Obesity without metabolic abnormality and incident CKD

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Metabolically healthy obesity is associated with a high risk of incident chronic kidney diseases compared with normal weight: A longitudinal study of 4.5 million participants from a United Kingdom primary care database

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Abstract

RATIONAL & OBJECTIVE Metabolically healthy obesity (obesity without any metabolic abnormality) is deemed not to be associated with increased risk of morbidity and mortality. We aimed to examine and quantify the potential association between metabolically healthy overweight/obesity and the risk of incident chronic kidney disease (CKD) in a contemporary Western population.

DESIGN Retrospective population-based cohort study

SETTING The Health Improvement Network (THIN), United Kingdom, 1995 to 2015

PARTICIPANTS 4,447,955 of the 5,182,908 adults in the THIN database with a valid body mass index (BMI) record from the registration date and initially free of CKD and cardiovascular disease were included.

EXPOSURES 11 body size phenotypes defined by body mass index categories (underweight, normal weight, overweight, and obesity) and 3 metabolic abnormalities (diabetes, hypertension, and hyperlipidaemia) were created.

MAIN OUTCOME MEASURES Incident CKD - composite of recorded end-stage kidney disease, recorded CKD, and eGFR (<60 ml/min/1.73m for ≥90 days) and albuminuria (ACR >3 mg/mmol for ≥90 days) based diagnoses of CKD.

RESULTS Of the 4.5 million individuals, 1,040,921 (23.4%) and 588,909 (13.2%) were metabolically healthy overweight and metabolically healthy obese respectively. During a mean follow-up of 5.4 (SD 4.3) years, compared with individuals with metabolically healthy normal weight (n=1,656,231), those who had metabolically healthy overweight (adjusted HR = 1.30, 95% CI 1.28 to 1.33) and metabolically healthy obesity (adjusted HR = 1.66, 95% CI 1.62 to 1.70) had a higher risk of incident CKD. The association was stronger in those below 65 years of age and male. The risk of incident CKD in all weight categories increased with increasing number of metabolic abnormalities in a graded fashion.

LIMITATIONS

CONCLUSIONS Overweight and obesity without metabolic abnormality are associated with a higher risk of CKD compared to those with normal body weight and no metabolic abnormality.

1

Plain summary

Title: **People with high body weight have a higher risk of chronic kidney disease even in the absence of other risk factors**

It is believed that risk factors like high blood pressure, diabetes and high cholesterol are responsible for the increased risk of complications of obesity like heart attack, stroke and kidney disease. Previously we showed that obese individuals without these risk factors have higher risk of heart attack and stroke. In this study of 4.5 million individuals from the UK, we have compared overweight and obese individuals without these risk factors with those with normal weight. It shows that these individuals have a high risk developing chronic kidney disease over time. The risk is higher in those below 65 years and male. Whether weight loss will help to reduce the risk will need to be confirmed in a well-designed trial,

Introduction

Chronic kidney disease (CKD) has a major impact on global health, both as a direct cause of global morbidity and mortality and as an important risk factor for cardiovascular disease. In 2017, 697.5 million people in the world had CKD, and it accounted for 1.2 million deaths and 35·8 million disability-adjusted life-years.[1] The prevalence of CKD and mortality attributable to CKD increased by 29.3% and 41.5% respectively between 1990 and 2017.[1] CKD is also costly to the health care systems; the UK National Health Service spent £1.45 billion on CKD in 2009-2010.[2] CKD is largely preventable, and therefore, it is important to identify and treat the underlying modifiable causes and risk factors.[1]

Similar to the global trends in the prevalence of CKD, the prevalence of obesity is also on the rise, tripling between 1975 and 2016.[3] Obesity is known to increase the risk of cardiovascular (CVD) disease[4] and chronic kidney disease (CKD)[5,6]. Metabolic risk factors like diabetes, dyslipidemia and hypertension are thought to mediate the increased risk of morbidity and mortality associated with obesity.[7-10] A subset of obese individuals without these metabolic abnormalities, described as "metabolically healthy obese" (MHO), have been suggested, particularly in the news media, not to be at increased risk due to a lack of measured conventional cardiovascular disease risk factors.[8-12]

Whilst obesity-related complications such as hypertension, Type 2 diabetes, and cardiovascular disease can explain the links between obesity and CKD observed in several cross-sectional and longitudinal studies[13,14]; whether obesity on its own, can cause CKD remains unclear. A number of studies examined the relationship between MHO and CKD, but the results were inconsistent.[15-26] All of these studies, but one, were done on Asian populations; there is no available data on European populations.[26] In addition the definition of MHO in these studies varied and included up to 2 components of the metabolic syndrome.[26] On the other hand, metabolically healthy overweight and obese CKD patients have been shown to have lower risk of mortality compared to metabolically healthy normal weight CKD patients suggesting a protective effect of metabolically healthy obesity.[27]

