Obesity Without Metabolic Abnormality and Incident CKD: A Population-Based British Cohort Study

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Rationale & Objective: Metabolically healthy obesity (obesity without any metabolic abnormality) is not considered to be associated with increased risk of morbidity and mortality. We examined and quantified the association between metabolically healthy overweight/obesity and the risk of incident chronic kidney disease (CKD) in a British primary care population.

Study Design: Retrospective population-based cohort study.

Setting & Participants: 4,447,955 of the 5,182,908 adults in The Health Improvement Network (THIN) database (United Kingdom, 1995-2015) with a recorded body mass index (BMI) at the time of registration date who were free of CKD and cardiovascular disease.

Exposure: 11 body size phenotypes were created, defined by BMI categories (underweight, normal weight, overweight, and obesity) and 3 metabolic abnormalities (diabetes, hypertension, and dyslipidemia).

Outcome: Incident CKD defined as a recorded code for kidney replacement therapy, a recorded diagnosis of CKD, or by an estimated glomerular filtration rate of <60 mL/min/1.73 m² for ≥90 days, or a urinary albumin-creatinine ratio >3 mg/mmol for ≥90 days.

Results: Of the 4.5 million individuals, 1,040,921 (23.4%) and 588,909 (13.2%) had metabolically healthy overweight and metabolically healthy obesity, respectively. During a mean follow-up interval of 5.4 ± 4.3 (SD) years, compared with individuals with a metabolically healthy normal weight (n = 1,656,231), there was a higher risk of incident CKD among those who had metabolically healthy overweight (adjusted HR, 1.30 [95% CI, 1.28-1.33]) and metabolically healthy obesity (adjusted HR, 1.66 [95% CI, 1.62-1.70]). The association was stronger in those younger than 65 years of age. In all BMI categories, there was greater risk of incident CKD with a greater number of metabolic abnormalities in a graded manner.

Limitations: Potential misclassification of metabolic status due to delayed diagnosis and residual confounding due to unmeasured factors.

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

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. The prevalence of CKD and mortality attributable to CKD increased by 29.3% and 41.5%, respectively, between 1990 and 2017. CKD is also costly to the health care systems; the UK National Health Service spent £1.45 billion on CKD in 2009-2010. CKD is largely preventable, and therefore it is important to identify and treat the underlying modifiable causes and risk factors.

Similar to the global trends in the prevalence of CKD, the prevalence of obesity is also on the rise, tripling between 1975 and 2016. Obesity is known to increase the risk of cardiovascular (CVD) disease and CKD. Metabolic risk factors like diabetes, dyslipidemia, and hypertension are thought to mediate the increased risk of morbidity and mortality associated with obesity. A subset of obese individuals without these metabolic abnormalities, described as having “metabolically healthy obesity” (MHO), has been suggested, particularly in the news media, not to be at increased risk due to a lack of measured conventional cardiovascular disease risk factors.

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

We previously demonstrated that MHO is associated with a higher risk of CVD and heart failure compared with
a metabolically healthy normal weight, but the risk was lower than in those with metabolically unhealthy obesity.\textsuperscript{29} Furthermore, obesity can be associated with reduced insulin sensitivity and increased oxidative stress and inflammation, all of which can contribute to CKD.\textsuperscript{30} 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, dyslipidemia) and incident CKD.

