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Short Communication

Sources of heterogeneity in studies of the BMI-mortality association

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ABSTRACT

Background: To date, the amount of heterogeneity among studies of the body mass index-mortality association attributable to differences in the age distribution and length of follow-up has not been quantified. Therefore, we wanted to quantify the amount of heterogeneity attributable to age and follow-up in results of studies on the body mass index-mortality relation.

Methods: We used optima of the body mass index mortality association reported for 30 populations and performed meta-regression to estimate the amount of heterogeneity attributable to sex, ethnicity, mean age at baseline, percentage smokers, and length of follow-up.

Results: Ethnicity as single factor accounted for 36% (95% CI, 11–56%) of heterogeneity. Mean age and length of follow-up had an interactive effect and together accounted for 56% (95% CI, 24–74%) of the remaining heterogeneity. Sex did not significantly contribute to the heterogeneity, after controlling for ethnicity, age, and length of follow-up.

Conclusions: A considerable amount of heterogeneity in studies of the body mass index-mortality association is attributable to ethnicity, age, and length of follow-up.

Introduction

Numerous studies have evaluated the association between body mass index (BMI) and mortality,[1,2] as such data is needed for developing and reevaluating weight guidelines. However, there is considerable heterogeneity in study results, with most studies finding mortality to be lowest within the normal weight category[2] or in the overweight category.[3,4] This heterogeneity might be related to differences in study cohorts, like age, ethnicity, and lifestyle (e.g., physical activity and smoking); study design (e.g., self-reported vs. measured weight and length of follow-up); or different statistical methods applied (e.g., different BMI categories and linear vs. quadratic models).

Differences in the age distribution probably contribute to the heterogeneity among study results, as differences can also be observed within studies when stratifying by age.[5,6] It has also been speculated that length of follow-up might be a contributor, as negative health consequences of overweight and/or obesity may take a long time to develop.[7] However, to date, the amount of heterogeneity among these studies attributable to differences in the age distribution and length of follow-up has not been quantified. Therefore, our objective was to quantify the amount of heterogeneity attributable to age and length of follow-up, while considering possible interactions.

Methods

The Diverse Populations Collaborative Group previously published estimates on the optimum of the mortality-BMI association (the nadir of the BMI-mortality curve) for 30 populations out of 15 cohort studies, with the aim of evaluating the effect of adjusting for smoking status on these optima.[8] For the present analysis, we solely used data extracted from this article. An additional 12 populations from the Diverse Populations Collaborative Group could not be used, as no optima were reported for the following reasons: no BMI-mortality association was found (eight populations), a direct monotonic association was found (one population), or the association differed by smoking status (three populations). Their investigation included cohorts from the United States (10 cohorts), Scotland (two cohorts), Israel (one cohort), Denmark (one cohort), and the former Yugoslavia (one cohort). The sample size varied among cohorts, from 4580 (the Tecumseh Community Health

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Study) to 121,208 (the National Health Interview Survey [NHIS]). NHIS also included Hispanics, which were classified as whites due to the low number of deaths in the Hispanic group. More detail on contributing cohorts may be found in the original publication of the Diverse Populations Collaborative Group.[8]

The Diverse Populations Collaborative Group used transformations of BMI originally suggested by Nevill and Holder within a Cox regression model. The applied transformations allowed the modeling of non-symmetric U-shaped associations, which have been repeatedly observed for BMI and mortality.[9] The authors reported estimated optima and corresponding standard errors, along with descriptive characteristics of study populations, including sex, ethnicity (black or white), mean age, proportion of smokers, and the number of years of follow-up. As optima for each population were determined using the same analytic strategy, heterogeneity in obtained optima must be the result of heterogeneity in study populations or in study design.

We used random-effects meta-regression to evaluate the associations of mean age and years of follow-up with optimum BMI, adjusting for other possible sources of heterogeneity. Backward elimination based on the corrected Akaike information criterion (AICc) was applied, starting with a model that included sex, mean age, ethnicity, proportion of smokers, length of follow-up, and possible two-way interactions between mean age or length of follow-up and other characteristics (see eTable 1, which summarizes the model selection process). The AICc is a small-sample bias-corrected version of the Akaike information criterion.[10] The amount of heterogeneity explained was quantified using the Sidik-Jonkman estimator.[11] Reported confidence intervals for the amount of heterogeneity explained were determined via non-parametric resampling and the BCa method.[12]

All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) version 3.0.2.

Results

Study characteristics and optima can be found in Fig. 1. Mean age at baseline of studies was 48.6 years (standard deviation [SD], 4.0 years), and mean length of follow-up was 14.4 years (SD, 6.5 years). Estimated BMI optima ranged from 20.9 kg/m^2 to 33.1 kg/m^2.

