Response to editorial and reviewers' comments

Chang et al, Adiposity and risk of eGFR decline

Editorial comments

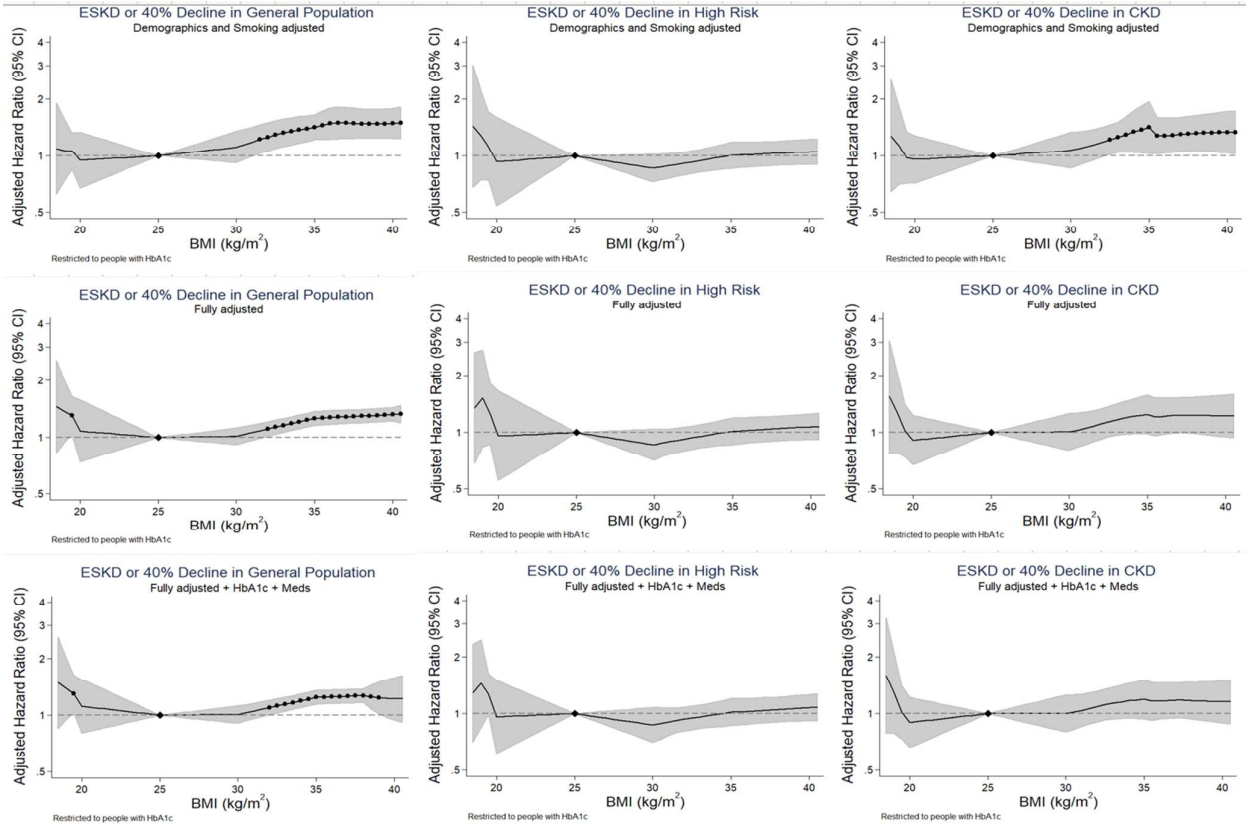
The observation that obesity is associated with renal decline is expected and perhaps the more important question is how much of the effect of obesity is independent of (or not mediated by) the other conditions. None of this is to lessen the importance of the association, but it would help us understand better the mechanism and might also direct decisions about therapy. Therefore, would it be possible to pay a bit more attention to adjustment for degree of hypertension (We think you did use SBP in a sensitivity analysis), diabetic control (eg HbA1c%), duration of diabetes, other comorbidities and medications rather than dichotomisation or ignoring them. If better adjustment is not possible in the analysis, then you could amplify the discussion some more to include unadjusted confounders and incomplete adjustment as likely contributors to the association between obesity and renal decline.

Thank you for these comments. We agree that both the minimally-adjusted association and the independent association of obesity with renal decline are of interest. In our analyses of over 5 million subjects, we observe that the risk increase begins at levels of BMI even before the standard threshold for obesity is reached. This is extremely important, given the enormous number of people worldwide in the overweight category of BMI and the previously uncertain risk profile of this segment of the population.

We appreciate that knowledge of mediators can be informative, and indeed we find attenuation of effect sizes when we adjusted for systolic blood pressure, eGFR, diabetes, cholesterol and history of CVD. As requested, we have devoted additional attention to the independent association of BMI with GFR decline in our results (page 12, 2nd paragraph; page 14, 1st paragraph; page 15, 1st and 2nd paragraphs; page 16, 1st paragraph) and discussion.