**Methods**

**Study Design and Setting**

This study is reported following the STROBE guideline.\textsuperscript{30} 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 across the United Kingdom. THIN captures coded data on patient characteristics (eg, smoking status, height, and weight), diagnosis (in primary care or secondary care), prescriptions, consultations, and investigations; these data could be recorded at 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.\textsuperscript{31} Comparisons with 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.\textsuperscript{12,33} 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 November 26, 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: 1 year after the registration date, 1 year after the practice acceptable mortality recording date, or 1 year after the Vision IT system implementation date. Individuals with any record of CKD or 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 18.5–25 kg/m\(^2\)), overweight (BMI of 25–30 kg/m\(^2\)), and obesity (BMI of ≥30 kg/m\(^2\)).\textsuperscript{34} The 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. The 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 that 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 United Kingdom. The 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 (≥160 mg/dL or ≥4.10 mmol/L) or triglycerides (≥200 mg/dL or ≥2.26 mmol/L), or low high-density lipoprotein cholesterol (<40 mg/dL or <1.00 mmol/L) at baseline. 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 0 metabolic abnormalities (absence of hypertension, hyperlipidemia, diabetes); underweight with 1 or more metabolic abnormalities; normal weight with 0 metabolic abnormalities; normal weight with 1 metabolic abnormality; normal weight with 2 or more metabolic abnormalities; overweight with 0 metabolic abnormalities; overweight with 1 metabolic abnormality; overweight with 2 or more metabolic abnormalities; obese with 0 metabolic abnormalities; obese with 1 metabolic abnormality; and obese with 2 or more metabolic abnormalities.

Outcome
The primary end point was a composite outcome of incident CKD, which was defined as patients with a recorded READ code of kidney replacement therapy or CKD, or by estimated glomerular filtration rate (eGFR; at least 2 assessments of <60 mL/min/1.73 m², using the CKD-EPI creatinine equation, 90 days apart), and/or by laboratory measurements of urinary albumin-creatinine ratio (UACR; at least 2 readings of >3 mg/mmol, 90 days apart [ie, moderately increased albuminuria]). Serum creatinine was measured using a method calibrated to be traceable to isotope-dilution mass spectrometry. The secondary end points of this study were eGFR-defined CKD (based on eGFR values only; ie, CKD G3-G5) and UACR-defined CKD (based on UACR values only; ie, CKD A2-A3). Any event occurring after the first CKD presentation was ignored. The end point definitions are described in Table S2.

Follow-up
Eligible participants were observed from the study entry until the earliest date of any censoring event (participants left the 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 indexes such as income, education, and employment.

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 SD for normally distributed continuous variables, median and interquartile range (IQR) for continuous variables with a skewed distribution, and proportion for categorical variables.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using the Cox proportional regression model. Adjusted HRs (AHRs) were constructed by including age, sex, smoking status, and Townsend index in the Cox proportional hazard regression models for associations of individual metabolic abnormalities or each body size phenotype (normal weight with 0 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 hazard 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 that are known to influence the risk and prevalence of CKD, we stratified associations of individual metabolic abnormalities or each body size phenotype with CKD events. Incidence curves were generated for each body size phenotype and age/sex/smoking status were conducted.