The final model included ethnicity, mean age at baseline, and years of follow-up, as well as an age-follow-up interaction term. These three variables accounted for 72% (95% CI, 46–83%) of total heterogeneity among studies. Ethnicity alone accounted for 36% (95% CI, 11–56%) of heterogeneity. Optimum BMI for blacks was 2.9 kg/m^2 (95% CI, 1.9–4.0 kg/m^2) higher than for whites. Mean age at baseline and length of follow-up accounted for a combined 56% (95% CI, 24–74%) of the remaining heterogeneity. The estimated optimum BMI decrease with increasing length of follow-up was greater in studies with older participants (Fig. 2A).

Most of the studies included a cross-section of the general population, except the Hypertension Detection and Follow-up Program, which solely included hypertensive individuals, and the hyperlipidemic sample of the Lipid Research Clinics Program. We therefore refitted the final model excluding the six cohorts provided by these studies. Results were mostly similar, although the age-follow-up interaction was somewhat less pronounced: age and follow-up together explained 42% of the heterogeneity in this analysis, compared to 56% when including all cohorts (Fig. 2B).

Discussion

Previous studies have found the excess risk due to high BMI to be lower for blacks compared to whites.[13,14] Durazo-Arvizu et al. found optimum BMI for black men and women to be higher than for whites.[15] The finding of higher optima in older individuals is

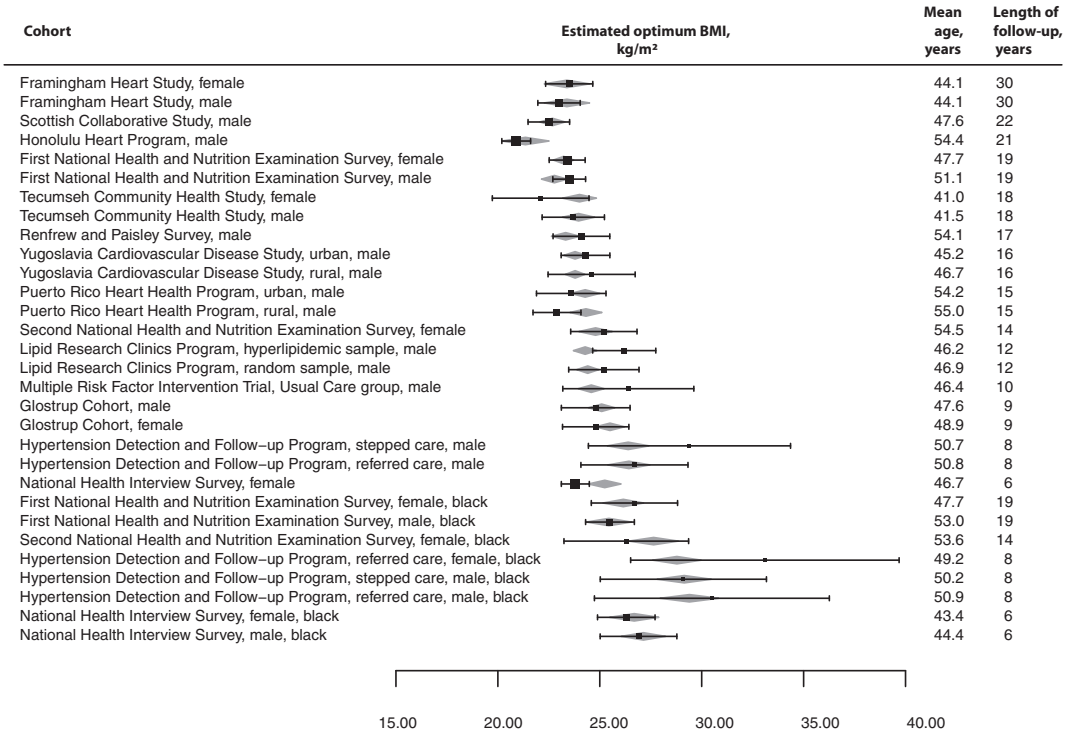

Fig. 1. Forest plot showing observed optima (black squares) as reported by the Diverse Populations Collaborative Group. Predicted optima (grey rhombs) are based on the final model, which included ethnicity, mean age, years of follow-up, and an age-follow-up interaction term. BMI, body mass index.

