

Obesity without metabolic abnormality and incident CKD

Wang, Jingya; Nirantharakumar, Krishnarajah; Gokhale, Krishna; Tahrani, Abd; Taverner, Thomas; Thomas, G Neil; Indranil, Dasgupta

DOI:

[10.1053/j.ajkd.2021.05.008](https://doi.org/10.1053/j.ajkd.2021.05.008)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Wang, J, Nirantharakumar, K, Gokhale, K, Tahrani, A, Taverner, T, Thomas, GN & Indranil, D 2021, 'Obesity without metabolic abnormality and incident CKD: a population-based British cohort study', *American Journal of Kidney Diseases*, vol. 79, no. 1, pp. 24-35.e1. <https://doi.org/10.1053/j.ajkd.2021.05.008>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

The VoR for this article can be found at <https://doi.org/10.1053/j.ajkd.2021.05.008>

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

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

4 Jingya Wang¹, PhD, Krishnarajah Niratharakumar^{1*}, MD, Krishna Gokhale¹, MSc, Abd A
5 Tahrani^{1,2}, PhD, Tom Taverner¹, PhD, G Neil Thomas^{1*}, PhD, and Indranil Dasgupta^{2,3}, MD

6 ¹Institute of Applied Health Research, University of Birmingham, Birmingham, UK

7 ²Heartlands Hospital, University Hospitals Birmingham NHS Foundation Trust, Birmingham,
8 UK

9 ³Warwick Medical School, University of Warwick, Coventry, UK

10

11 Corresponding authors*:

12 Professor G Neil Thomas: gneilthomas@yahoo.co.uk / g.n.thomas@bham.ac.uk

13 Dr Krishnarajah Niratharakumar: K.Nirantharan@bham.ac.uk

14

15 Key words: overweight, obesity, metabolically healthy, chronic kidney disease, GFR,
16 albuminuria

1 **Abstract**

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

7 **DESIGN** Retrospective population-based cohort study

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

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

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

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

18 **RESULTS** Of the 4.5 million individuals, 1,040,921 (23.4%) and 588,909 (13.2%) were
19 metabolically healthy overweight and metabolically healthy obese respectively. During a
20 mean follow-up of 5.4 (SD 4.3) years, compared with individuals with metabolically healthy
21 normal weight (n=1,656,231), those who had metabolically healthy overweight (adjusted HR
22 = 1.30, 95% CI 1.28 to 1.33) and metabolically healthy obesity (adjusted HR = 1.66, 95% CI
23 1.62 to 1.70) had a higher risk of incident CKD. The association was stronger in those below
24 65 years of age and male. The risk of incident CKD in all weight categories increased with
25 increasing number of metabolic abnormalities in a graded fashion.

26 **LIMITATIONS**

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

1 **Plain summary**

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

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

1 Introduction

2 Chronic kidney disease (CKD) has a major impact on global health, both as a direct cause of
3 global morbidity and mortality and as an important risk factor for cardiovascular disease. In
4 2017, 697.5 million people in the world had CKD, and it accounted for 1.2 million deaths and
5 35.8 million disability-adjusted life-years.¹ The prevalence of CKD and mortality attributable
6 to CKD increased by 29.3% and 41.5% respectively between 1990 and 2017.¹ CKD is also costly
7 to the health care systems; the UK National Health Service spent £1.45 billion on CKD in 2009-
8 2010.² CKD is largely preventable, and therefore, it is important to identify and treat the
9 underlying modifiable causes and risk factors.¹

10 Similar to the global trends in the prevalence of CKD, the prevalence of obesity is also on the
11 rise, tripling between 1975 and 2016.³ Obesity is known to increase the risk of cardiovascular
12 (CVD) disease⁴ and chronic kidney disease (CKD)^{5,6}. Metabolic risk factors like diabetes,
13 dyslipidemia and hypertension are thought to mediate the increased risk of morbidity and
14 mortality associated with obesity.⁷⁻¹⁰ A subset of obese individuals without these metabolic
15 abnormalities, described as “metabolically healthy obese” (MHO), have been suggested,
16 particularly in the news media, not to be at increased risk due to a lack of measured
17 conventional cardiovascular disease risk factors.⁸⁻¹²