We previously demonstrated that metabolically healthy obesity (MHO) was associated with a higher risk of CVD and heart failure compared with metabolically healthy normal weight (MHNW), but the risk was lower than in those with metabolically unhealthy obesity (MUHO).[28] Furthermore, obesity can be associated with reduced insulin sensitivity, oxidative

stress and increased inflammation, all of which can contribute to CKD.[29] Therefore, we hypothesized that compared with metabolically healthy normal weight individuals, those with MHO were at a higher risk of developing CKD.

Using a large contemporary UK primary care cohort based on linked electronic health records, we examined associations among body size phenotypes (underweight, normal weight, overweight, and obesity) with or without metabolic abnormalities (diabetes, hypertension, hyperlipidemia) and incident CKD.

Methods

This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[30]

Study design and setting

We undertook a cohort study with prospectively collected data from The Health Improvement Network (THIN) database, which contains computerized primary care records covering approximately 6% of the population from 787 general practices scattered in the UK. THIN captures coded data on patient characteristics (e.g. smoking status, height, and weight), diagnosis (in the primary care or secondary care), prescriptions, consultations, and investigations; these data could be recorded at the patient registration, opportunistically during care, reported back from the secondary care to the primary care physician, or as deemed clinically relevant by the primary care physicians. The THIN database is made up predominantly of a white British population, and is representative of the age structure of the UK population.[31] The comparisons to external statistics and other independent studies have shown that both the clinical diagnostic and prescribing information in the THIN database are well recorded and accurate.[32,33] Individual informed consent was obtained for all individuals who agreed to participate in the THIN study when they first registered with general practitioners. Data collection began in January 1995, and we used all data to May 2017.

Ethics

The THIN data collection scheme and research performed using THIN data were approved by the National Health Service South-East Multicenter Research Ethics Committee in 2003. Under the terms of the approval, studies must undergo independent scientific review. The

use of THIN data for this study was approved by the Scientific Review Committee on 26th November 2018 (SRC reference number: 18THIN094).

Participants

All adult participants (18 years and above) in THIN with available body mass index (BMI) records from the registration date were eligible for this study. To ensure only incident CKD events were captured, the study entry began 12 months after registration to limit the possibility that the diagnosis of outcomes documented after registration reflected pre-existing or historical disease. We considered the study entry date was the latest of the following: one year after the registration date, one year after the practice acceptable mortality recording date, or one year after the Vision IT system implementation date. Individuals with any record of CKD or Cardiovascular diseases (CVD) events no later than the study entry date or with implausible BMI values (below 13 kg/m^2 or over 100 kg/m^2) were excluded.

Exposure

BMI was categorized based on the World Health Organization Criteria: underweight (BMI of <18.5 kg/m^2), normal weight (BMI of 18.5 kg/m^2 to <25 kg/m^2), overweight (BMI of 25 kg/m^2 to <30 kg/m^2), and obesity (BMI of ≥30 kg/m^2).[34] Baseline BMI was extracted from the dataset as the first BMI recorded from the registration date or the first one recorded after the Vision IT system was initiated but before the start of the observation period. Baseline BMI date was the latest date of either of the above events. This approach minimized the chance that the BMI was recorded due to particular clinical reasons but more likely to have been recorded for administrative purposes.

Diabetes and hypertension diagnoses were identified by Read code diagnoses at study entry (***Table S1***). Read Codes are a coded thesaurus of clinical terms, which have been used in the National Health service (NHS) since 1985. It provides a standard vocabulary for clinicians to record patient findings, operations, procedures, interventions, and drugs, in health and social care IT systems across primary and secondary care in the UK. Dyslipidemia diagnosis was defined as those who were recorded to have been prescribed lipid-lowering agents using prescription codes or by laboratory measurements of elevated serum total cholesterol (≥ 240 mg/dL or ≥ 6.2 mmol/L), low-density lipoprotein-cholesterol (LDL-C, ≥ 160 mg/dL or ≥ 4.10 mmol/L), or triglycerides (≥ 200 mg/dL or ≥ 2.26 mmol/L), or low high-density lipoprotein-

cholesterol (HDL-C, < 40 mg/dL or < 1.00 mmol/L) at baseline.[35,36] Metabolically healthy individuals were defined as those without evidence in THIN for hypertension, diabetes, or dyslipidemia.