"Adjustment for potential mediators attenuated the BMI-GFR decline relationship, although BMIs of 35 and 40 kg/m^2 remained associated with 28% and 46% increased risk of GFR decline, compared to a BMI of 25 kg/m^2."

Unfortunately, only a subset of the cohorts and cohort populations had the additional potential mediators suggested by the Editors. Among the 217,038 individuals with HbA1c and ACE/ARB, statin, insulin, and other diabetes medication data, the relationship between higher BMI and risk of GFR decline after adjustment for these additional variables (bottom panel) was fairly similar to that observed in our fully adjusted model (middle panel).



Cohorts with additional data on HbA1c, ACE/ARB, statin, insulin, and other diabetes medications: ***General population cohorts*** *(Aichi ARIC AusDiab BeaverDamCKD Beijing ChinaNS CHS CIRCS COBRA ESTHER FRAMINGHAM Geisinger Gubbio HUNT JMS MESA MRC NHANES, Ohasama PREVEND Rancho_Bernardo REGARDS Takahata TLGS Tromso ULSAM);* **High risk cohorts** (ADVANCE NZDCS Pima SMART ZODIAC); **CKD cohorts (**AASK CanPREDDICT "CARE FOR HOMe" CRIB GCKD Gonryo, MASTERPLAN MDRD MMKD Nefrona NephroTest SRR-CKD PSP-CKD)_

As suggested, we have now referred to the possibility of incomplete adjustment in Discussion (p16):

"We were unable to fully adjust for risk factors such as glycated haemoglobin, diabetes duration, or medications, which could contribute to the association between obesity and GFR decline."

What the review registered? Was the appropriate reporting guideline followed? In the abstract you suggest the study type is "Individual participant data meta-analysis" which suggests PRISMA-IPD. The report would benefit if it followed the appropriate guideline in EQUATOR.
This is important as there are a lot of assumptions in the approach that has been taken - following the appropriate guideline will ensure these have all been addressed. This may also help with the readability.

Although this is indeed an individual participant meta-analysis, it is not a systematic review. CKD-PC is a collaborative project involving the majority of major studies that include data on eGFR and albumin-creatinine ratio, plus clinical outcomes. Our methodology is stated in reference #17: "CKD-PC was first established at a collaborators meeting held in London in October of 2009 with the support of the Kidney Disease: Improving Global Outcomes (KDIGO) organization and the US National Kidney Foundation (NKF). More than 100 investigators, representing >50 cohorts worldwide, participated and discussed approaches to improve the definition and staging of CKD. KDIGO, NKF and the participants were enthusiastic about extending this meta-analysis exercise into a consortium to

address critical questions related to CKD prognosis". Over the first 9 years of the project we have now published over 20 papers, including in The Lancet, NEJM, JAMA and BMJ (Nitsch et al, 2013). This success has led to many more studies joining the consortium. We operate by suggesting topics to our collaborators in phases that last 1-3 years – the current paper being part of phase 4. Investigators are able to vote on topics and then choose whether or not to participate in any specific paper. To express this succinctly we have edited the Study Design and Data Sources section on p8 to say:

"The Chronic Kidney Disease Prognosis Consortium (CKD-PC) was established initially in 2009 after the Kidney Disease: Improving Global Outcomes Controversies Conference to provide data to support the definition and staging of CKD. It now includes more than 70 cohorts spanning 40 countries with data on estimated glomerular filtration rate and clinical outcomes [17]. Periodically, collaborators are invited to vote on topics for research in successive phases; the current work is part of the fourth such phase. We invited cohorts with follow-up data for ESRD, eGFR decline, and mortality to participate in this study. We categorized cohorts as general population, high CVD risk (participants with at least one CVD risk factor), or CKD and, because selection into these cohorts differs, conducted separate meta-analyses for each. "

We agree that the PRISMA guidelines are useful in assuring a standard approach to reporting results, and for transparency in methodology. We now provide the PRISMA-IPD checklist, and we have made several small changes to Methods (page 8, 9, 10) to further improve transparency (insertions highlighted):

