National Center for Health Statistics

Supplemental Analyses for Estimates of Excess Deaths Associated with Underweight, Overweight, and Obesity in the U.S. Population

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Introduction

The recent JAMA article (Flegal et al. 2005) on excess deaths associated with different levels of body mass index (BMI) estimated relative risks of mortality associated with different levels of BMI from the nationally representative National Health and Nutrition Examination Survey (NHANES) I (1971-1975) and NHANES II (1976-1980), with follow-up through 1992, and from NHANES III (1988-1994), with follow-up through 2000. This combined data set represents a large prospective study of the U.S. population with 36,859 participants and 8,849 deaths. (For comparison, after 24 years of follow-up the Nurses Health Study with 116,564 participants recorded 10,282 deaths (Hu et al., 2004).) The relative risks estimated from the combined NHANES I, II, and III data set were applied to the distribution of BMI and other covariates from NHANES 1999-2002 to estimate attributable fractions and number of excess deaths, adjusted for confounding factors and for effect modification by age. Flegal et al (2005) estimated that relative to the normal weight category (BMI 18.5 to < 25), obesity (BMI ≥ 30) was associated with 111,909 excess deaths (95% confidence interval [CI], 53,754-170,064) and underweight with 33,746 excess deaths (95% CI, 15,726-51,766). Overweight was not associated with excess mortality (–86,094 deaths; 95% CI, –161,223 to –10,966).

In studies of the relation of BMI to mortality, it is sometimes recommended that participants with certain characteristics be excluded from the analytic sample to calculate relative risks. This is thought to possibly give results that more clearly represent the true effect of BMI by avoiding biases due to illness-induced weight loss (reverse causation) and to residual confounding by smoking and prevalent illness at baseline. For example, the underweight group might consist disproportionately of individuals who have a low weight because of illness or because of smoking.

Flegal et al (2005) found that underweight was associated with a relative risk greater than 1, that overweight was associated with a relative risk less than 1, and obesity with a risk greater than 1. If these results were biased by reverse causation and by residual confounding, one would expect in analyses that take these factors into account that the relative risk associated with underweight would be closer to 1 or below 1, the relative risk associated with overweight would be greater than 1, and the relative risk associated with obesity would be higher.

Related research

The exclusions used to address these issues vary from study to study but fall into four main types. First, it is not uncommon to exclude current or former smokers (Ajani et al. 2004, Calle et al. 1999, Hu et al. 2004, Manson et al. 1995, Stevens et al. 1998). Second, deaths occurring within the first few years after the baseline examination may be excluded in order to eliminate those with prevalent undiagnosed illness at baseline. These ‘early deaths’ exclusions may eliminate the first 5

years (Baik et al. 2000) or 2 years (Ajani et al. 2004) or 4 years (Manson et al. 1995) of deaths. A third set of exclusions is to eliminate those with various self-reported health conditions at baseline. The most common is to exclude those with self-reported cancer or cardiovascular disease at baseline (Manson et al. 1995, Baik et al. 2000). Calle et al. (1999) excluded those with self-reported history of cancer, heart disease, stroke, respiratory disease, or any current illness. Stevens et al. (1998) excluded those with self-reported heart disease, cancer, stroke, or poor health. A fourth set of exclusions has to do with recent weight stability, although the exact exclusions vary. Baik et al. (2000) excluded those with a self-reported weight change of 4.5 kg or more over the first 5 years of the study, Calle et al. (1999) excluded those with a self-reported weight loss of 4.5 kg in 1 year prior to baseline, Stevens et al. (1998) excluded those with a self-reported weight loss of 4.5 kg in 2 years prior to baseline, and Manson et al. (1995) excluded those with a self-reported weight change of 4 kg or more in the first 4 years after baseline. These exclusions are intended to eliminate people who may have experienced recent weight loss due to illness, although Manson et al. (1995) also excluded people who reported weight gain after baseline.

The excess deaths estimates in the recent JAMA article (Flegal et al. 2005) used no exclusions, because the goal was to make estimates for the entire population, not for a single subgroup. However the relative risks within subgroups were examined to assess the possibility of systematic biases arising from the factors mentioned above. The published article (Flegal et al 2005) reported the results of analyses limited to never-smokers. Analyses that excluded the first 3 or 5 years of deaths, and analyses (for NHANES I only) that were limited to persons whose measured weight had not changed (in either direction) by more than 2 kg over an approximately 10 year period were also reported. Additional analyses not discussed in the paper were performed using all four types of exclusions above. The results of those analyses are presented here.

Methods

The object of these analyses is not to make statistical comparisons between subgroups, which are not independent of each other, nor to assess the statistical significance of the relative risk within a small subgroup. Rather, the object is to examine the changes in the relative risks for indications that the estimates of excess deaths might be affected by systematic biases, such as those potentially due to reverse causation or to residual confounding by smoking or prevalent illness.

There were several approaches to baseline health status. In all surveys, respondents were asked to evaluate their own health as excellent, very good, good, fair, or poor. This self-reported health variable with five levels is a significant predictor of mortality in all surveys. These responses were grouped into two categories (very good or excellent health; good, fair, or poor health) and results are reported stratified by these two levels of health status. These self-reports are comparable to the use of self-reported health conditions to exclude participants from analyses in other data sets.