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

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

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

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

8

9 **Methods**

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

12 Study design and setting

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

27 Ethics

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

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

3 Participants

4 All adult participants (18 years and above) in THIN with available body mass index (BMI)
5 records from the registration date were eligible for this study. To ensure only incident CKD
6 events were captured, the study entry began 12 months after registration to limit the
7 possibility that the diagnosis of outcomes documented after registration reflected pre-
8 existing or historical disease. We considered the study entry date was the latest of the
9 following: one year after the registration date, one year after the practice acceptable
10 mortality recording date, or one year after the Vision IT system implementation date.
11 Individuals with any record of CKD or Cardiovascular diseases (CVD) events no later than the
12 study entry date or with implausible BMI values (below 13 kg/m² or over 100 kg/m²) were
13 excluded.

14 Exposure

15 BMI was categorized based on the World Health Organization Criteria: underweight (BMI of
16 <18.5 kg/m²), normal weight (BMI of 18.5 kg/m² to <25 kg/m²), overweight (BMI of 25 kg/m²
17 to <30 kg/m²), and obesity (BMI of ≥30 kg/m²).³⁴ Baseline BMI was extracted from the dataset
18 as the first BMI recorded from the registration date or the first one recorded after the Vision
19 IT system was initiated but before the start of the observation period. Baseline BMI date was
20 the latest date of either of the above events. This approach minimized the chance that the
21 BMI was recorded due to particular clinical reasons but more likely to have been recorded for
22 administrative purposes.

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

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

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

12 Outcome

13 The primary endpoint was the composite incident CKD, which was defined as those with a
14 recorded diagnosis of renal replacement therapy (RRT) or CKD using Read codes or by
15 estimated Glomerular Filtration Rate (eGFR, at least two measurements < 60 ml/min/1.73 m²,
16 using the CKD EPI Equation,³⁷ 90 days apart) and/ or laboratory measurements of
17 Albumin/Creatinine Ratio (ACR, at least two readings > 3 mg/mmol, 90 days apart,
18 microalbuminuria). Serum creatinine was measured using the internationally standardized
19 isotope dilution mass spectrometry (IDMS) method.³⁸ The secondary endpoints of this study
20 were eGFR-defined CKD (based on eGFR values only) and ACR-defined CKD (based on ACR
21 values only). Any event occurring after the first CKD presentation was ignored. Endpoint
22 definitions are described in **Table S2**.

23 Follow-up

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

27 Covariates

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

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

3 Statistical analysis

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

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

19 To investigate if there were any differences in the risk of CKD by baseline characteristics which
20 are known to influence the risk and prevalence of CKD, we stratified associations by sex, age
21 (< 65 years of age and \geq 65 years of age), and smoking status (non-smoker and ever-smoker).
22 The cut-off at 65 years of age was chosen because this is commonly used to designate an
23 individual as an older person.⁴⁰ In prior to the subgroup analysis, an interaction test for body
24 size phenotypes and age/sex/smoking status were conducted.

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

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

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

6 **Patient and public involvement**

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

10

11 **Results**

12 Of the 5,182,908 adults in the THIN database, we excluded a total number of 734,953
13 participants - 1) those without a valid BMI value at baseline ($n = 224,032$); 2) those with
14 recorded CVD at baseline ($n = 418,091$); 3) those with recorded CKD at baseline ($n = 189,365$)
15 (**Figure 1**). Among the remaining 4,447,955 participants, 114,951 (2.6%), 1,656,231 (37.2%),
16 1,040,921 (23.4%), and 588,909 (13.2%) individuals were classified as underweight, normal
17 weight, overweight, and obese with no metabolic abnormalities, respectively (**Table 1**).
18 Individuals with MHO were more likely to be younger, female, current smokers, and
19 socioeconomically deprived compared with MUHO.

20 *Body weight, Metabolic Health Status and Composite CKD Events*

21 Over a mean of 5.4 years' follow-up, there were 114,950 incident composite CKD
22 presentations. **Table S3** shows that participants diagnosed with diabetes (adjusted HR = 1.78,
23 95%CI 1.75 to 1.81), hypertension (adjusted HR = 1.72, 95%CI 1.70 to 1.74), and dyslipidemia
24 (adjusted HR = 1.08, 95%CI 1.07 to 1.10) had a higher risk of developing composite CKD during
25 follow up. Compared to participants with normal weight at baseline, participants with
26 overweight (adjusted HR = 1.27, 95%CI 1.25 to 1.29) or obesity (adjusted HR = 1.72, 95%CI
27 1.70 to 1.75) had a higher risk of incident composite CKD, while participants who were
28 underweight had a lower risk of incident composite CKD (adjusted HR = 0.87, 95%CI 0.83 to
29 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 abnormality (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.