Participants were divided into 11 body size phenotypes based on their BMI categories and metabolic status at baseline: underweight with zero metabolic abnormalities (absence of hypertension, hyperlipidemia, diabetes); underweight with one or more metabolic abnormalities; normal weight with zero metabolic abnormalities; normal weight with one metabolic abnormality; normal weight with two or more metabolic abnormalities; overweight with zero metabolic abnormalities; overweight with one metabolic abnormality; overweight with two or more metabolic abnormalities; obese with zero metabolic abnormalities; obese with one metabolic abnormality; and obese with two or more metabolic abnormalities.

Outcome

The primary endpoint was the composite incident CKD, which was defined as those with a recorded diagnosis of renal replacement therapy (RRT) or CKD using Read codes or by estimated Glomerular Filtration Rate (eGFR, at least two measurements < 60 ml/min/1.73 m^2, using the CKD EPI Equation,[37] 90 days apart) and/ or laboratory measurements of Albumin/Creatinine Ratio (ACR, at least two readings > 3 mg/mmol, 90 days apart, microalbuminuria). Serum creatinine was measured using the internationally standardized isotope dilution mass spectrometry (IDMS) method.[38] The secondary endpoints of this study were eGFR-defined CKD (based on eGFR values only) and ACR-defined CKD (based on ACR values only). Any event occurring after the first CKD presentation was ignored. Endpoint definitions are described in ***Table S2***.

Follow-up

Eligible participants were followed-up from the study entry until the earliest date of any censoring event (participants left dataset or transferred out, death, study end, most recent data upload from practice, or outcome event happened).

Covariates

Covariates addressed in the analyses were age, sex, ethnicity, self-reported smoking status (never smokers, ex-smokers, or current smokers) and social deprivation on the patient's record at study entry. Social deprivation was described using the Townsend index (quintile of

the index of multiple deprivations), a score calculated for each participant's neighborhood on the basis of indices such as income, education, and employment.[39]

Statistical analysis

The baseline characteristics of participants, including age, sex, Townsend index, smoking status, and metabolic abnormalities, were summarized using appropriate descriptive statistics (Mean and Standard deviation [SD] for normally distributed continuous variables, Median and Interquartile range [IQR] for skewed distributed continuous variables, and proportion for categorical variables).

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional regression model Adjusted HRs were constructed by including age, sex, smoking status, and Townsend index in the Cox proportional regression models for associations of individual metabolic abnormalities or each body size phenotype (normal weight with zero metabolic abnormalities was the reference group) with CKD events. Missing data for Townsend index and smoking status were included in analyses as a missing categorical variable. To avoid the impact of death, a potential competing event, on the association of body size phenotypes with CKD, competing risk Cox proportional regression models were conducted as sensitivity analyses. Cumulative incidence curves were generated for each body size phenotype group (death was treated as a competing event).

To investigate if there were any differences in the risk of CKD by baseline characteristics which are known to influence the risk and prevalence of CKD, we stratified associations by sex, age (< 65 years of age and ≥ 65 years of age), and smoking status (non-smoker and ever-smoker). The cut-off at 65 years of age was chosen because this is commonly used to designate an individual as an older person.[40] In prior to the subgroup analysis, an interaction test for body size phenotypes and age/sex/smoking status were conducted.

Since some individuals in the metabolically healthy group may have transitioned to metabolic unhealthy status during the follow-up period, the time period after transition could be misclassified. With the adjustment of covariates at baseline, Cox proportional regression model and Cox proportional regression model with time-dependent covariates (incorporate follow-up metabolic abnormalities) were performed parallelly as sensitivity analyses to

compare the risk of developing composite CKD between individuals with and without metabolic abnormalities in underweight, normal weight, overweight, and obese groups.

All statistical tests were two-tailed and a $P < 0.05$ was considered statistically significant. All analyses were conducted in Stata 16.0 (College Station, Texas, USA) and R 4.0.4 (The R Foundation for Statistical Computing).

Patient and public involvement

We did not include patient and public directly throughout the research process (formulation of research questions, outcome measures development, study design, recruitment, the conduct of the study, and dissemination of the results).