In NHANES III only, the examining physician was asked to rate the respondent's overall health condition using the same five categories of excellent, very good, good, fair, or poor. This physician-reported health variable was a significant predictor of mortality in NHANES III. Physician-reported health condition was also grouped into two categories: excellent or very good health; good, fair, or poor health. Many large epidemiologic cohort studies do not include a baseline evaluation by a physician.

In NHANES II, participants were asked if they had had unintentional weight loss in the previous 6 months. This question should identify respondents with recent weight loss due to illness. Some analyses for NHANES II were limited to those participants who did not report recent unintentional weight loss.

Various combinations of these exclusions were examined. To have sufficient deaths for analyses in younger age groups, the sample was divided into two age groups: < 70 years and 70 years or more. For the combined sample, analyses were first stratified by self-reported health status (excellent or very good vs. good, fair, or poor). Analyses were then repeated for never-smokers stratified by health status, and then for never-smokers stratified by health status after excluding the first 3 years of deaths. Thus there were six sets of relative risks for each age group (excellent or very good health; good, fair, or poor health; never-smokers with excellent or very good health; never-smokers with good, fair, or poor health; never-smokers with excellent or very good health, excluding the first 3 years of deaths; never-smokers with good, fair, or poor health excluding the first 3 years of deaths).

Results

The estimates of relative risk from these analyses are shown in table 1 for the categories underweight (BMI < 18.5), overweight (BMI 25 to <30) and grade 1 obesity (BMI 30 to <35).
In the combined analyses the following results were observed. Stratification by health status, limiting the sample to never-smokers, and excluding the first 3 years of deaths did not change the direction of the relative risk estimates. In all cases, the relative risk for underweight was greater than 1, the relative risk for overweight was below 1, and the relative risk for grade 1 obesity was greater than 1.

For underweight, the relative risks did not tend to be closer to 1 after these exclusions. For example, for never-smokers ages 70 years and over in excellent or very good health at baseline, after exclusion of the first 3 years of deaths, the relative risk for underweight was 2.20, as compared with 1.69 for the full sample.

For overweight, the relative risk for ages 70 and over was 0.91 in the full sample. Depending on the exact exclusions or stratifications, the relative risk for overweight ranged from 0.89 to 0.99. Of the six categories for ages 70 and over, four of the relative risk estimates were lower (further away from 1.0) than the estimates for the full sample. For ages under 70, the relative risks for overweight varied from 0.40 to 0.91. For never-smokers ages 25-69 years in excellent or very good health at baseline, after excluding the first 3 years of deaths, the relative risk for overweight was 0.45 (significantly below 1.0).

For grade 1 obesity, the relative risks for those ages 70 and over ranged from 1.00 (for those in good, fair, or poor health at baseline) to 1.18 (for never-smokers in good, fair, or poor health at baseline after excluding the first 3 years of deaths). For grade 1 obesity for younger never-smokers, regardless of baseline health status and regardless of excluding the first 3 years of deaths, the relative risks were always below 1.0.

If these biases due to illness-induced weight loss or residual confounding by smoking or prevalent illness at baseline had been operating, one would expect to see a lower relative risk for underweight (closer to 1) and a higher relative risk for overweight and for obesity after controlling for baseline health status, smoking, and early deaths. However, the relative risks did not follow this pattern. Thus, these analyses of the effects of exclusions and of stratification by health status for the combined data set did not suggest that the results for the full data set were affected in any important or systematic way by residual confounding due to smoking or to prevalent illness at baseline. These analyses did not suggest that Flegal et al (2005) had overestimated the risks associated with underweight or underestimated the risks associated with overweight or obesity.

For NHANES III, where data were available on physician-evaluated health status at baseline, these analyses were repeated stratifying by the physician-determined health status at baseline, with results as shown in table 2. These analyses use data only from one survey and the prevalence of underweight is quite low (2.2%) so for some subgroups for underweight for the younger age group, the relative risk could not be estimated. However, the sample size was adequate to estimate these risks for the older age group. In these NHANES III analyses for older people, underweight was associated with higher risk and overweight with lower risk. For younger people, overweight was generally associated with lower risk, with a single exception. These results, based on physician-evaluated health status at baseline, do not suggest that our results were affected in any large or systematic way by residual confounding due to illness. Even when analyses were restricted to never-smokers judged to be in very good or excellent health by the physician, and after eliminating the first 3 years of deaths, the relative risks for overweight were below 1 and for underweight were greater than 1.

For NHANES II only, these analyses were repeated, stratifying by self-reported baseline health status, with results as shown in table 3. Respondents who reported involuntary weight loss within the 6 months prior to baseline were also excluded. For older individuals only, it was possible to use all four exclusionary criteria. For older individuals who had never smoked, had very good or excellent health at baseline, and did not report recent involuntary weight loss, after excluding the first 3 years of deaths, the relative risk was 2.98 for underweight, 0.70 for overweight and 1.36 for grade 1 obesity. Although the relatively small sample size in this single survey made it difficult to estimate relative risks within the younger group in all cases, the relative risks estimated after these exclusions did not suggest that residual confounding or reverse causation had any systematic effects. Even when results were limited to never-smokers in excellent or very good health who did not report recent involuntary weight loss, and after excluding the first 3 years of deaths (that is, using all four exclusions), the relative risk for underweight was well above 1 and the relative risk for overweight was well below 1.