"We used a 2-stage analytic approach, whereby each study was analyzed separately, allowing for an examination of outliers and bias, and then meta-analyzed using random effects models. Most participating cohorts in the CKD-PC transfer individual-level participant data to the data coordinating centre at Johns Hopkins University. Cohorts that cannot transfer data due to legal or other logistical reasons were sent standardized code. Summary statistics are then returned to the data coordinating center for examination and meta-analysis. As an exposure, BMI was modeled continuously using linear splines with knots at 20, 25, 30, and 35 kg/m^2. WC and WHtR were modeled continuously using linear splines with knots corresponding to those for BMI (eFigure 1). Since WC thresholds used to assess health risks are different by sex,[20] we used sex-specific references.
Hazard ratios and 95% confidence intervals were obtained from Cox regression models adjusted for age, sex, black race, and current smoking. We also pre-specified tests for effect modification with BMI in general population cohorts, by including interaction terms for age (< or ≥65 y), sex, black race, baseline hypertension, diabetes, eGFR (<30, 30-59, 60-89, ≥90 ml/min/1.73m^2), and albuminuria (ACR <30, ACR 30-299, ACR ≥300 mg/g). We quantified heterogeneity in meta-analysis using the I^2 statistic, and conducted a meta-regressions to examine whether length of follow-up time or calendar year of study explained heterogeneity."

As anticipated there is a lot of heterogeneity between studies, you do not present the pooled estimates in the text, but you may also want to exclude the pooled results from the forest plots. It does not seem to make sense to combine, although displaying the individual estimates is useful.

In our view, quantitative heterogeneity is often distinct from qualitative, or clinically significant, heterogeneity. In our study, the clinical significance of effects is the same across most, if not all, studies. For example in Fig 1B, 20 out of 23 studies show effects that are qualitatively the same. Random effects meta-analysis accounts for statistical heterogeneity directly. We include the (now-routine) I-squared statistic, which measures the percentage of overall variation due to between-study differences. This statistic is informative but does have some drawbacks. The key drawback in studies such as ours, where some constituent datasets are huge, is that studies with small confidence

intervals will tend to inflate the I-squared artificially should they be outside the range of the confidence interval for a pooled estimate when that study is excluded. In the same way, a large study can increase the confidence interval of the pooled estimate when added to a meta-analysis that excludes it, which is counter-intuitive. Hence, our view is that the I-squared statistic should be regarded with some caution in this context. For example, in Fig 1B, the I-squared is 89%, which is generally considered to be large, but the overall forest plot suggests rather greater homogeneity.

We do acknowledge that sometimes heterogeneity is important, and here the forest plot is extremely useful to identify its source. For example, in Fig 3B there is one outlier. But even in this situation, the addition of the line presenting the overall pooled estimate can be useful to highlight the differential. We adhere to the PRISMA-IPD guideline 21 which states, "Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity."

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below. In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

We have followed this advice in what follows.

Reviewer Comments

Reviewer: 1

Comments:
The authors have investigated the relationship between body mass index (BMI), waist circumference (WC), waist to height ration and GFR decline in a substantive population. The data had been collected from 1070 to 2017 and comprised of subjects from 39 general populations (5,459,014), 84,417 in 6 high CVD risk cohorts and 91,607 in CKD cohorts.
The relationship between obesity and health is an important area of research. The authors suggest that markers of adiposity are independent risk factors for GFR decline and death in individuals with normal or reduced eGFR. This conclusion is perhaps not surprising but assuming the statistical analysis of the cohort data is robust would be an important statement, particularly for those developing public health initiatives. This information would be important for health care professional to share for individuals in the general population as well as those in early stages of CKD.

We thank the reviewer for his valued comments on the study's relevance to patients and for public health initiatives.

Reviewer: 2

Comments:
authors impressively analyze a large, global cohort of patients to investigate the link between adiposity measures and renal outcomes. this is important because ckd carries significant health burden on society; moreover, if a link between obesity and ckd progression can be shown, it would imply the epidemic of obesity may increase significant societal burden through a CKD pathway. these are my suggestions -authoirs should do additional sensitivity using methodologies to account for competing risk of death; higher death rates would lower risk of renal progression

We thank the reviewer for his comments. We agree that consideration of the competing risk of death is important, and have included these analyses as sensitivity analyses, which demonstrate similar findings (supplement eFigure 2C, eFigure 4C, eFigure 5C).

