PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Obesity in young men and individual and combined risks of type 2 diabetes, cardiovascular morbidity, and death before 55 years of age: A Danish 33-year follow-up study
AUTHORS	Schmidt, M; Johannesdottir, Sigrun; Lemeshow, Stanley; Lash, Timothy; Ulrichsen, Sinna; Botker, Hans Erik; Toft Sorensen, Henrik

VERSION 1 - REVIEW

REVIEWER	Anders Gaarsdal Holst, MD, PhD Department of Cardiology, B2142 University Hospital Rigshospitalet Blegdamsvej 9, 2100 Copenhagen Denmark No competing interests to declare.
REVIEW RETURNED	21-Feb-2013

GENERAL COMMENTS	Using a combination of different Danish registries, including a military conscription database, Schmidt et al. examined the association of BMI at the median age of 19 years with type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before 55 years of age. They found that overweight was associated with all of the noted end points. I do not have much knowledge in the field of obesity research and thus I have focused my review on the data and statistical methods used. Both of which I have experience with. Data was analyzed using well accepted and contemporary methods, among these Fine & Gray competing risk regression. In general the manuscript is very well written, their methods are sound and the conclusions valid. Thus, I only have some minor comments: Minor comments There is no reporting of follow-up time: As mentioned in the STROBE-statement this should be reported. The authors used the “Aarhus University Prescription Database”, which as far as I understand, only holds data on some dispensed prescriptions, unlike the Danish National Prescription Registry which holds data on all dispensed prescriptions (but only from 1995 and onwards). Do the authors have references comparing the two? Furthermore using only the local database instead of the national registry means that all subjects emigrating from central/northern Jutland are lost to follow-up with regard to prescription data.

	Page 10, line 46: “Supporting the robustness of our results, previous studies have found similar mortality rates among smokers and non-smokers17 or even higher mortality rates among non-smokers.16” Please state that this is with regards to obesity and not in general. When I look at figure 2 - Death, I see no indication of a (linear) dose response relationship but on page 7, line 18 the authors state that “There was no suggestion that BMI was not linear in the log hazard for the individual outcomes”. Can the authors explain this for me? If true, I find it interesting that especially with regards to death there were no indication of a (linear) dose response relationship. I think this is relevant with regard to the current discussion about what the ideal weight is. The, without doubt, weakest endpoint with regard to validity is hypertension as taken from the National Patient Registry. Especially the sensitivity of this, I believe is very low. Also I think it is very likely that the chance of a subject receiving a hypertension diagnosis code is associated to being hospitalized or seen in an outpatient clinic because of some of the other endpoints studied. This is especially true for type 2 diabetes as the cut off for hypertension is lower in subjects with this disease and there is a much greater probability that they will be seen in an outpatient clinic. This will lead to some degree of diagnostic bias and artificial correlation between the endpoints. I would prefer to state the BMI cut offs for each BMI group instead of normal, underweight, etc.. In tables, please indicate that the numbers in parentheses are 95% confidence intervals.

REVIEWER	PD Dr Harald J. Schneider Staff Medizinische Klinik und Poliklinik IV LMU Munich No conflicts of interest
REVIEW RETURNED	28-Feb-2013

THE STUDY	A large and broadly discussed meta-analsis showed that mortality was not increased in overweight and grade 1-obesity. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. Flegal KM, Kit BK, Orpana H, Graubard BI. JAMA. 2013 Jan 2;309(1):71-82. doi: 10.1001/jama.2012.113905. Review. This should be discussed ion the light of the current findings.
RESULTS & CONCLUSIONS	Many other studies report a U-shaped association of BMI with mortality and health risks as opposed to this study (not only underweight but also normal weight being associated with increased risks). This previously reported obesity paradox should be

	discussed. Possibly it is an effect of age, as most studies reporting this paradox studied older populations. Please put into context.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Anders Gaarsdal Holst, MD, PhD
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No competing interests to declare.

Using a combination of different Danish registries, including a military conscription database, Schmidt et al. examined the association of BMI at the median age of 19 years with type 2 diabetes, hypertension, myocardial infarction, stroke, venous thromboembolism, and death before 55 years of age. They found that overweight was associated with all of the noted end points.

I do not have much knowledge in the field of obesity research and thus I have focused my review on the data and statistical methods used. Both of which I have experience with. Data was analyzed using well accepted and contemporary methods, among these Fine & Gray competing risk regression. In general the manuscript is very well written, their methods are sound and the conclusions valid. Thus, I only have some minor comments:

Minor comments

1.1. There is no reporting of follow-up time: As mentioned in the STROBE-statement this should be reported.

Reply: In the method statistical section we write: "…follow-up started at examinee´s 22nd birthday… Follow-up continued until first occurrence of an outcome, emigration, or 33 years of follow-up (*i.e.*, their 55th birthday), whichever came first." Thus, we had a potential 33 years of follow-up time for all persons as indicated in the subtitle: "A Danish 33-year follow-up study". Moreover, we have now added the following sentence to the result section:

"The cohort contributed a total of 199,430 person years of follow-up, providing a mean follow-up time of 31 years."

1.2. The authors used the "Aarhus University Prescription Database", which as far as I understand, only holds data on some dispensed prescriptions, unlike the Danish National Prescription Registry, which

holds data on all dispensed prescriptions (but only from 1995 and onwards). Do the authors have references comparing the two? Furthermore using only the local database instead of the national registry means that all subjects emigrating from central/northern Jutland are lost to follow-up with regard to prescription data.