Results

Of the 5,182,908 adults in the THIN database, we excluded a total number of 734,953 participants - 1) those without a valid BMI value at baseline (n = 224,032); 2) those with recorded CVD at baseline (n = 418,091); 3) those with recorded CKD at baseline (n = 189,365) (***Figure 1***). Among the remaining 4,447,955 participants, 114,951 (2.6%), 1,656,231 (37.2%), 1,040,921 (23.4%), and 588,909 (13.2%) individuals were classified as underweight, normal weight, overweight, and obese with no metabolic abnormalities, respectively (***Table 1***). Individuals with MHO were more likely to be younger, female, current smokers, and socioeconomically deprived compared with MUHO.

Body weight, Metabolic Health Status and Composite CKD Events

Over a mean of 5.4 years' follow-up, there were 114,950 incident composite CKD presentations. ***Table S3*** shows that participants diagnosed with diabetes (adjusted HR = 1.78, 95%CI 1.75 to 1.81), hypertension (adjusted HR = 1.72, 95%CI 1.70 to 1.74), and dyslipidemia (adjusted HR = 1.08, 95%CI 1.07 to 1.10) had a higher risk of developing composite CKD during follow up. Compared to participants with normal weight at baseline, participants with overweight (adjusted HR = 1.27, 95%CI 1.25 to 1.29) or obesity (adjusted HR = 1.72, 95%CI 1.70 to 1.75) had a higher risk of incident composite CKD, while participants who were underweight had a lower risk of incident composite CKD (adjusted HR = 0.87, 95%CI 0.83 to 0.92).

Body Size Phenotypes and Metabolic Status with CKD Events

Incidence rates of CKD events by body size phenotype and metabolic status are shown in ***Table 2*** and ***Figure 2***. ***Figure 3*** depicts the associations between the 11 body size phenotypes with or without metabolic abnormalities and CKD events (composite CKD, eGFR-defined CKD, and ACR-defined CKD) with the normal weight with zero metabolic abnormalities group as the reference. The crude/adjusted HRs and its 95% CIs of CKD events (Composite CKD, eGFR defined CKD, and ACR defined CKD) by body size phenotypes and metabolic status are presented in ***Table 3***.

Composite CKD Events

Compared to the reference group (normal weight with no metabolic abnormality), individuals who were overweight with zero metabolic abnormality (adjusted HR = 1.30, 95% CI 1.28 to 1.33) and obesity with zero metabolic abnormality (MHO) (adjusted HR = 1.66, 95% CI 1.62 to 1.70) had a higher risk of developing composite CKD events, while those who were underweight with zero metabolic abnormality (adjusted HR = 0.96, 95% CI 0.90 to 1.03) had a similar risk. The risk of composite CKD events in the underweight, normal weight, overweight, and obese groups was higher with the higher number of metabolic abnormalities present (***Figure 2***). The results of competing risk Cox proportional hazard model were generally similar to the results of standard Cox proportional hazard model (**Table S4**).

Sensitivity analyses (**Table S5**) show that individuals with metabolic abnormalities had significantly higher risks of developing composite CKD during follow up, compared to individuals without metabolic abnormalities, in all BMI groups. The HRs derived from the conventional competing risk Cox regression and the competing risk Cox regression with time-dependent covariate were broadly similar.

eGFR-defined CKD Events

Compared to the reference group, individuals who were overweight with zero metabolic abnormality (adjusted HR = 1.35, 95% CI 1.31 to 1.40) and obesity with zero metabolic abnormity (adjusted HR = 1.58, 95% CI 1.52 to 1.64) had a higher risk of eGFR defined CKD events. The risk of eGFR defined CKD events in the normal weight, overweight, and obesity groups was higher with the higher number of metabolic abnormalities present (***Figure 3***). Individuals who were underweight with zero metabolic abnormality (adjusted HR = 0.75, 95% CI 0.67 to 0.84) had a lower risk of eGFR defined CKD Events.

ACR-defined CKD Events

Compared to the reference group, individuals who were overweight with zero metabolic abnormality (adjusted HR = 1.56, 95% CI 1.49 to 1.64) and obesity with zero metabolic abnormality (adjusted HR = 2.82, 95% CI 2.70 to 2.96) had a higher risk of developing ACR defined CKD events, while those who were underweight with zero metabolic abnormality had an unchanged risk. The risk of ACR defined CKD events in the underweight, normal weight, overweight, and obesity groups was higher with higher number of metabolic abnormalities, especially among those with two or more metabolic abnormities (***Figure 3***).

Subgroup analysis

Figure 4 shows the association of body size phenotype and metabolic status with composite CKD events by sex, age, and smoking status. The risk of composite CKD in individuals with metabolic abnormalities differed significantly by age. Individuals under the age of 65 had much stronger positive associations between body size phenotype and metabolic status and composite CKD than those 65 years or older. There was no difference between non-smoker and ever-smoker (ex-smoker & current smoker) individuals, and between male and female.