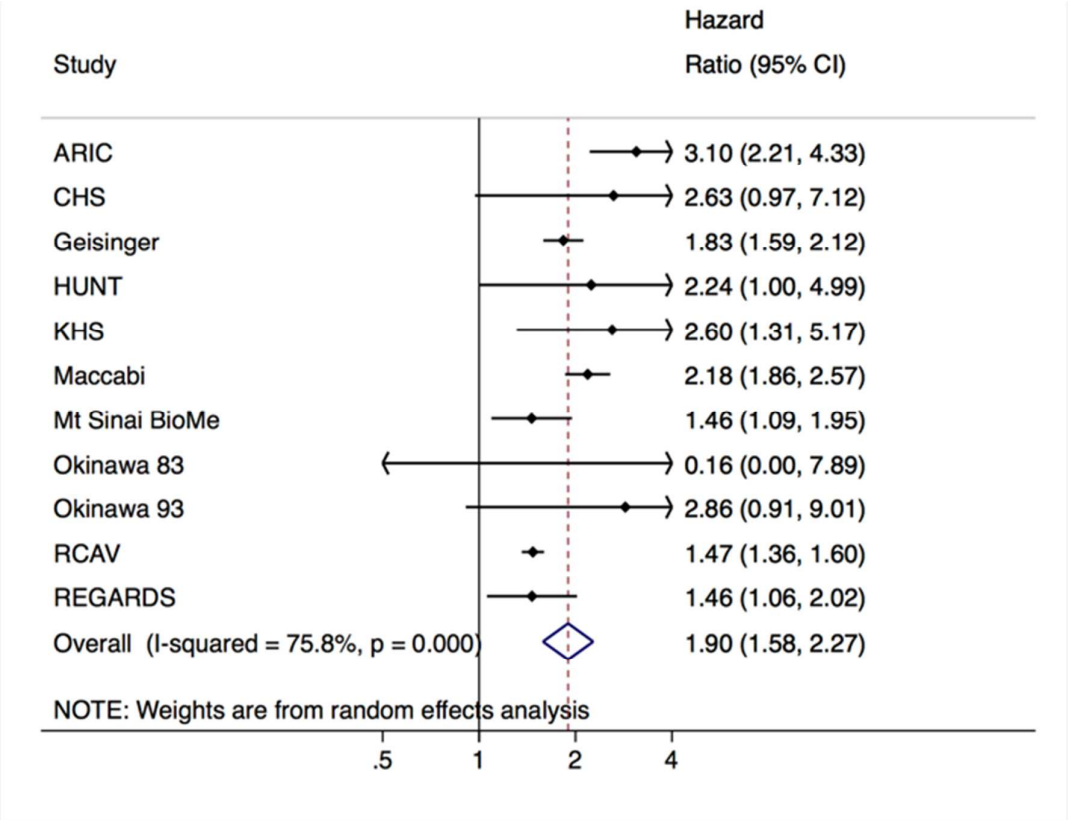
-please provide outcomes for hospitalization; this is a better measure of morbidity which is a measure of burden on society

We agree that hospitalization is an interesting, highly relevant measure of morbidity. Unfortunately, we did not collect hospitalization data from our participating cohorts, and so we are unable to perform this interesting analysis.

-please provide table of HR for individual outcomes of the composite renal outcome

Thank you for this suggestion. Below, we now provide the forest plot for eFigure 3b, which demonstrates the hazard ratio for end-stage kidney disease (ESKD). Results look similar when using ESKD as the outcome.

Hazard Ratios at 35 vs. 25 kg/m2 in Individual General Population Cohorts for ESKD Outcome



-clarify how this analysis implies reverse causation explains null relationship; this is an abstract term for general bmj reader; it more commonly used in renal but rarely mentioned outside of the renal field

We thank the reviewer for this critique. We have added more in the statistical analysis section and to the discussion to help the general BMJ audience in understanding the concept of reverse causation (page 10 and 16).

***Page 10: "*To address the possibility of bias from reverse causation, or the possibility that non-obese participants had lost weight due to a condition that also affected risk of eGFR decline…"**

Page 16: "We only used one baseline measurement of BMI, and changes in weight due to disease that occurred prior to cohort entry could introduce bias, potentially weakening associations between higher BMI and adverse outcomes (i.e., reverse causality). This concept may explain the weaker association in high-risk cohorts…"

-why are results not presented stratified by level of albuminuria?

We present results stratified by level of albuminuria in the subset of general population cohorts that had albuminuria data (see eFigure 3D). We did not include albuminuria in primary analyses since it was not present in all cohorts and could be considered a potential mediator of the relationship between obesity and risk of kidney function decline.

-authors report findings as binary variables (35 vs 25) and don't leverage full longitudinal advantage of data set. can they treat BMI, WC as continuous variable to see trend over entire spectrum of adiposity measures

We agree that the strength of this analysis is the ability to treat the measures of obesity as continuous variables. All were treated as continuous variables, using linear splines with knots at 20, 25, 30, and 35 kg/m^2 for BMI, and corresponding knots for waist circumference and waist-to-height ratio (page 9, 1st paragraph of statistical analysis). The continuous relationships can be seen in Figure 1A, Figure 2A-D, Figure 3A, 3C, and Figure 4A-B. As the amount of data presented in the manuscript is quite large, we opted to show the continuous relationships in graphs, and describe the adjusted HRs for specific points (BMI 35 vs. 25 kg/m^2 and 20 vs 25 kg/m^2), overall and by cohort. If desired by the editorial team, we can include similar figures using alternative BMI cutpoints as additional supplemental figures.

-there are many weaknesses and potential sources of bias/selection in this and any observational studies; authors have not acknowledged any potential limitations of their study in the discussion

We thank the reviewer for this critique. We have expanded our limitations section to include the possibility of incomplete adjustment/residual confounding and other sources of bias (page 16).