1 ACR-defined CKD Events

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

9 Subgroup analysis

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

16

17 **Discussion**

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

29 Studies examining the association between MHO and incident CKD have produced conflicting
30 results.¹⁵⁻²⁶ In view of this, two systematic review and meta-analyses have been performed,

1 with 166,718 (from 4 studies) and 181,505 (from 11 studies) participants respectively, both
2 showing higher risk of incident CKD in MHO compared with MHNW individuals.^{19,41} However,
3 the number of studies included in these two meta-analyses were small and there were variable
4 degrees of bias. There was also significant heterogeneity in sample size, length of follow-up,
5 genetic background, the GFR estimation equation used, potential confounders controlled for,
6 and the use of metabolically defined body size phenotypes. The definition of MHO varied and
7 most studies included some components of the metabolic syndrome. Furthermore, most of
8 the studies were carried out in Asian populations, with only two originating outside Asia.
9 These factors limit the generalizability and applicability of the results, especially in the
10 Western population. One study of 1.4 million participants from English general practice
11 showed higher risk of CKD with higher BMI over 25 kg/m² and the log-linear relationship
12 between the two remained even after adjusting for prior diabetes, hypertension and history
13 of cardiovascular disease.⁴² Our study cohort is much larger than this study and the two
14 meta-analyses combined, is derived from a homogeneous British primary care population, is
15 controlled for major confounders, categories participants into 11 distinct sub-phenotypes
16 based on BMI and metabolic risk factors, uses 3 different measures of incident CKD, and uses
17 a GFR estimating equation most applicable to the obese populations.⁴³

18 A putative explanation for the increased risk of CKD in metabolically healthy overweight and
19 obese individuals is reduced insulin sensitivity which has been shown to be associated with
20 kidney dysfunction independent of glucometabolic and cardiovascular risk factors.⁴⁴ Impaired
21 insulin sensitivity and compensatory hyperinsulinemia are associated with activation of IGF-
22 1, transforming growth factor- β , endothelin-1, components of the renin-angiotensin-
23 aldosterone system and adipokines^{45,46}; increased oxidative stress⁴⁷, reduced availability of
24 nitric oxide⁴⁸ and formation of glycoxidation and lipid peroxidation products^{49,50}. All of these
25 promote mitogenic and fibrotic processes in the kidney and contribute to the pathogenesis
26 and progression of CKD⁴⁵⁻⁵³. Furthermore, Fetuin-A, a hepatokine, which induces pro-
27 inflammatory signaling in adipose tissue, has been shown to increase perivascular kidney
28 sinus fat which plays a role in blood pressure regulation and CKD.^{14,54} Chronic low grade
29 inflammation associated with obesity may also play a part in the causation of CKD.⁵⁵ The other
30 plausible explanation is the gradual development of metabolic and cardiovascular risk factors
31 over time and thus transitioning to an unrecognized metabolically unhealthy status.

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

6 This study and our previously published study showing higher risks of coronary heart disease,
7 heart failure and cerebrovascular disease in MHO²⁸ demonstrate that these individuals
8 develop target organ damage over time. Therefore, MHO should not be considered “benign”
9 or harmless and addressing obesity in people with MHO might reduce target organ damage
10 including CKD. In addition, this study also shows that even in the absence of obesity, based
11 on BMI, people with normal weight and metabolic abnormalities are also at a higher risk of
12 CKD. Whether weight loss in normal weight individuals will reduce the risk of CKD is unknown,
13 but previous RCT showed that weight loss in normal weight individuals can reverse obesity
14 complications such as non-alcoholic fatty liver disease.⁵⁶