Discussion

In this study of approximately 4.5 million individuals from the UK primary care population, followed up for a mean of 5.4 years, we have demonstrated that metabolically healthy overweight and obese individuals (those without a metabolic risk factor – hypertension, diabetes or dyslipidemia, nor known CVD) have 30% and 66% higher risks respectively of incident CKD compared with those with metabolically healthy normal weight individuals. This association is stronger in those under the age of 65 years. We have also shown that within each weight category, there is a potential graded relationship between the risk of developing CKD and the presence of number of metabolic abnormalities, i.e. higher the number of metabolic risk factors, greater is the risk of developing CKD. Furthermore, those with normal weight and metabolic risk factors also have higher risk of incident CKD. The results were similar irrespective of the way CKD was defined; i.e. composite, eGFR-based or ACR-based.

Studies examining the association between MHO and incident CKD have produced conflicting results.[15-26] In view of this, two systematic review and metanalyses have been performed,

with 166,718 (from 4 studies) and 181,505 (from 11 studies) participants respectively, both showing higher risk of incident CKD in MHO compared with MHNW individuals.[19,41] However, the number of studies included in these two metanalyses were small and there were variable degrees of bias. There was also significant heterogeneity in sample size, length of follow-up, genetic background, the GFR estimation equation used, potential confounders controlled for, and the use of metabolically defined body size phenotypes. The definition of MHO varied and most studies included some components of the metabolic syndrome. Furthermore, most of the studies were carried out in Asian populations, with only two originating outside Asia. These factors limit the generalizability and applicability of the results, especially in the Western population. One study of 1.4 million participants from English general practice showed higher risk of CKD with higher BMI over 25 kg/m^2 and the log-linear relationship between the two remained even after adjusting for prior diabetes, hypertension and history of cardiovascular disease.[42] Our study cohort is much larger than this study and the two metanalyses combined, is derived from a homogeneous British primary care population, is controlled for major confounders, categories participants into 11 distinct sub-phenotypes based on BMI and metabolic risk factors, uses 3 different measures of incident CKD, and uses a GFR estimating equation most applicable to the obese populations.[43]

A putative explanation for the increased risk of CKD in metabolically healthy overweight and obese individuals is reduced insulin sensitivity which has been shown to be associated with kidney dysfunction independent of glucometabolic and cardiovascular risk factors.[44] Impaired insulin sensitivity and compensatory hyperinsulinemia are associated with activation of IGF-1, transforming growth factor-β, endothelin-1, components of the renin-angiotensin-aldosterone system and adipokines[45,46]; increased oxidative stress[47], reduced availability of nitric oxide[48] and formation of glycoxidation and lipid peroxidation products[49,50]. All of these promote mitogenic and fibrotic processes in the kidney and contribute to the pathogenesis and progression of CKD[45-53]. Furthermore, Fetuin-A, a hepatokine, which induces pro-inflammatory signaling in adipose tissue, has been shown to increase perivascular kidney sinus fat which plays a role in blood pressure regulation and CKD.[14,54] Chronic low grade inflammation associated with obesity may also play a part in the causation of CKD.[55] The other plausible explanation is the gradual development of metabolic and cardiovascular risk factors over time and thus transitioning to an unrecognized metabolically unhealthy status.

In our study, underweight individuals with no metabolic abnormalities had a lower risk of incident CKD which may reflect reduced muscle mass in these individuals rather than truly lower risk, as the GFR estimating equation used is based on serum creatinine. This is further supported by the observation that the risk of albuminuria-defined CKD in this group was comparable with the reference group.

This study and our previously published study showing higher risks of coronary heart disease, heart failure and cerebrovascular disease in MHO[28] demonstrate that these individuals develop target organ damage over time. Therefore, MHO should not be considered "benign" or harmless and addressing obesity in people with MHO might reduce target organ damage including CKD. In addition, this study also shows that even in the absence of obesity, based on BMI, people with normal weight and metabolic abnormalities are also at a higher risk of CKD. Whether weight loss in normal weight individuals will reduce the risk of CKD is unknown, but previous RCT showed that weight loss in normal weight individuals can reverse obesity complications such as non-alcoholic fatty liver disease.[56]