"We were unable to fully adjust for risk factors such as glycated haemoglobin, diabetes duration, or medications, which could contribute to the association between obesity and GFR decline."

Reviewer: 3

Comments:
This is individual-level meta-analysis of the association between adiposity and the risk of GFR decline or all-cause mortality. The study included more than a total of 6 million patients from general population cohorts, high CVD-risk and CKD cohorts. The study had the following findings: 1) high BMI was associated with increased risk of GFR decline and all-cause mortality in general population cohorts but less so in CKD and CVD cohorts, 2) waist-circumference and waist-to-height ratio was a stronger predictor of outcomes than BMI, and 3) the risk associated with BMI was increased in CKD and CVD-cohorts after excluding the first three years of follow-up in high risk cohorts, indicating possible reverse causality bias.

The study is the largest one in the area, very well conducted, internally consistent and extensively documented. The findings are interesting and provides new knowledge to the discussion about the obesity paradox in chronic kidney disease. I have no major concerns regarding the validity of the data, the statistical analyses, the presentation of data or the discussion of results. However, I do believe that a revision could improve the manuscript:

1. I am not sure that Table 1 is the best presentation of baseline characteristic. The main comparison in the study is between BMI groups, not between participating cohorts. I think that Table 1 should present overall baseline characteristics across BMI groups, independent of specific cohort, but stratified on type of cohort (general population, high CVD-risk, etc.) which would be more condensed and easier to read for the average reader (who would probably not have time to scrutinize the many supplementary tables).

We thank the reviewer for the kind comments. We agree that a suggested summary table across BMI groups would be a nice addition. Whilst such a summary table is easier to read, it shows pooled data across BMI groups, which is inconsistent with how our analyses were conducted as a 2-stage meta-analysis. We have thus decided to add a new table showing results by BMI subgroups, as suggested, in the supplement as eTable 2. If the editors wish, we can switch it with our current Table 1, but we worry that it may be misleading to the reader.

eTable 2. Summary Baseline Characteristics by BMI Category

General Population Cohorts					
	18.5--to <25	**25 to <30**	**30 to <35**	**≥35**	**Total**
n	1837795	1958101	1055261	607857	5459014
Age, years	51 (15)	57 (14)	57 (13)	55 (13)	55 (14)
Female	705942 (38%)	415334 (21%)	199411 (19%)	150168 (25%)	1470855 (27%)
Black	137038 (7%)	201712 (10%)	141229 (13%)	87869 (14%)	567848 (10%)
Asian	757467 (41%)	314566 (16%)	36442 (3%)	4330 (1%)	1112805 (20%)
Current smoking	200241 (11%)	116930 (6%)	35394 (3%)	22490 (4%)	375055 (7%)
Systolic blood pressure (mmHg)	124 (18)	131 (18)	134 (17)	136 (17)	130 (18)
Cholesterol (mmol/L)	4.89 (1.02)	4.98 (1.07)	4.97 (1.11)	4.91 (1.09)	4.95 (1.07)
Diabetes	142016 (8%)	320314 (16%)	280521 (27%)	229211 (38%)	972062 (18%)
History of CVD	168230 (9%)	277506 (14%)	175473 (17%)	106849 (18%)	728058 (13%)
eGFR (ml/min/1.73m2)	89 (18)	85 (17)	85 (17)	87 (18)	86 (17)
ACR > 30 mg/g	41588 (6%)	34388 (9%)	17873 (16%)	13772 (24%)	107621 (8%)
Waist Circumference (cm)	75 (12)	87 (12)	99 (12)	113 (14)	80 (14)
Waist Height Ratio	0.46 (0.13)	0.53 (0.15)	0.60 (0.07)	0.69 (0.08)	0.49 (0.14)
High CVD Risk Cohorts					
n	19049	29495	19559	16314	84417
Age, years	63 (14)	62 (13)	59 (12)	53 (12)	60 (13)
Female	9553 (50%)	12021 (41%)	9076 (46%)	9436 (58%)	40086 (47%)
Black	21 (0%)	41 (0%)	25 (0%)	20 (0%)	107 (0%)
Asian	2708 (14%)	2524 (9%)	576 (3%)	136 (1%)	5944 (7%)
Current smoking	2529 (13%)	3508 (12%)	2083 (11%)	1714 (11%)	9834 (12%)
Systolic blood pressure (mmHg)	135 (21)	138 (20)	138 (20)	137 (20)	137 (20)
Cholesterol (mmol/L)	5.10 (1.22)	5.12 (1.22)	5.17 (1.22)	5.15 (1.18)	5.13 (1.21)
Diabetes	11297 (59%)	20248 (69%)	14919 (76%)	12730 (78%)	59194 (70%)
History of CVD	4959 (26%)	8147 (28%)	4455 (23%)	2747 (17%)	20308 (24%)
eGFR (ml/min/1.73m2)	77 (22)	77 (21)	79 (22)	85 (23)	79 (22)
CKD Cohorts					
n	26502	33654	19061	12390	91607
Age, years	69 (13)	70 (11)	69 (11)	66 (11)	69 (12)
Female	14131 (53%)	14662 (44%)	9183 (48%)	7661 (62%)	45637 (50%)
Black	1335 (5%)	2125 (6%)	1517 (8%)	1400 (11%)	6377 (7%)
Asian	4877 (18%)	2520 (7%)	619 (3%)	166 (1%)	8182 (9%)
Current smoking	2811 (11%)	2833 (8%)	1588 (8%)	965 (8%)	8197 (9%)

