BMJ - Decision on
Manuscript ID
BMJ.2018.045978

Body: 05-Sep-2018

Dear Dr. Chang

Manuscript ID BMJ.2018.045978 entitled "Adiposity and the risk of glomerular filtration rate decline: results from a global consortium including over 5 million subjects"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

dr. Wim Weber
European editor, The BMJ
wweber@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Sophie Cook (Chair), Jamie Kirkham (statistician), Elizabeth Loder, José Merino, Georg Rőggla, Tiago Villanueva, Wim Weber, Daoxin Yin

Decision: Put points

Detailed comments from the meeting:

We thought your study addresses an interesting and potentially important research question.
We had the following concerns.

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.

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.

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.

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.

Comments from Reviewers

Reviewer: 1

Recommendation:

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.

Additional Questions:
Please enter your name: Prof Andrew Demaine

Job Title: expert patient

Institution: retired

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

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If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: no

Reviewer: 2

Recommendation:

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
-please provide outcomes for hospitalization; this is a better measure of morbidity which is a measure of burden on society
-please provide table of HR for individual outcomes of the composite renal 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
-why are results not presented stratified by level of albuminuria?
-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

-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

Additional Questions:
Please enter your name: kevin chan

Job Title: assistant professor

Institution: harvard medical school

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 3

Recommendation:

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).
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.
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.
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.
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 (see https://www.theanswerpage.com/study.php?specialty_id=7&topic_id=32&q=3), and a sensitivity analysis with adjustment for exact age (the authors should have power enough) could be reasonable.
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.

Additional Questions:

Please enter your name: Anders Nissen Bonde

Job Title: Research fellow

Institution: Department of Cardiology, University Hospital Herlev-Gentofte, Copenhagen, Denmark

Reimbursement for attending a symposium?: No

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A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 4

Recommendation:

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.

Additional Questions:
Please enter your name: Kristine Hommel

Job Title: Consultant doctor, PhD

Institution: Holbaek, Sealand University Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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