Because 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...
### Table 1. Baseline Characteristics of the Study Population by Body Size and Metabolic Health Status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (N = 4,447,955)</th>
<th>Underweight (n = 125,085)</th>
<th>Normal Weight (n = 1,906,237)</th>
<th>Overweight (n = 1,448,577)</th>
<th>Obese (n = 968,056)</th>
<th>Without Metabolic Abnormalities (n = 588,909)*</th>
<th>With Metabolic Abnormalities (n = 379,147)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>40.9 [29.1-55.6]</td>
<td>35.2 [26.1-50.8]</td>
<td>45.2 [33.0-58.6]</td>
<td>39.2 [29.8-49.7]</td>
<td>55.7 [46.6-64.5]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>1,909,234 (42.9%)</td>
<td>379,147 (1.8%)</td>
<td>756,197 (52.2%)</td>
<td>229,399 (39.0%)</td>
<td>189,848 (50.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.4 ± 5.6</td>
<td>17.4 ± 0.9</td>
<td>22.2 ± 1.7</td>
<td>27.2 ± 1.4</td>
<td>34.5 ± 4.7</td>
<td>34.9 ± 4.9</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>White</td>
<td>1,870,908 (42.1%)</td>
<td>46,744 (32.4%)</td>
<td>795,352 (41.7%)</td>
<td>612,602 (42.3%)</td>
<td>253,363 (43.0%)</td>
<td>162,847 (43.0%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>72,756 (1.6%)</td>
<td>1,607 (1.3%)</td>
<td>26,735 (1.4%)</td>
<td>25,441 (1.8%)</td>
<td>12,916 (2.2%)</td>
<td>6,057 (1.6%)</td>
<td></td>
</tr>
<tr>
<td>South Asian</td>
<td>114,464 (2.6%)</td>
<td>5,751 (4.6%)</td>
<td>54,827 (2.9%)</td>
<td>37,292 (2.6%)</td>
<td>10,358 (1.8%)</td>
<td>6,236 (1.6%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>57,807 (1.3%)</td>
<td>4,472 (3.6%)</td>
<td>34,003 (1.8%)</td>
<td>13,732 (1.0%)</td>
<td>3,917 (0.7%)</td>
<td>1,683 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>25,393 (0.6%)</td>
<td>981 (0.8%)</td>
<td>12,606 (0.7%)</td>
<td>7,451 (0.5%)</td>
<td>3,137 (0.5%)</td>
<td>1,218 (0.3%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>2,306,627 (51.9%)</td>
<td>65,530 (52.4%)</td>
<td>982,714 (51.6%)</td>
<td>752,059 (51.9%)</td>
<td>305,218 (51.8%)</td>
<td>201,106 (53.0%)</td>
<td></td>
</tr>
<tr>
<td>Townsend index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st (least deprived)</td>
<td>898,026 (20.2%)</td>
<td>18,466 (14.8%)</td>
<td>382,828 (20.1%)</td>
<td>317,824 (21.9%)</td>
<td>104,774 (17.8%)</td>
<td>74,134 (19.6%)</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>813,478 (18.3%)</td>
<td>18,251 (14.6%)</td>
<td>337,345 (17.7%)</td>
<td>282,070 (19.5%)</td>
<td>103,232 (17.5%)</td>
<td>72,580 (19.1%)</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>849,375 (19.1%)</td>
<td>23,020 (18.4%)</td>
<td>358,383 (18.8%)</td>
<td>277,034 (19.1%)</td>
<td>116,229 (19.7%)</td>
<td>74,709 (19.7%)</td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>790,809 (17.8%)</td>
<td>27,159 (21.7%)</td>
<td>343,700 (18.0%)</td>
<td>239,648 (16.5%)</td>
<td>112,411 (19.1%)</td>
<td>67,891 (17.9%)</td>
<td></td>
</tr>
<tr>
<td>5th (most deprived)</td>
<td>565,517 (12.7%)</td>
<td>21,851 (17.5%)</td>
<td>245,182 (12.9%)</td>
<td>165,651 (11.4%)</td>
<td>84,112 (14.3%)</td>
<td>48,721 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>530,750 (11.9%)</td>
<td>16,338 (13.1%)</td>
<td>238,799 (12.5%)</td>
<td>166,350 (11.5%)</td>
<td>68,151 (11.6%)</td>
<td>41,112 (10.8%)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
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<td></td>
<td></td>
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<tr>
<td>Never smoker</td>
<td>2,473,695 (55.6%)</td>
<td>68,856 (55.1%)</td>
<td>1,085,900 (57.0%)</td>
<td>793,169 (54.8%)</td>
<td>324,454 (55.1%)</td>
<td>201,316 (53.1%)</td>
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</tr>
<tr>
<td>Ex-smoker</td>
<td>839,698 (18.9%)</td>
<td>12,643 (10.1%)</td>
<td>292,844 (15.4%)</td>
<td>311,358 (21.5%)</td>
<td>116,076 (19.7%)</td>
<td>106,777 (28.2%)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1,076,118 (24.2%)</td>
<td>40,998 (32.8%)</td>
<td>503,488 (26.4%)</td>
<td>326,428 (22.5%)</td>
<td>138,008 (23.4%)</td>
<td>67,196 (17.7%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>58,444 (1.3%)</td>
<td>2,588 (2.1%)</td>
<td>24,005 (1.3%)</td>
<td>17,622 (1.2%)</td>
<td>10,371 (1.8%)</td>
<td>3,858 (1.0%)</td>
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<tr>
<td>OSA</td>
<td>15,322 (0.3%)</td>
<td>91 (0.1%)</td>
<td>1,776 (0.1%)</td>
<td>4,004 (0.3%)</td>
<td>3,706 (0.6%)</td>
<td>5,745 (1.5%)</td>
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<tr>
<td>NAFLD</td>
<td>7,022 (0.2%)</td>
<td>11 (0.0%)</td>
<td>588 (0.0%)</td>
<td>2,291 (0.2%)</td>
<td>1,315 (0.2%)</td>
<td>2,817 (0.7%)</td>
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<tr>
<td>Diabetes</td>
<td>191,804 (4.3%)</td>
<td>1,502 (1.2%)</td>
<td>37,084 (2.0%)</td>
<td>65,778 (4.5%)</td>
<td>0</td>
<td>87,440 (23.1%)</td>
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<tr>
<td>Hypertension</td>
<td>565,672 (12.7%)</td>
<td>5,524 (4.4%)</td>
<td>125,863 (6.6%)</td>
<td>214,041 (14.8%)</td>
<td>0</td>
<td>220,275 (58.1%)</td>
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<tr>
<td>Dyslipidemia</td>
<td>727,601 (16.4%)</td>
<td>5,520 (4.4%)</td>
<td>162,599 (8.5%)</td>
<td>290,748 (20.1%)</td>
<td>0</td>
<td>268,734 (70.9%)</td>
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<tr>
<td>Lipid-lowering drug</td>
<td>337,578 (7.6%)</td>
<td>2,561 (2.1%)</td>
<td>72,885 (3.8%)</td>
<td>134,405 (9.3%)</td>
<td>0</td>
<td>127,727 (33.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Values for continuous data presented as mean ± SD or median [interquartile range]; values for categorical variables as count (%). Abbreviations: BMI, body mass index; OSA, obstructive sleep apnea; NAFLD, nonalcoholic fatty liver disease.