Systolic blood pressure (mmHg)	132 (20)	134 (19)	135 (19)	136 (19)	134 (19)
Cholesterol (mmol/L)	4.85 (1.19)	4.77 (1.25)	4.75 (1.19)	4.75 (1.23)	4.78 (1.22)
Diabetes	5604 (21%)	9316 (28%)	7008 (37%)	5990 (48%)	27918 (30%)
History of CVD	6160 (23%)	9041 (27%)	5285 (28%)	3368 (27%)	23854 (26%)
eGFR (ml/min/1.73m2)	47 (18)	46 (15)	46 (14)	46 (14)	46 (16)
ACR > 30 mg/g	8483 (58%)	11314 (62%)	6650 (62%)	4229 (60%)	30676 (61%)
Waist Circumference (cm)	83 (8)	98 (8)	109 (9)	122 (11)	98 (14)
Waist Height Ratio	0.50 (0.05)	0.58 (0.05)	0.65 (0.05)	0.73 (0.06)	0.59 (0.08)

2. Some studies have suggested that collider bias can explain the discrepancy between risk associated with high BMI in general population cohorts and high-risk population cohorts (see "The Obesity Paradox Explained" by Banack and Kaufman, Epidemiology 2013). Baseline characteristics in the current study also suggest that there is some form of selection bias into high CVD-risk and CKD cohorts that results in a smaller difference in co-morbidity burden between normal weight and adipose patients in high risk cohorts compared to general population cohorts. Is it possible and relevant to adjust for selection bias in the current study? If not, I think that a discussion of this subject in the manuscript could be reasonable.

We agree that collider bias, a special form of selection bias, could partially explain the discrepancy in findings between the general population cohorts, the CKD cohorts and the high CVD-risk cohorts: unmeasured factors (U) influence both the stratification variable (CKD or high CVD risk status) and the outcome (kidney function decline). However, adjustment for selection bias would require knowing the prevalence of U in the cohorts, the effect of U on the risk of CKD in obese and nonobese individuals, and the effect of U on the risk of kidney function decline among those with CKD. (see: Glymour and Vittinghoff. Epidemiology 2014; PMID: 24296924). Because selection into the cohorts differs by cohort type, we opted to analyze general population cohorts separately from high CVD risk cohorts, and CKD cohorts. We have included additional discussion on page 16 to describe this issue with a relevant reference.

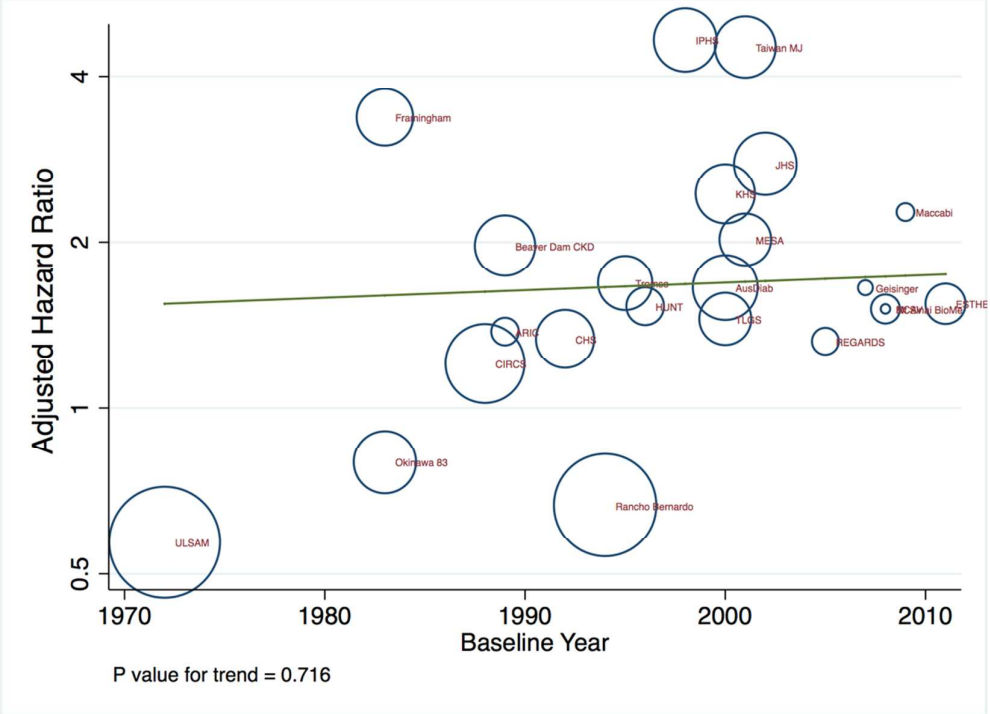
"…the difference may be due in part to collider bias. For example, if obesity increases the risk for cardiovascular disease, then other risk factors, some of which are unmeasured, can be expected to be greater in individuals with cardiovascular disease who are not obese." (*ref: Lajous et al, Am J Med 2015.)*