Our study has a few limitations. Using BMI as a surrogate of body fat, is simple and reproducible[57], but it does not discriminate between high percentage of body fat and increased lean mass, especially in young adults with a BMI of <30 kg/m^2 who undertake regular physical exercise. We did not have access to data on diet and physical activity. With the increasing age, it is more likely that individuals transitioned to higher BMI categories rather than to lower BMI categories over the follow up period given the known difficulty in losing weight.[58] This makes some misclassification of weight category possible. Metabolic abnormality was defined on the basis of baseline data in the main analysis. Some of the individuals, categorized as metabolically healthy overweight and obese at baseline, might have developed diabetes or hypertension during the follow-up period, as such the period after transition might be misclassified. In the sensitivity analyses, we compared the results of the conventional competing risk Cox regression model and competing risk Cox regression model with time-dependent covariates. The similar HRs derived from two models demonstrated that the transition from metabolic healthy to metabolic unhealthy state during the follow-up period does not have a major impact on the results of our main analyses. As such, diabetes and hypertension might have acted as mediators of CKD in some of these individuals. The development of diabetes and hypertension might also have prompted

screening for CKD in some of these individuals. On the other hand, improvement in BP and glycemic control in metabolically unhealthy obese, over time, through treatment, may potentially reduce the risk of developing CKD compared with those uncontrolled, making our HR estimates conservative. Finally, despite matching and adjusting the analysis for age, sex, smoking status, and deprivation (Townsend) index, there may have been residual confounding from unmeasured factors accounting for some of the findings (e.g. family history of CKD).

Since individuals with hypertension, diabetes, or dyslipidemia are often asymptomatic and these conditions are slowly progressive, we acknowledge that there is a potential risk of late diagnoses (the period between disease onset and the actual diagnosis date). Therefore, there might have been some misclassification of metabolic status due to late diagnosis. Given the nature of the analysis, it was not feasible for us to investigate associations between metabolic status as continuous measures with the risk of developing CKD in part due to the use of the real-world clinical data in the form of both laboratory measured parameters and physician-diagnosed Read codes. It should be noted that the associations between metabolic status and the risk of developing CKD is more linear, rather than dichotomized, from a biologic standpoint.

In addition to the strengths and limitations of the study already mentioned, this was by far the largest prospective study of the association between body size phenotypes with or without metabolic abnormalities and incident CKD providing unprecedented statistical power and precision. Dividing our participants into 11 sub-phenotypes based on BMI and metabolic risk factors allowed a more granular analysis of the CKD risk in these sub-phenotypes than done ever before. We believe these results are generalizable to Western populations.

Our results demonstrate that individuals with metabolically healthy obesity might have a higher risk of developing chronic kidney disease compared with normal weight individuals, especially those younger than 65 years. Metabolically healthy obesity is not benign. Weight loss interventions could be considered in these individuals to reduce the high risk of chronic kidney disease and examined in randomized controlled trials. Furthermore, individuals with normal weight who have metabolic abnormalities are also at a higher risk of CKD and meticulous metabolic control in this group of patients is essential to reduce CKD. Whether

weight loss in this group will reduce the risk of chronic kidney disease will also need to be examined in a randomized trial.

Authors' Contributions: Conceived the research question: ID, KN, NT; wrote the protocol: ID; contributed to the protocol: KN, NT, JW; extracted the data: KG; performed the data analysis: JW; contributed to data interpretation: JW, ID, KN, AT, and NT; checked the analysis externally: TT. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Funding: This work was carried out without any grant support.

Competing interests: There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethical approval: The study was approved by the Scientific Review Committee on 26th November 2018 (SRC reference number: 18THIN094).

Data sharing: No additional data available.

The manuscript guarantors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: There are no plans to disseminate the results of the research directly to the study participants. Dissemination to the population, in general, will be through media outreach (eg, press release) on the publication of this study.

Table Legends:

Table 1 Baseline characteristics of the Study Population by Body Size and Metabolic Health Status

Table 2 Incidence rate of chronic kidney diseases (CKD) by body size phenotype and metabolic status

Table 3 Hazard ratios for diagnosis of chronic kidney diseases (CKD) based on the number of metabolic abnormalities and body size phenotype.