*Obese with 0 metabolic abnormalities.

*Obese with ≥1 metabolic abnormalities.
abnormalities) were performed in parallel as sensitivity analyses to compare the risk of developing the composite CKD outcome between individuals with and without metabolic abnormalities in the underweight, normal weight, overweight, and obese groups.

All statistical tests were 2-tailed, and a \( P < 0.05 \) was considered statistically significant. All analyses were conducted in Stata 16.0 (StataCorp) and R 4.0.4 (R Foundation for Statistical Computing).

### Results

#### Cohort Characteristics

Of the 5,182,908 adults in the THIN database, we excluded a total of 734,953 participants, comprising those without a valid BMI value at baseline (\( n = 224,032 \)), those with recorded CVD at baseline (\( n = 418,091 \)), and those with recorded CKD at baseline (\( n = 189,365 \)) (Fig 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%) were classified as underweight, normal weight, overweight, and obese with no metabolic abnormalities, respectively (Table 1). The MHO individuals were more likely to be younger, female, current smokers, and socioeconomically deprived compared with metabolically unhealthy obesity.

#### Body Weight, Metabolic Health Status, and the Composite CKD Outcome

Over a mean of 5.4 years’ follow-up period, there were 114,950 incident CKD events based on the composite outcome. Table S3 shows that participants with a diagnosis of diabetes (AHR, 1.78 [95% CI, 1.75-1.81]), hypertension (AHR, 1.72 [95% CI, 1.70-1.74]), and dyslipidemia (AHR, 1.08 [95% CI, 1.07-1.10]) had a higher risk of developing the composite CKD outcome during the follow-up period. Compared with the participants who had a normal weight at baseline, the participants with overweight (AHR, 1.27 [95% CI, 1.25-1.29]) or obesity (AHR, 1.72 [95% CI, 1.70-1.75]) had a higher risk of incident CKD; the participants who were underweight had a lower risk of incident CKD (AHR, 0.87 [95% CI, 0.83-0.92]).

#### Association of 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 outcome, eGFR-defined CKD, and UACR-defined CKD) with the normal weight with 0 metabolic abnormalities group as the reference. The crude/adjusted HRs of CKD events (composite CKD outcome, eGFR-defined CKD, and UACR-defined CKD) by body size phenotypes and metabolic status are presented in Table 3.