3. The study has data from cohorts from 1970 until 2017, but the authors have not adjusted for inclusion year in the study. Inclusion year appears to me as a confounder (associated with both exposure and outcome) as BMI is increasing over time whereas all-cause mortality is decreasing. Inclusion year has also been described as an effect modifier (see "Change in Body Mass Index Associated with Lowest Mortality in Denmark 1976-2013", Afzal et al, JAMA 2013) with effect of high BMI on all-cause mortality weakening over time. I think that it would improve the study if the authors addressed this issue with adjustment and/or stratified analyses.

Thank you for this suggestion. We explored this issue through meta-regression, regressing the log hazard ratios against the median baseline year of each cohort, and presented them in a bubble plot. This did not suggest that heterogeneity in findings was explained by median baseline cohort year (p=0.72). These data have been added as eFigure 2, and a comment provided on p12 of the text.

"…considerable heterogeneity, which was not explained by cohort follow-up time (p = 0.43 from meta-regression), or by median cohort baseline year (p = 0.72 from meta-regression) (eFigure 2).

eFigure 2. Hazard Ratios at 35 vs. 25 kg/m^2 in Individual General Population Cohorts, by Median Baseline Year



4. Why did the authors choose to exclude patients with BMI<18.5 kg/m2? This exclusion criterium is not intuitive for me and the authors provide no explanation.

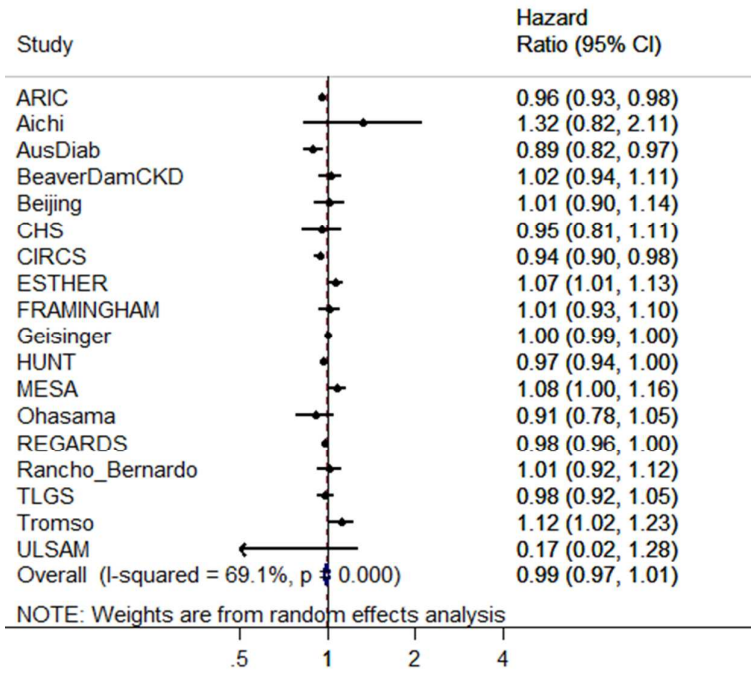
Being underweight (<18.5 kg/m^2) has been shown to be consistently associated with many adverse outcomes in patients with and without CKD. As we were primarily interested in the relationship between overweight and obesity with GFR decline, we excluded these patients. We have expanded upon this in the methods (page 8).

"We excluded individuals with history of ESRD and those who were underweight (<18.5 kg/m^2) as our objective was to study the relationship between overweight and obesity with GFR decline."

5. How did the authors choose to adjust for age? If age is included in the manuscript as a linear variable, then I would like to have the linearity assumption tested. Residual confounding from age is widespread in observational studies, and a sensitivity analysis with adjustment for exact age (the authors should have power enough) could be reasonable.