15 Our study has a few limitations. Using BMI as a surrogate of body fat, is simple and
16 reproducible⁵⁷, but it does not discriminate between high percentage of body fat and
17 increased lean mass, especially in young adults with a BMI of $<30 \text{ kg/m}^2$ who undertake
18 regular physical exercise. We did not have access to data on diet and physical activity. With
19 the increasing age, it is more likely that individuals transitioned to higher BMI categories
20 rather than to lower BMI categories over the follow up period given the known difficulty in
21 losing weight.⁵⁸ This makes some misclassification of weight category possible. Metabolic
22 abnormality was defined on the basis of baseline data in the main analysis. Some of the
23 individuals, categorized as metabolically healthy overweight and obese at baseline, might
24 have developed diabetes or hypertension during the follow-up period, as such the period
25 after transition might be misclassified. In the sensitivity analyses, we compared the results of
26 the conventional competing risk Cox regression model and competing risk Cox regression
27 model with time-dependent covariates. The similar HRs derived from two models
28 demonstrated that the transition from metabolic healthy to metabolic unhealthy state during
29 the follow-up period does not have a major impact on the results of our main analyses. As
30 such, diabetes and hypertension might have acted as mediators of CKD in some of these
31 individuals. The development of diabetes and hypertension might also have prompted

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

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

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

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

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

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

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

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

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

15 **Data sharing:** No additional data available.

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

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

24 **Table Legends:**

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

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

- 1 Table 3 Hazard ratios for diagnosis of chronic kidney diseases (CKD) based on the number of
- 2 metabolic abnormalities and body size phenotype.
- 3 **Figure Legends:**
- 4 Figure 1 Flow chart
- 5 Figure 2 The cumulative incidence curves of composite chronic kidney diseases (CKD) by
- 6 body size phenotypes
- 7 Figure 3 Association between body size phenotypes and metabolic status and chronic kidney
- 8 disease (CKD) events in 4.4 million UK adults
- 9 Figure 4 Association of body size phenotype and metabolic status with composite chronic
- 10 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/m²)	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						
1 st (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)
2 nd	813,478 (18.3)	18,251 (14.6)	337,345 (17.7)	282,070 (19.5)	103,232 (17.5)	72,580 (19.1)
3 rd	849,375 (19.1)	23,020 (18.4)	358,383 (18.8)	277,034 (19.1)	116,229 (19.7)	74,709 (19.7)
4 th	790,809 (17.8)	27,159 (21.7)	343,700 (18.0)	239,648 (16.5)	112,411 (19.1)	67,891 (17.9)
5 th (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 \pm 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.

References:

1. Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2020;395(10225):709-733.
2. NHS: Kidney Care. Chronic Kidney Disease in England: The Human and Financial Cost. 2012; <https://www.england.nhs.uk/improvement-hub/wp-content/uploads/sites/44/2017/11/Chronic-Kidney-Disease-in-England-The-Human-and-Financial-Cost.pdf>. Accessed 21 June, 2020.
3. World Health Organization. Overweight and obesity. 2020; <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>. Accessed 14 April, 2021.
4. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC public health*. 2009;9(1):1-20.
5. Ting SM, Nair H, Ching I, Taheri S, Dasgupta I. Overweight, obesity and chronic kidney disease. *Nephron Clinical Practice*. 2009;112(3):c121-c127.
6. Chang AR, Grams ME, Ballew SH, et al. Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. *BMJ*. 2019;364.
7. Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1· 8 million participants. *Lancet*. 2013;383(9921):970-983.
8. Rey-López JP, de Rezende LF, de Sá TH, Stamatakis E. Is the metabolically healthy obesity phenotype an irrelevant artifact for public health? *Am J Epidemiol*. 2015;182(9):737-741.
9. Bradshaw PT, Stevens J. Invited commentary: limitations and usefulness of the metabolically healthy obesity phenotype. *Am J Epidemiol*. 2015;182(9):742-744.
10. Tomiyama AJ, Hunger JM, Nguyen-Cuu J, Wells C. Weight and cardiometabolic health: new perspectives. *International Journal of Obesity*. 2016;40(8):1331-1331.
11. Dhurandhar E. The downfalls of BMI-focused policies. *International Journal of Obesity*. 2016;40(5):729-730.
12. Tomiyama AJ, Hunger JM, Nguyen-Cuu J, Wells C. Misclassification of cardiometabolic health when using body mass index categories in NHANES 2005–2012. *International journal of obesity*. 2016;40(5):883-886.
13. Kovesdy CP, Furth SL, Zoccali C, World Kidney Day Steering Committee. Obesity and kidney disease: hidden consequences of the epidemic. *Canadian Journal of Kidney Health and Disease*. 2017;104 (1):1-14.
14. Stefan N, Artunc F, Heyne N, Machann J, Schleicher ED, Häring H-U. Obesity and renal disease: not all fat is created equal and not all obesity is harmful to the kidneys. *Nephrology Dialysis Transplantation*. 2016;31(5):726-730.
15. Jung CH, Lee MJ, Kang YM, et al. The risk of chronic kidney disease in a metabolically healthy obese population. *Kidney international*. 2015;88(4):843-850.
16. Mottaghi A, Mirmiran P, Delshad H, Azizi F. Effect of different obesity phenotypes on incidence of chronic kidney disease in Tehranian adults. *Journal of the American College of Nutrition*. 2016;35(7):587-596.
17. Chang Y, Ryu S, Choi Y, et al. Metabolically healthy obesity and development of chronic kidney disease: a cohort study. *Annals of internal medicine*. 2016;164(5):305-312.

