Exploring the association between BMI and mortality in Australian women and men with and without diabetes: the AusDiab study

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Abstract

Aims/hypothesis There is conflicting evidence about the obesity paradox—the counterintuitive survival advantage of obesity among certain subpopulations of individuals with chronic conditions. It is believed that results supporting the obesity paradox are due to methodological flaws, such as collider bias. The aim of this study was to examine the association between obesity and mortality in Australian men and women. In addition, we explored whether obesity would appear to be protective if the analysis was restricted to a subpopulation with disease, and to discuss the potential role of collider bias in producing such a result.

Methods The examined cohort included 10,575 Australian adults (4844 men and 5731 women) aged 25–91 years who were recruited for the AusDiab baseline survey in 1999 and followed-up through 2014. The main predictor variable was BMI categorized as normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2) and obese (≥30 kg/m^2), and the outcome of interest was all-cause mortality. Hazard ratios were estimated from Cox proportional hazards regression models in the entire cohort and then in subpopulations with and without diabetes.

Results A total of 1477 deaths occurred during 145,384 person-years (median 14.6 years) of follow-up. Mortality was higher in obese than in normal-weight individuals for the full population (HR 1.18; 95% CI 1.05, 1.32). When an interaction between diabetes status and BMI category was added to the model, there was no evidence of an interaction between BMI and diabetes status (p = 0.92). When participants with and without diabetes were analysed separately, there was no evidence of an association between obesity and mortality in those with diabetes (HR 0.91; 95% CI 0.62, 1.33).

Conclusions/interpretation In the entire AusDiab cohort, we found a significantly higher mortality among obese participants as compared with their normal-weight counterparts. We found no difference in the obesity–mortality association between individuals with and without diabetes.

Keywords Collider bias · Diabetes · Men · Mortality · Obesity paradox · Women

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Abbreviations
AusDiab Australian Diabetes, Obesity and Lifestyle Study
IFG Impaired fasting glucose
IGT Impaired glucose tolerance

Introduction
There is conflicting evidence on the ‘obesity paradox’, the putative survival advantage of obesity among individuals with chronic conditions [1, 2]. Current weight management guidelines recommend that a BMI <25 kg/m² should be maintained [3]. However, in light of these paradoxical findings, some researchers have advocated the need for revision of these guidelines for individuals with chronic diseases [4]. It is therefore crucial to understand whether these findings reflect true causal effects or result from methodological flaws in the studies reporting the paradox.

Although many hypotheses have been put forward to explain the counterintuitive survival advantage of obesity, the evidence is still inconclusive [5–7]. Collider bias has emerged as the most recent explanation of the obesity paradox [2, 8]. Collider bias is defined as bias due to conditioning on a variable affected by exposure and sharing common causes with the outcome. While previous studies have shown that bias caused by stratification by diabetes status might be responsible for the obesity paradox in people with chronic conditions [2, 8], no such study has been conducted in an Australian cohort. Our primary research objective was to examine the association between obesity and mortality in Australian men and women and to explore the effect of restricting the analysis to individuals with diabetes. In addition, we explored the BMI–mortality association in individuals with and without diabetes relative to normal-weight individuals without diabetes.

Methods
Study participants The cohort included 10,575 adult participants (4844 men and 5731 women, aged 25 to 91 years) enrolled in the Australian Diabetes, Obesity and Lifestyle (AusDiab) study. A flow chart of study population derivation is given in ESM Fig. 1. Participants were followed from the date of their baseline examination until 31 December 2014, or until death if sooner. All participants provided written informed consent and the study protocol was approved by the ethics committee of the Baker Heart and Diabetes Institute. Additional details are presented in the ESM Methods.

Variables BMI at baseline was the primary exposure variable for this study. During biomedical examination, standard anthropometric measures were obtained by trained staff. Participants were classified as per WHO guidelines as normal weight (18.5 to <25 kg/m²), overweight (25 to <30 kg/m²) and obese (≥30 kg/m²). Participants were classified as having diabetes based on venous plasma glucose levels as recommended by WHO (ESM Table 1) [9], or if they were currently being treated with insulin or oral glucose-lowering drugs (see ESM variables in ESM Methods for details). The outcome of this
study was all-cause mortality, which was defined as death from any cause until 31 December 2014. Mortality status was identified by linking the AusDiab data to the Australian National Death Index.

**Statistical analysis** Cox proportional hazards regression was used to model the association between BMI category and all-cause mortality. Models were adjusted for sex, level of education, weekly income, smoking status, physical activity and cluster of census collection district area. The baseline hazard function in the model was stratified by age and marital status, as the proportional hazards assumption was satisfied after their inclusion.

We estimated hazard ratios for (1) the full population; (2) for participants with and without diabetes separately; (3) for men and women separately; and (4) to compare mortality for each BMI/diabetes status relative to ‘normal-weight participants without diabetes’, the addition of diabetes status to the model with an interaction term with BMI category. Evidence for effect modification of the association between BMI category and mortality by diabetes status was examined by testing the significance of this interaction term (please see ESM statistical analysis for additional details).

Sensitivity analyses included consideration of diabetes status, BMI, smoking and physical activity as time-dependent variables. Variables used in time-varying analyses were measured at baseline, and then at the two follow-up surveys (2004–2005 and 2011–2012). Additional sensitivity analyses of our final models (1) and (2) were conducted after exclusion of ever smokers; exclusion of deaths within the first 3 and then 5 years; (4) after excluding or reclassifying individuals with IFG and IGT as having diabetes; and when BMI was used as a continuous variable with relaxation of linearity (ESM Tables 6–10, ESM Fig. 2).