Our analyses used exact age as a continuous variable. We found that the association between age and GFR decline was log-linear in the cohorts. To demonstrate that the linearity assumption is correct, in the figure below, we added a spline at the median age for each general population study for which we had "in-house" data (78% of the cohorts with the 40% decline outcome), and meta-analyzed the difference in the hazard ratios for the spline terms (HR 0.99, 95% CI: 0.97-1.01).

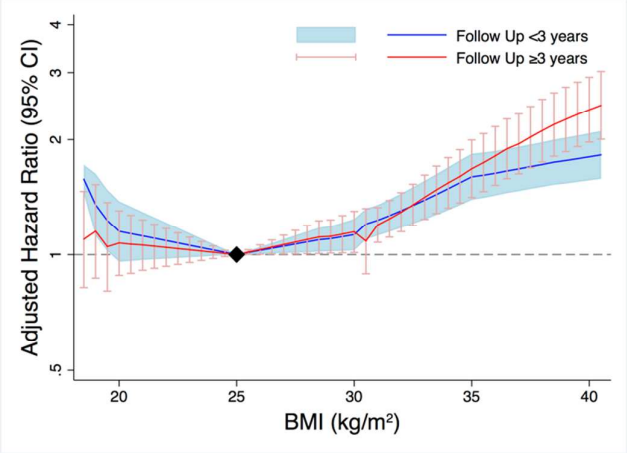
Difference in Hazard Ratios for Splines above and below Median Age for General Population Studies



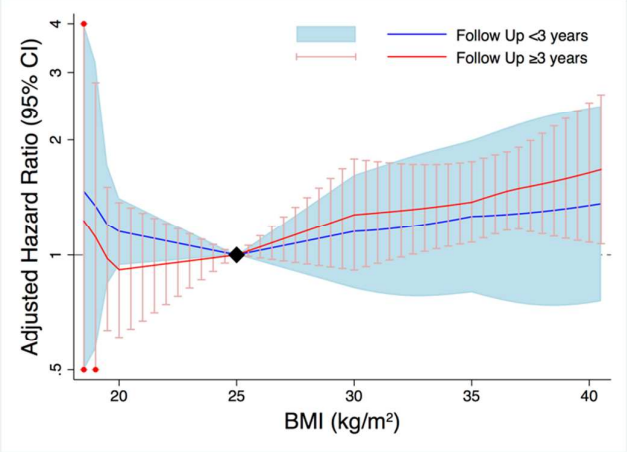
6. The primary model for the association between BMI and outcomes in the manuscript is a Cox Model, which has the assumption that the effect of BMI on outcome is constant over time. However, the effect of BMI in high CVD-risk cohorts and CKD-cohorts changes after exclusion of the first three years of follow-up, indicating that effect of BMI is in fact not constant over time. I think that some formal test of the proportional hazards assumption would be reasonable to have in the manuscript, alternatively a graphical illustration of risk over time (cumulative incidence curves or Kaplan-Meier curves where appropriate). If the proportional hazards assumption is not meet then the authors could consider presenting landmark analyses as their main analyses.

To address the reviewer's comment, we examined proportionality of the association between BMI and GFR decline by adding an interaction term with follow-up time. We found that the association between BMI and GFR decline did not substantively differ over time. Here, we show the relationship between BMI and GFR decline for those with < or >=3 years of follow-up in the general population, high cardiovascular risk, and CKD cohorts.

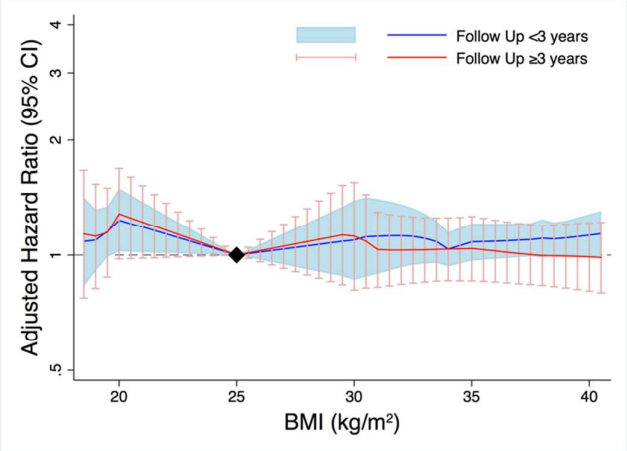
BMI Interaction by Follow Up Time (< or >= 3 years) in General Population Cohorts



BMI Interaction by Follow Up Time (< or >= 3 years) in High CVD Risk Cohorts



BMI Interaction by Follow Up Time (< or >= 3 years) in CKD Cohorts



Reviewer: 4

Comments:
I was very delighted to read this fantastic paper on adiposity and the risk of renal impairment. I have no further comments and in my opinion the paper can be accepted as it is.

We thank the reviewer for the supportive comments.