18. Lin L, Peng K, Du R, et al. Metabolically healthy obesity and incident chronic kidney disease: The role of systemic inflammation in a prospective study. *Obesity*. 2017;25(3):634-641.
19. Zhang J, Jiang H, Chen J. Combined effect of body mass index and metabolic status on the risk of prevalent and incident chronic kidney disease: a systematic review and meta-analysis. *Oncotarget*. 2017;8(22):35619.
20. Nam KH, Yun HR, Joo YS, et al. Changes in obese metabolic phenotypes over time and risk of incident chronic kidney disease. *Diabetes, Obesity & Metabolism*. 2018;20(12):2778-2791.
21. Uehara S, Sato KK, Koh H, et al. The Association Between Metabolically Healthy Obesity and the Risk of Proteinuria: The Kansai Healthcare Study. *Journal of epidemiology*. 2018;28(8):361-366.
22. Sesti G, Succurro E, Arturi F, et al. IGF-1 levels link estimated glomerular filtration rate to insulin resistance in obesity: a study in obese, but metabolically healthy, subjects and obese, insulin-resistant subjects. *Nutrition, Metabolism & Cardiovascular Diseases*. 2011;21(12):933-940.
23. Chen S, Zhou S, Wu B, et al. Association between metabolically unhealthy overweight/obesity and chronic kidney disease: The role of inflammation. *Diabetes & metabolism*. 2014;40(6):423-430.
24. Hashimoto Y, Tanaka M, Okada H, et al. Metabolically healthy obesity and risk of incident CKD. *Clinical journal of the American Society of nephrology*. 2015;10(4):578-583.
25. Chang AR, Surapaneni A, Kirchner HL, et al. Metabolically healthy obesity and risk of kidney function decline. *Obesity*. 2018;26(4):762-768.
26. Youngran Y. Metabolically Healthy Obesity and Risk of Incident Chronic Kidney Disease in a Korean Cohort Study. *Iranian Journal of Public Health*. 2019;48(11):2007.
27. Hanks LJ, Tanner RM, Muntner P, et al. Metabolic subtypes and risk of mortality in normal weight, overweight, and obese individuals with CKD. *Clinical Journal of the American Society of nephrology*. 2013;8(12):2064-2071.
28. Caleyachetty R, Thomas GN, Toulis KA, et al. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. *Journal of the American College of Cardiology*. 2017;70(12):1429-1437.
29. Gajjala PR, Sanati M, Jankowski J. Cellular and molecular mechanisms of chronic kidney disease with diabetes mellitus and cardiovascular diseases as its comorbidities. *Frontiers in immunology*. 2015;6:340.
30. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *International journal of surgery*. 2014;12(12):1495-1499.
31. Blak B, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Journal of Innovation in Health Informatics*. 2011;19(4):251-255.
32. Doran T, Fullwood C, Gravelle H, et al. Pay-for-performance programs in family practices in the United Kingdom. *New England Journal of Medicine*. 2006;355(4):375-384.
33. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiology and drug safety*. 2007;16(4):393-401.