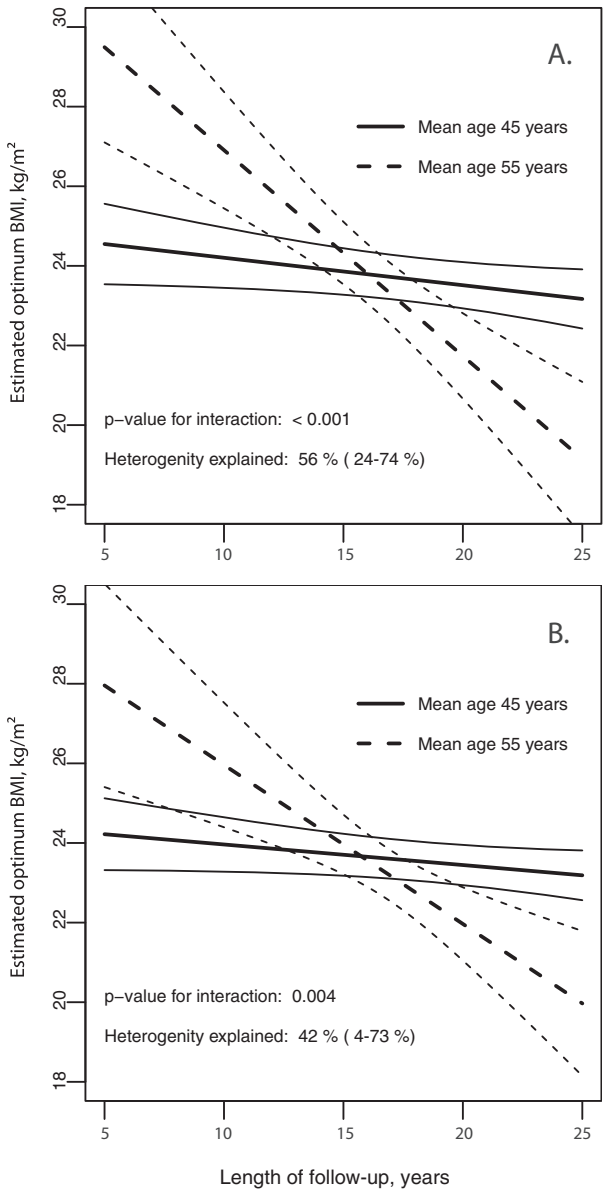

Fig. 2. Predicted optimum body mass index by length of follow-up for studies with mean age of participant of 45 or 55 years. A. all study samples, B. excluding hypertensive- and hyperlipidemic-only samples. BMI, body mass index.

also in line with other studies[16]; unfortunately, in most cases these studies in older populations also have short follow-up.[16] Studies of single cohorts investigating the effect of age on BMI optima indeed found a tendency for BMI optima to increase with age. However, patterns may differ by sex.[17]

He demonstrated, using a single dataset, that results depend heavily on the design of the study.[18] The author found optimum BMI in men to increase with follow-up time, while optimum BMI in women increased with age. Unfortunately, only nine studies in this meta-regression included females, so the total sample was not enough for a sex-stratified analysis. Multiple phenomena may contribute to the association of follow-up time with optimum BMI. Individuals may have lost weight due to prevalent or occult disease, hence increasing the optimum found in the study (reverse causation). This increase should be more pronounced with shorter follow-up. Also, individuals with longer follow-up have more time to develop obesity-related diseases (higher cumulative exposure). In addition, individuals on average gain weight with aging, so baseline BMI usually underestimates BMI at later time points (misclassification of weight during follow-up). Hence the estimated optimum would decrease with longer follow-up.

The stronger association between follow-up and optimum BMI in studies with older participants could be explained by reverse causation, as the prevalence of chronic diseases increases with age; thus, the impact of reverse causation should be more pronounced in older subjects. This would also be in line with the somewhat weaker interaction in the analysis that excluded hypertensive and hyperlipidemic samples.

The conclusions we can draw from this analysis are limited in several ways. We used all-cause mortality as the outcome; the distribution of causes of death may vary by population and contribute to the heterogeneity found. However, all-cause mortality is the most studied outcome in relation to BMI and probably the most relevant for health policy.

It should be noted that the data used in this analysis did not include Asian populations, which may affect heterogeneity. Included study populations were those whose investigators participate in the Diverse Populations Collaborative Group and do not represent a random sample of available study cohorts.[8] However, the Diverse Populations Collaborative Group includes a wide range of studies of different design (national samples, cohort studies, and clinical trials) and from different counties.[8] An advantage of the Diverse Populations Collaborative Group's results is that one single analytic method was used to derive optima for each of the 30 populations, which eliminates the analysis method as a source of variation.

In this analysis, length of follow-up influenced the BMI-mortality association, indicating that hazards may be non-proportional over follow-up time. Hence, scientists should check the proportional hazard assumption in their data when modeling the BMI-mortality association.

Conclusion

In conclusion, we found a considerable amount of heterogeneity in studies of the BMI-mortality association to be attributable to ethnicity, age, and length of follow-up. Future studies on BMI and mortality should consider age as modifying factor in their analysis. Authors should discuss their findings with regard to the length of follow-up, as short- and long-term consequences of over/underweight may differ.

Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.je.2016.06.007.

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