in individuals at increased risk of type 2 diabetes. Diabetologia. 2012;55(7):2054–8.
41. Nam KH, Chang TI, Joo YS, Kim J, Lee S, Lee C, et al. Association between Serum High-Density Lipoprotein Cholesterol Levels and progression of chronic kidney disease: results from the KNOW-CKD. J Am Heart Assoc. 2019;8(6):e011162.
42. Tsuruya K, Yoshida H, Nagata M, Kitazono T, Hirakata H, Iseki K, et al. Association of the triglycerides to high-density lipoprotein cholesterol ratio with the risk of chronic kidney disease: analysis in a large Japanese population. Atherosclerosis. 2014;233(1):260–7.
43. Bobulescu IA. Renal lipid metabolism and lipotoxicity. Curr Opin Nephrol Hypertens. 2010;19(4):393–402.

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