### Composite CKD Outcome

Compared with the reference group (normal weight with no metabolic abnormality), individuals who were overweight with 0 metabolic abnormalities (AHR, 1.30 [95% CI, 1.28-1.33]) and who had obesity with 0 metabolic abnormalities (MHO) (AHR, 1.66 [95% CI, 1.62-1.70]) had a higher risk of developing the composite CKD outcome, while those who were underweight with 0 metabolic abnormalities (AHR, 0.96 [95% CI, 0.90-1.03]) had a similar risk. The risk of incident CKD in the underweight, normal weight, overweight, and obese groups was higher with a higher number of metabolic abnormalities present (Fig 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 in all BMI groups the individuals with metabolic abnormalities had significantly higher risks of developing the composite CKD outcome during the follow-up period compared with individuals without metabolic abnormalities. 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 Outcome**

Compared with the reference group, individuals who were overweight with 0 metabolic abnormalities (AHR, 1.35 [95% CI, 1.31-1.40]) and who had obesity with 0 metabolic abnormalities (AHR, 1.58 [95% CI, 1.52-1.64]) had a higher risk of eGFR-defined CKD events. The risk of eGFR-defined CKD events in the normal weight, overweight, and obese groups was higher with a higher number of metabolic abnormalities present (Fig 3). Individuals who were underweight with 0 metabolic abnormality (AHR, 0.75 [95% CI, 0.67-0.84]) had a lower risk of eGFR-defined CKD events.

**UACR-Defined CKD Outcome**

Compared with the reference group, individuals who were overweight with 0 metabolic abnormalities (AHR, 1.56 [95% CI, 1.49-1.64]) and who had obesity with 0 metabolic abnormalities (AHR, 2.82 [95% CI, 2.70-2.96]) had a higher risk of developing UACR-defined CKD events, while those who were underweight with 0 metabolic abnormality had an unchanged risk. The risk of UACR-defined CKD events in the underweight, normal weight, overweight, and obese groups was higher with a higher number of metabolic abnormalities, especially among those with 2 or more metabolic abnormalities (Fig 3).

**Subgroup Analysis**

Figure 4 shows the association of body size phenotype and metabolic status with the composite CKD outcome by sex, age, and smoking status. The risk of the composite CKD outcome 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 incident CKD than those 65 years or older. There was no difference between nonsmoker and ever-smoker (ex-smoker and current smoker) individuals, or between male and female individuals.

**Discussion**

In this study of approximately 4.5 million individuals from the UK primary care population evaluated for a mean of 5.4 years, we have demonstrated that individuals with metabolically healthy overweight and obesity (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 metabolic abnormalities: that is, the higher the number of metabolic risk factors, the greater the risk of developing CKD. Furthermore, those with normal weight and metabolic risk factors also have higher risk of incident CKD.
results were similar irrespective of the way CKD was defined (the composite outcome, eGFR-based CKD, or albuminuria-based CKD).

Studies examining the association between MHO and incident CKD have produced conflicting results. In view of this, 2 systematic review and meta-analyses 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 metabolically healthy normal weight individuals. However, the number of studies included in these 2 meta-analyses were small, and there were variable degrees of...
bias. There was also significant heterogeneity in sample size, length of follow-up period, genetic background, GFR estimation equation used, potential confounders controlled for, and use of metabolically defined body size phenotypes. The definition of MHO also varied, and most studies included some components of the metabolic syndrome. Furthermore, most of the studies were carried out in Asian populations, with only 2 originating outside Asia. These factors limit the generalizability and applicability of the results, especially in populations outside Asia. One study of 1.4 million participants from English general practice showed a higher risk of CKD with higher BMI over 25 kg/m²; the log-linear relationship between the 2 remained even after adjusting for prior diabetes, hypertension, and history of cardiovascular disease.42

Our study cohort, which is much larger than the latter study and the 2 meta-analyses combined, is derived from a homogeneous British primary care population. We controlled for major confounders, categorized participants into 11 distinct subphenotypes based on BMI and metabolic risk factors, used 3 different measures of incident CKD, and used a GFR estimating equation most applicable to those with obesity.43

A putative explanation for the increased risk of CKD in individuals with metabolically healthy overweight and obesity 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 insulin-like growth factor 1 (IGF-1), transforming growth factor β (TGF-β), endothelin 1, components of the renin-angiotensin-aldosterone system, and adipokines45,46; increased oxidative stress,47 reduced availability of nitric oxide,48 and formation of glycoxidation and lipid peroxidation products.49,50 All 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 that induces proinflammatory 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.