Reply: The reviewer understands correctly. The Aarhus University Prescription Database have similar data as the Danish National Prescription Registry, except it does not contain data on drugs that do not receive general or conditional reimbursement (for example, oral contraceptives). All drugs obtained in this study are reimbursed and thus included in the registry. Reference 35 is a review of the registry, which also provide a cross-tabulation between the two prescription datebases that shows good correlation.[1]

The Aarhus University Prescription Database covers the population of the Central Denmark Region and the North Denmark Region. These are two of the five Danish regions, with a combined population of 1.8 million inhabitants, or about one-third of the total Danish population. Thus, the coverage area are actually considerable larger than the Fifth Military Conscription District in Denmark, populated by approximately 700,000 inhabitants, from which our cohort originated. Still, as the reviewer points out, some examinee could have moved outside the community pharmacies of the two regions and thus would not be covered for the whole study period. It should be noted that the hospital data on diabetes had nationwide coverage. Still, we agree that the limitation should be mentioned. We therefore now write in the discussion:

"The Aarhus University Prescription Database did not cover the entire study period. However, any potential underreporting of diabetes and hypertension in the Danish National Registry of Patients would provide underestimates of the absolute risks, and thus cannot explain the increased risks."

1.3. Page 10, line 46: "Supporting the robustness of our results, previous studies have found similar mortality rates among smokers and non-smokers17 or even higher mortality rates among non-smokers.16" Please state that this is with regards to obesity and not in general.

Reply: We have revised as recommended and now write:

"Supporting the robustness of our results, previous studies <u>on young obese adults</u> have found similar mortality rates among smokers and non-smokers[2] or even higher mortality rates among non-smokers.[3]"

1.4. When I look at figure 2 - Death, I see no indication of a (linear) dose response relationship but on page 7, line 18 the authors state that "There was no suggestion that BMI was not linear in the log hazard for the individual outcomes". Can the authors explain this for me? If true, I find it interesting

that especially with regards to death there were no indication of a (linear) dose response relationship. I think this is relevant with regard to the current discussion about what the ideal weight is.

Reply: We used Cox proportional hazards regression to compute hazard ratios associating BMI with all outcomes. BMI was analysed both as a categorical and continuous variable. We assessed the scale of the continuous BMI variable using fractional polynomials and found no evidence of nonlinearity in the log hazard. The fact that it was nonlinear in the log hazard suggests that there was no fractional polynomial that fitted the model better than the linear model.

Please note that for the continuous BMI variable, we only calculated hazard ratios and not cumulative incidence function (as figure 2). Thus, the linear function should not be reflected in figure 2.

1.5. The, without doubt, weakest endpoint with regard to validity is hypertension as taken from the National Patient Registry. Especially the sensitivity of this, I believe is very low. Also I think it is very likely that the chance of a subject receiving a hypertension diagnosis code is associated to being hospitalized or seen in an outpatient clinic because of some of the other endpoints studied. This is especially true for type 2 diabetes as the cut off for hypertension is lower in subjects with this disease and there is a much greater probability that they will be seen in an outpatient clinic. This will lead to some degree of diagnostic bias and artificial correlation between the endpoints.

Reply: The combined outcome measures the first diagnoses of <u>any</u> of the outcomes. Thus, correlation between the individual outcomes will not affect the risk of the combined outcome. Regarding the completeness of the hypertension diagnoses we agree with the reviewer and comment on the limitation in the discussion (please see reply to comment 1.2).

1.6. I would prefer to state the BMI cut offs for each BMI group instead of normal, underweight, etc.

Reply: In the section “Body mass index”, we define the terms of the BMI categories: “We categorized BMI as underweight (<18.5 kg/m^2), normal (18.5 to <25.0 kg/m^2), overweight (25.0 to <30.0 kg/m^2), or obese (≥30 kg/m^2).” We hope the reviewer will agree that it is a matter of preference whether to use the category names or the cut offs consistently throughout the paper. By defining the BMI categories as above, we believe the cut offs for each category is clear. We prefer using the category terms throughout instead of the cut offs because we believe it makes the text easier to read.

1.7. In tables, please indicate that the numbers in parentheses are 95% confidence intervals.

Reply: We have revised as recommended.

Reviewer 2:
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No conflicts of interest

2.1. A large and broadly discussed meta-analysis showed that mortality was not increased in overweight and grade 1-obesity. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. Flegal KM, Kit BK, Orpana H, Graubard BI. JAMA. 2013 Jan 2;309(1):71-82. doi: 10.1001/jama.2012.113905. Review. This should be discussed ion the light of the current findings.

Reply: We thank the reviewer for his insight into the literature. However, an important difference between our study and the study by Flegal et al (JAMA. 2013 Jan 2;309(1):71-82) is the age group studied. Thus, previous reports indicate that age modifies the effect of obesity on cardiovascular death, with greater impact in younger age groups, including childhood and young adulthood.[4 5] This was the reason for undertaking this study and the discussion is therefore based on the previous literature on this specific age group. In the introduction, we therefore write ""Several studies have examined the association between body mass index (BMI) in young adults and premature death.[2-4 6-14]" and in the discussion we state that all studies on the association between young adulthood BMI and premature death show consistent results. We cite all 12 studies.[2-4 6-14]

2.2. Many other studies report a U-shaped association of BMI with mortality and health risks as opposed to this study (not only underweight but also normal weight being associated with increased risks). This previously reported obesity paradox should be discussed. Possibly it is an effect of age, as most studies reporting this paradox studied older populations. Please put into context.

Reply: Please see reply to comment 2.1 on the specific age group of interest. We agree this should be mentioned in relation to the studies reporting on the association between young adulthood BMI and premature death. In the discussion, we therefore write:

"In contrast to reports of a U-shaped relationship between BMI and mortality in young adults,[6] our results supported the absence of any association between underweight and premature mortality.[2]"