Figure Legends:

Figure 1 Flow chart

Figure 2 The cumulative incidence curves of composite chronic kidney diseases (CKD) by body size phenotypes

Figure 3 Association between body size phenotypes and metabolic status and chronic kidney disease (CKD) events in 4.4 million UK adults

Figure 4 Association of body size phenotype and metabolic status with composite chronic kidney disease (CKD) events by age, sex, and smoking status

Table 1 Baseline characteristics of the Study Population by Body Size and Metabolic Health Status

Characteristics	Overall (n=4,447,955)	Underweight (n= 125,085)	Normal weight (n= 1,906,237)	Overweight (n=1,448,577)	Obese (n= 968,056)	
					Without metabolic abnormalities (n=588,909) *	With metabolic abnormalities (n=379,147) ¶
Age#	40.9 (29.1-55.6)	28.2 (22.2-44.2)	35.2 (26.1-50.8)	45.2 (33.0-58.6)	39.2 (29.8-49.7)	55.7 (46.6-64.5)
Male	1,909,234 (42.9)	32,191 (25.7)	701,599 (36.8)	756,197 (52.2)	229,399 (39.0)	189,848 (50.1)
BMI (kg/m^2)	26.4 ± 5.6	17.4 ± 0.9	22.2 ± 1.7	27.2 ± 1.4	34.5 ± 4.7	34.9 ± 4.9
Ethnicity						
White	1,870,908 (42.1)	46,744 (37.4)	795,352 (41.7)	612,602 (42.3)	253,363 (43.0)	162,847 (43.0)
Black	72,756 (1.6)	1,607 (1.3)	26,735 (1.4)	25,441 (1.8)	12,916 (2.2)	6,057 (1.6)
South Asian	114,464 (2.6)	5,751 (4.6)	54,827 (2.9)	37,292 (2.6)	10,358 (1.8)	6,236 (1.6)
Others	57,807 (1.3)	4,472 (3.6)	34,003 (1.8)	13,732 (1.0)	3,917 (0.7)	1,683 (0.4)
Mixed	25,393 (0.6)	981 (0.8)	12,606 (0.7)	7,451 (0.5)	3,137 (0.5)	1,218 (0.3)
Missing	2,306,627 (51.9)	65,530 (52.4)	982,714 (51.6)	752,059 (51.9)	305,218 (51.8)	201,106 (53.0)
Townsend index						
1st (least deprived)	898,026 (20.2)	18,466 (14.8)	382,828 (20.1)	317,824 (21.9)	104,774 (17.8)	74,134 (19.6)
2nd	813,478 (18.3)	18,251 (14.6)	337,345 (17.7)	282,070 (19.5)	103,232 (17.5)	72,580 (19.1)
3rd	849,375 (19.1)	23,020 (18.4)	358,383 (18.8)	277,034 (19.1)	116,229 (19.7)	74,709 (19.7)
4th	790,809 (17.8)	27,159 (21.7)	343,700 (18.0)	239,648 (16.5)	112,411 (19.1)	67,891 (17.9)
5th (most deprived)	565,517 (12.7)	21,851 (17.5)	245,182 (12.9)	165,651 (11.4)	84,112 (14.3)	48,721 (12.9)
Missing	530,750 (11.9)	16,338 (13.1)	238,799 (12.5)	166,350 (11.5)	68,151 (11.6)	41,112 (10.8)
Smoking status						
Never smoker	2,473,695 (55.6)	68,856 (55.1)	1,085,900 (57.0)	793,169 (54.8)	324,454 (55.1)	201,316 (53.1)
Ex-smoker	839,698 (18.9)	12,643 (10.1)	292,844 (15.4)	311,358 (21.5)	116,076 (19.7)	106,777 (28.2)
Current smoker	1,076,118 (24.2)	40,998 (32.8)	503,488 (26.4)	326,428 (22.5)	138,008 (23.4)	67,196 (17.7)
Missing	58,444 (1.3)	2,588 (2.1)	24,005 (1.3)	17,622 (1.2)	10,371 (1.8)	3,858 (1.0)

OSA	15,322 (0.3)	91 (0.1)	1,776 (0.1)	4,004 (0.3)	3,706 (0.6)	5,745 (1.5)
NAFLD	7,022 (0.2)	11 (0.01)	588 (0.03)	2,291 (0.2)	1,315 (0.2)	2,817 (0.7)
Diabetes	191,804 (4.3)	1,502 (1.2)	37,084 (2.0)	65,778 (4.5)	0	87,440 (23.1)
Hypertension	565,672 (12.7)	5,524 (4.4)	125,863 (6.6)	214,010 (14.8)	0	220,275 (58.1)
Dyslipidemia	727,601 (16.4)	5,520 (4.4)	162,599 (8.5)	290,748 (20.1)	0	268,734 (70.9)
Lipid-lowering drug	337,578 (7.6)	2,561 (2.1)	72,885 (3.8)	134,405 (9.3)	0	127,727 (33.7)

Data are presented as mean ± SD or n (%). # Median (Inter-Quartile Range)

* Obese with zero metabolic abnormalities

⁋ Obese with one or more metabolic abnormalities

Abbreviations: OSA, Obstructive sleep apnoea; NAFLD, Non-alcoholic fatty liver disease.