This study and our previously published study28 showing higher risks of coronary heart disease, heart failure, and cerebrovascular disease in MHO 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

<p>| Table 3. Hazard Ratios for Diagnosis of CKD Based on the Number of Metabolic Abnormalities and Body Size Phenotype |
|-----------------------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|</p>
<table>
<thead>
<tr>
<th>Individual Condition</th>
<th>Composite CKD (n = 114,950 Events)</th>
<th>UACR-Defined CKD (n = 43,875 Events)</th>
<th>eGFR-Defined CKD (n = 43,875 Events)</th>
<th>Adjusted HR a</th>
<th>Adjusted HR a</th>
<th>Adjusted HR a</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Metabolic abnormalities</td>
<td>0.96 (0.90-1.03)</td>
<td>0.98 (0.94-1.06)</td>
<td>0.97 (0.95-1.00)</td>
<td>0.96 (0.93-1.00)</td>
<td>0.94 (0.91-0.97)</td>
<td>0.93 (0.89-0.96)</td>
</tr>
<tr>
<td>Underweight</td>
<td>0.96 (0.90-1.03)</td>
<td>0.98 (0.94-1.06)</td>
<td>0.97 (0.95-1.00)</td>
<td>0.96 (0.93-1.00)</td>
<td>0.94 (0.91-0.97)</td>
<td>0.93 (0.89-0.96)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>0.96 (0.90-1.03)</td>
<td>0.98 (0.94-1.06)</td>
<td>0.97 (0.95-1.00)</td>
<td>0.96 (0.93-1.00)</td>
<td>0.94 (0.91-0.97)</td>
<td>0.93 (0.89-0.96)</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
</tr>
<tr>
<td>Obese</td>
<td>1.74 (1.69-1.78)</td>
<td>1.74 (1.69-1.78)</td>
<td>1.74 (1.69-1.78)</td>
<td>1.74 (1.69-1.78)</td>
<td>1.74 (1.69-1.78)</td>
<td>1.74 (1.69-1.78)</td>
</tr>
<tr>
<td>1 Metabolic abnormality</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
</tr>
<tr>
<td>Underweight</td>
<td>1.55 (1.44-1.68)</td>
<td>1.55 (1.44-1.68)</td>
<td>1.55 (1.44-1.68)</td>
<td>1.55 (1.44-1.68)</td>
<td>1.55 (1.44-1.68)</td>
<td>1.55 (1.44-1.68)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>1.50 (1.54-1.56)</td>
<td>1.50 (1.54-1.56)</td>
<td>1.50 (1.54-1.56)</td>
<td>1.50 (1.54-1.56)</td>
<td>1.50 (1.54-1.56)</td>
<td>1.50 (1.54-1.56)</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.66 (1.62-1.70)</td>
<td>1.66 (1.62-1.70)</td>
<td>1.66 (1.62-1.70)</td>
<td>1.66 (1.62-1.70)</td>
<td>1.66 (1.62-1.70)</td>
<td>1.66 (1.62-1.70)</td>
</tr>
<tr>
<td>Obese</td>
<td>1.74 (1.69-1.78)</td>
<td>1.74 (1.69-1.78)</td>
<td>1.74 (1.69-1.78)</td>
<td>1.74 (1.69-1.78)</td>
<td>1.74 (1.69-1.78)</td>
<td>1.74 (1.69-1.78)</td>
</tr>
<tr>
<td>≥2 Metabolic abnormalities</td>
<td>6.98 (6.77-7.20)</td>
<td>6.98 (6.77-7.20)</td>
<td>6.98 (6.77-7.20)</td>
<td>6.98 (6.77-7.20)</td>
<td>6.98 (6.77-7.20)</td>
<td>6.98 (6.77-7.20)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% CI. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; UACR, urinary albumin-creatinine ratio.