**Sex-specific analysis** For the full population (participants with and without diabetes), obesity appeared to be associated with higher mortality in women (HR 1.31; 95% CI 1.07, 1.61), but not in men (HR 1.10; 95% CI 0.91, 1.34) (Table 2). However, the interaction term was non-significant ($p = 0.38$), indicating no statistical evidence of a difference between men and women with regard to the association between obesity and mortality.

**Table 1** Hazard ratios for all-cause mortality by BMI category for all participants and participants without and with diabetes

| Population        | Deaths/n | BMI category: HR (95% CI) | $p$ value |
|-------------------|----------|---------------------------|-----------|
|                   |          | Normal weight | Overweight | Obese   |           |
| Total             | 1438/10394 | 1.00       | 0.97 (0.87,1.09) | 1.18 (1.05,1.32) | 0.001     |
| Without diabetes  | 1131/9557 | 1.00       | 1.00 (0.88,1.13) | 1.16 (1.01,1.34) | 0.06      |
| With diabetes     | 307/837   | 1.00       | 0.86 (0.60,1.21) | 0.91 (0.62,1.33) | 0.65      |

Adjusted for sex, educational attainment, weekly income, smoking status, physical activity, cluster, and strata of age group and marital status

**Discussion**

Our findings illustrate that obesity was associated with higher mortality in the entire cohort, and there was no evidence of a protective effect of obesity on mortality when the analysis was restricted to individuals with diabetes. There was no statistical
evidence that the obesity–mortality association was different between those with and without diabetes \( (p = 0.92 \text{ for interaction between BMI and diabetes status}) \). However, if the study had only included participants with diabetes, these findings could have been interpreted as evidence of a lack of association between obesity and mortality in individuals with diabetes.

Studies reporting the obesity paradox have been criticised for restricting analyses to individuals with disease [2, 8], which could result in a form of selection bias termed collider bias. When analyses are conducted on a selected group of individuals (including people with diabetes and ignoring those without diabetes in the same population), conditioning on the collider (diabetes in this case) occurs, which affects the exposure–outcome association in an unpredictable way. Our study is consistent with previous studies that confirm that restricting analysis to individuals with diabetes in the AusDiab cohort, and found no difference between participants with and without diabetes with regard to the association between obesity and mortality.

To summarise, studies reporting the obesity paradox present a confusing message for clinicians and policy makers, leading to a risk of misinforming obese individuals about healthy lifestyle management plans. In this study we found no evidence of the obesity paradox in individuals with diabetes in the AusDiab cohort, and found no difference between participants with and without diabetes with regard to the association between obesity and mortality.

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Data availability The data that support the findings of this study are available from AusDiab but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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Contribution statement SFZ contributed to study conception and design, data acquisition, analysis and interpretation of data, and was the major contributor to writing this manuscript. AG analysed and interpreted data, wrote statistical analysis section of this manuscript and provided feedback on the entire manuscript. DJM, JES and JLV contributed to the interpretation of results and critically reviewed the manuscript. KALC and AMM were involved in study supervision, study conception, interpretation of results and drafting the manuscript. All authors read and approved the final manuscript. SFZ is responsible for the integrity of the work as a whole.

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References

1. Carnethon MR, De Chavez PJ, Biggs ML et al (2012) Association of weight status with mortality in adults with incident diabetes. JAMA 308:581–590
2. Lajous M, Bijon A, Fagherazzi G et al (2014) Body mass index, diabetes, and mortality in French women: explaining away a “paradox”. Epidemiology 25(1):10–14. https://doi.org/10.1097/EDE.0000000000000313
3. Jensen MD, Ryan DH, Apovian CM et al (2014) 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. Circulation 129(25 suppl 2):S102–S138. https://doi.org/10.1161/01.cir.0000437739.71477.ee
4. Brown RE, Kuk JL (2015) Consequences of obesity and weight loss: a devil’s advocate position. Obes Rev 16(1):77–87. https://doi.org/10.1111/obr.12232
5. Lavie CJ, Milani RV (2003) Obesity and cardiovascular disease: the Hippocrates paradox? J Am Coll Cardiol 42(4):677–679. https://doi.org/10.1016/S0735-1097(03)00784-8
6. Sperrin M, Candlish J, Badrick E, Renehan A, Buchan I (2016) Collider bias is only a partial explanation for the obesity paradox. Epidemiology 27(4):525–530. https://doi.org/10.1097/EDE.0000000000000493
7. Preston SH, Stokes A (2014) Obesity paradox: conditioning on disease enhances biases in estimating the mortality risks of obesity. Epidemiology 25(3):454–461. https://doi.org/10.1097/EDE.0000000000000775
8. Banack HR, Kaufman JS (2014) The obesity paradox: understanding the effect of obesity on mortality among individuals with cardiovascular disease. Prev Med 62:96–102. https://doi.org/10.1016/j.ypmed.2014.02.003
9. World Health Organization (1999) Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. WHO, Geneva
10. Peeters A (2018) Journals should no longer accept ‘obesity paradox’ articles. Int J Obes 42(3):584–585. https://doi.org/10.1038/s41366-017-2599
11. Badrick E, Sperrin M, Buchan IE, Renehan AG (2017) Obesity paradox and mortality in adults with and without incident type 2 diabetes: a matched population-level cohort study. BMJ Open Diabetes Res Care 5(1):e000369. https://doi.org/10.1136/bmjdrc-2016-000369
12. Berrington de Gonzalez A, Hartge P, Cerhan JR et al (2010) Body mass index and mortality among 1.46 million white adults. N Engl J Med 363(23):2211–2219. https://doi.org/10.1056/NEJMoa1000367
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