Table 2 Incidence rate of chronic kidney diseases (CKD) by body size phenotype and metabolic status

Body size phenotype	Total number	Incident composite CKD	Person-years	Incident rate (per 1,000 person-years)
Individuals with 0 metabolic abnormalities				
Underweight	114,951	1,001	500,790.10	2.00
Normal weight	1,656,231	16,558	8,329,413.00	1.99
Overweight	1,040,921	17,636	5,770,290.00	3.06
Obese	588,909	11,377	3,308,630.00	3.44
Individuals with 1 metabolic abnormality				
Underweight (≥1 metabolic abnormalities)	10,134	676	44,243.59	15.28
Normal weight	181,915	11,241	1,020,034.00	11.02
Overweight	265,843	15,431	1,561,540.00	9.88
Obese	217,783	12,763	1,276,219.00	10.00
Individuals with ≥2 metabolic abnormalities				
Normal weight	68,091	5,300	381,682.50	13.89
Overweight	141,813	10,660	839,908.90	12.69
Obese	161,364	12,307	935,643.90	13.15
Overall	**4,447,955**	**114,950**	**23,968,394.99**	**4.80**

Table 3 Hazard ratios for diagnosis of chronic kidney diseases (CKD) based on the number of metabolic abnormalities and body size phenotype.

HR (95% CI)	Composite CKD (event number = 114,950)		eGFR defined CKD (event number = 43,875)		ACR defined CKD (event number = 36,105)	
	Crude HR	Adjusted HR*	Crude HR	Adjusted HR*	Crude HR*	Adjusted HR*
Individuals with 0 metabolic abnormalities						
Underweight	1.00 (0.94, 1.06)	0.96 (0.90, 1.03)	0.84 (0.75, 0.94)	0.75 (0.67, 0.84)	0.98 (0.84, 1.13)	1.01 (0.87, 1.18)
Normal weight	Reference	Reference	Reference	Reference	Reference	Reference
Overweight	1.54 (1.51, 1.58)	1.30 (1.28, 1.33)	1.60 (1.55, 1.66)	1.35 (1.31, 1.40)	1.74 (1.66, 1.82)	1.56 (1.49, 1.64)
Obese	1.74 (1.69, 1.78)	1.66 (1.62, 1.70)	1.59 (1.53, 1.65)	1.58 (1.52, 1.64)	3.02 (2.89, 3.17)	2.82 (2.70, 2.96)
Individuals with 1 metabolic abnormality						
Underweight (≥1 metabolic abnormalities)	7.60 (7.04, 8.21)	1.55 (1.44, 1.68)	5.44 (4.73, 6.27)	0.91 (0.79, 1.04)	8.33 (7.05, 9.85)	4.68 (3.95, 5.54)
Normal weight	5.55 (5.42, 5.69)	1.79 (1.75, 1.84)	5.08 (4.89, 5.29)	1.42 (1.37, 1.48)	5.63 (5.34, 5.93)	3.64 (3.44, 3.84)
Overweight	4.99 (4.88, 5.10)	1.96 (1.91, 2.00)	4.74 (4.57, 4.91)	1.67 (1.61, 1.73)	5.68 (5.42, 5.96)	3.76 (3.58, 3.95)
Obese	5.05 (4.93, 5.17)	2.50 (2.44, 2.56)	4.51 (4.34, 4.68)	2.11 (2.03, 2.19)	7.85 (7.49, 8.21)	5.64 (5.39, 5.92)
Individuals with ≥2 metabolic abnormalities						
Normal weight	6.98 (6.77, 7.20)	1.71 (1.66, 1.76)	6.78 (6.45, 7.12)	1.44 (1.37, 1.51)	13.43 (12.71, 14.19)	7.65 (7.22, 8.1)
Overweight	6.40 (6.24, 6.55)	1.95 (1.91, 2.00)	6.44 (6.20, 6.69)	1.77 (1.70, 1.84)	14.59 (13.96, 15.24)	8.68 (8.28, 9.09)
Obese	6.63 (6.47, 6.78)	2.57 (2.51, 2.63)	6.20 (5.97, 6.43)	2.26 (2.18, 2.35)	18.56 (17.81, 19.35)	11.99 (11.48, 12.52)

*Adjusted for age, sex, ethnicity, smoking status, and Townsend index. The reference category is normal weight with zero metabolic abnormalities.

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