aAdjusted for age, sex, ethnicity, smoking status, and Townsend index. The reference category for the entire table is normal weight with 0 metabolic abnormalities.
absence of BMI-defined obesity, 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 a previous RCT showed that weight loss in normal weight individuals can reverse obesity complications such as nonalcoholic 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/m² 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 analysis, we evaluated the impact of sequential BMI categories on the risk of CKD events. The results of these analyses are consistent with the main findings, suggesting that metabolic abnormalities play a role in the risk of CKD.

Figure 4. Association of body size phenotype and metabolic status with composite chronic kidney disease (CKD) events by age, sex, and smoking status. Abbreviation: HR, hazard ratio. *This group comprised individuals with 1 or more metabolic abnormality.
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 2 models demonstrated that the transition from a metabolically healthy to a metabolically 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 blood pressure and glycemic control in those with metabolically unhealthy obesity, 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 (eg, family history of CKD).

Because 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 from a biological standpoint the associations between metabolic status and the risk of developing CKD are more linear, rather than dichotomized.

In addition to the strengths and limitations of the study already mentioned, this was to our knowledge 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 subphenotypes based on BMI and metabolic risk factors allowed a more granular analysis of the CKD risk in these subphenotypes than has ever been done previously. We believe these results are generalizable to Western populations.

Our results demonstrate that individuals with obesity without metabolic abnormality might have a higher risk of developing CKD compared with normal weight individuals, especially those younger than 65 years. Weight loss interventions could be considered in these individuals to reduce the high risk of CKD and could be examined in randomized controlled trials. Furthermore, our results suggest that individuals with normal weight who have metabolic abnormalities are also at a higher risk of CKD and as such might benefit from meticulous metabolic control to reduce the risk of CKD. Whether weight loss in this group will reduce the risk of CKD will also need to be examined in a randomized trial.

### Supplementary Material

**Table S1:** Overview of codes used to define metabolic abnormalities.

**Table S2:** Overview of codes used to define CKD events.

**Table S3:** HRs for incident CKD based on metabolic health status.

**Table S4:** HRs for incident CKD based on the number of metabolic abnormalities and body size phenotype (competing risk Cox proportional hazard model).

**Table S5:** HRs for incident CKD based on metabolic abnormalities status in underweight, normal weight, overweight, and obese groups.

**Table S6:** Association of body size phenotype and metabolic status with incident CKD by Townsend index.

### Article Information

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**Authors' Contributions:** Conceived the research question: ID, KN, GNT; wrote the protocol: ID; contributed to the protocol: KN, GNT, JW; extracted the data: KG; performed the data analysis: JW; contributed to data interpretation: JW, ID, KN, AAT, GNT; 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.

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### References


Obesity Without Metabolic Abnormality and Incident CKD: A Population-Based British Cohort Study

**Settings & Participants**
- 787 general practices across the UK
- 4,447,955 adults with available BMI records from the registration date
- Jan 1995 – May 2017
- Mean follow-up 5.4 years

**Exposure:**
- 11 body size phenotypes defined by BMI categories, diabetes, hypertension, and dyslipidemia

**Outcome:**
- Incident chronic kidney disease (CKD)

**Analysis:**
- Cox proportional hazards regression model

**Composite CKD**
- 0 metabolic abnormalities
- Underweight
- Normal weight
- Overweight
- Obese
- 1 metabolic abnormality
- Underweight
- (≥1 metabolic abnormalities)
- Normal weight
- Overweight
- Obese
- ≥2 metabolic abnormalities
- Normal weight
- Overweight
- Obese

**Results**

CONCLUSION: Overweight and obesity without metabolic abnormality are associated with 30% and 66% higher risk of CKD, respectively, compared to those with normal body weight and no metabolic abnormality.

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