34. World Health Organization. Body mass index - BMI. <http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi>. Accessed 06 Jan, 2020.
35. US Department of Health. Your Guide to Lowering Cholesterol with TLC. *Therapeutic Lifestyle Changes*. 2005(06-5235).
36. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocrine Practice*. 2017;23:1-87.
37. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Annals of internal medicine*. 2009;150(9):604-612.
38. National Clinical Guideline Centre. Chronic kidney disease (partial update): early identification and management of chronic kidney disease in adults in primary and secondary care. 2014; <https://www.nice.org.uk/guidance/cg182/evidence/full-guideline-pdf-191905165>. Accessed 14 April, 2021.
39. UK Data Service | Census Data. 2011 UK Townsend Deprivation Scores. 2017; <https://www.statistics.digitalresources.jisc.ac.uk/dataset/2011-uk-townsend-deprivation-scores>. Accessed 06 Jan, 2020.
40. Orimo H, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of “elderly”. *Geriatrics & gerontology international*. 2006;6(3):149-158.
41. Alizadeh S, Esmaeili H, Alizadeh M, et al. Metabolic phenotypes of obese, overweight, and normal weight individuals and risk of chronic kidney disease: a systematic review and meta-analysis. *Archives of endocrinology & metabolism*. 2019;63(4):427-437.
42. Herrington WG, Smith M, Bankhead C, et al. Body-mass index and risk of advanced chronic kidney disease: Prospective analyses from a primary care cohort of 1.4 million adults in England. *PloS one*. 2017;12(3):e0173515.
43. Lemoine S, Guebre-Egziabher F, Sens F, et al. Accuracy of GFR estimation in obese patients. *Clinical Journal of the American Society of nephrology*. 2014;9(4):720-727.
44. Nerpin E, Risérus U, Ingelsson E, et al. Insulin sensitivity measured with euglycemic clamp is independently associated with glomerular filtration rate in a community-based cohort. *Diabetes care*. 2008;31(8):1550-1555.
45. Sarafidis PA, Ruilope LM. Insulin resistance, hyperinsulinemia, and renal injury: mechanisms and implications. *American journal of nephrology*. 2006;26(3):232-244.
46. Suzuki D, Miyata T, Saotome N, et al. Immunohistochemical evidence for an increased oxidative stress and carbonyl modification of proteins in diabetic glomerular lesions. *Journal of the American Society of Nephrology*. 1999;10(4):822-832.
47. Risérus U, Basu S, Jovinge S, Fredrikson GN, Ärnlöv J, Vessby B. Supplementation with conjugated linoleic acid causes isomer-dependent oxidative stress and elevated C-reactive protein: a potential link to fatty acid-induced insulin resistance. *Circulation*. 2002;106(15):1925-1929.
48. Prabhakar SS. Role of nitric oxide in diabetic nephropathy. Paper presented at: Seminars in nephrology 2004.
49. Horie K, Miyata T, Maeda K, et al. Immunohistochemical colocalization of glycoxidation products and lipid peroxidation products in diabetic renal glomerular lesions. Implication for glycoxidative stress in the pathogenesis of diabetic nephropathy. *The Journal of clinical investigation*. 1997;100(12):2995-3004.
50. Miyata T, Sugiyama S, Suzuki D, Inagi R, Kurokawa K. Increased carbonyl modification by lipids and carbohydrates in diabetic nephropathy. *Kidney International*. 1999;56:S54-S56.

51. Knight SF, Imig JD. Obesity, insulin resistance, and renal function. *Microcirculation*. 2007;14(4-5):349-362.
52. Adamczak M, Wiecek A. The adipose tissue as an endocrine organ. Paper presented at: Seminars in nephrology 2013.
53. Wolf G, Hamann A, Han DC, et al. Leptin stimulates proliferation and TGF- β expression in renal glomerular endothelial cells: potential role in glomerulosclerosis. *Kidney international*. 1999;56(3):860-872.
54. Foster MC, Hwang S-J, Porter SA, Massaro JM, Hoffmann U, Fox CS. Fatty kidney, hypertension, and chronic kidney disease: the Framingham Heart Study. *Hypertension*. 2011;58(5):784-790.
55. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Archives of medical science: AMS*. 2017;13(4):851.
56. Wong VW-S, Wong GL-H, Chan RS-M, et al. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. *Journal of hepatology*. 2018;69(6):1349-1356.
57. Prentice AM, Jebb SA. Beyond body mass index. *Obesity reviews*. 2001;2(3):141-147.
58. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. *Annals of internal medicine*. 2013;159(11):758-769.