Additional analyses were performed to evaluate whether the results for those ages 70 years and over differed according to whether the original measurements of weight and height had been made at younger ages or after age 70 years. The majority of deaths in the sample occurred in persons whose BMI had been measured before the age of 70 years. Data were stratified according to whether BMI was based on measurements made before the age of 70 years or at the age of 70 years or over, with results as presented in table 4 by survey for the age group 70 years and over.

Taken together, these results do not suggest that the analyses on the full sample in the paper by Flegal et al (2005) were affected by any systematic biases related to illness-induced weight loss (reverse causation) or to residual confounding by smoking or by illness. Even when analyses were restricted to a subset of healthy individuals who had never smoked and deaths occurring in the first part of the study were excluded, the relative risks were still elevated for underweight and below 1 for overweight and the relative risks for obesity did not show an increase. Thus, these analyses do not suggest that the hypothesized biases due to illness-induced weight loss or to residual confounding by smoking and prevalent illness affected the results reported by Flegal et al. (2005).

References

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Tables

Table 1. Relative risks for mortality after stratifying by self-reported health status: NHANES I, II, and III combined

	Underweight		Overweight		Grade 1 obesity	
Subsample	**25-69 y**	**70 + y**	**25-69 y**	**70+ y**	**25-69 y**	**70+ y**
Excellent or very good health	1.33	1.73	0.91	0.90	1.01	1.02
Good, fair, or poor health	1.74	1.65	0.85	0.91	1.05	1.00
Never-smokers, excellent or very good health	3.36	2.00	0.40	0.97	0.53	1.14
Never-smokers, good, fair, or poor health	1.45	1.23	0.77	0.89	0.92	1.15
Never-smokers, excellent or very good health, first 3 years of death excluded	–	2.20	0.45	0.99	0.50	1.11
Never-smokers, good, fair, or poor health, first 3 years of death excluded	1.47	1.21	0.76	0.89	0.89	1.18

Table 2. Relative risks for mortality after stratifying by physician-evaluated health status at baseline: NHANES III only

	Underweight		Overweight		Grade 1 obesity	
Subsample	**25-69 y**	**70+ y**	**25-69 y**	**70+ y**	**25-69 y**	**70+ y**
Excellent or very good health	0.89	1.61	1.04	0.9	1.23	0.77
Good, fair, or poor health	2.41	1.50	0.77	0.86	0.74	0.85
Never-smokers, excellent or very good health	–	1.30	0.49	0.97	0.54	1.12
Never-smokers, good, fair, or poor health	9.61	1.22	0.94	0.93	0.54	0.98
Never-smokers, excellent or very good health, first 3 years of death excluded	–	1.38	0.58	0.97	0.38	1.27
Never-smokers, good, fair, or poor health, first 3 years of death excluded	2.00	1.26	0.58	0.92	0.50	1.04

Table 3. Relative risks of mortality after stratifying by health status and excluding respondents with involuntary weight loss in 6 months prior to baseline: NHANES II only

	Underweight		Overweight		Grade 1 obesity	
Subsample	**25-69 y**	**70+ y**	**25-69 y**	**70+ y**	**25-69 y**	**70+ y**
Excellent or very good health	–	2.98	0.69	0.83	0.80	1.48
Good, fair, or poor health	1.49	1.16	0.81	0.86	0.80	0.99
Excellent or very good health, recent weight loss excluded	–	3.16	0.63	0.84	0.84	1.51
Good, fair, or poor health, recent weight loss excluded	0.88	1.25	0.82	0.93	0.75	1.06
Never-smokers, excellent or very good health, recent weight loss excluded	–	2.78	–	0.67	–	1.22
Never-smokers, good, fair, or poor health, recent weight loss excluded	–	0.74	–	0.97	–	1.20
Never-smokers, excellent or very good health, recent weight loss excluded, first 3 years of death excluded	–	2.98	–	0.70	–	1.36
Never-smokers, good, fair, or poor health, recent weight loss excluded, first 3 years of death excluded	–	0.74	–	0.94	–	0.99

Table 4. Relative risks for ages 70 years and over, according to whether BMI was originally measured at age < 70 years or age 70 years and over, by survey

Subsample	Underweight	Overweight	Grade 1 obesity
NHANES I: **BMI measured at age <70 y**	2.16	1.03	1.23
BMI measured at age 70 y or over	1.69	0.90	1.15
NHANES II: **BMI measured at age <70 y**	1.53	0.88	1.16
BMI measured at age 70 y or over	1.30	0.81	0.88
NHANES III: **BMI measured at age <70 y**	2.07	0.70	0.67

Subsample	Underweight	Overweight	Grade 1 obesity
BMI measured at age 70 y or over	1.56	0.94	1.01

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