Reverse Causality and Confounding and the Associations of Overweight and Obesity with Mortality

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Abstract

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Objective: To examine the effect of reverse causality and confounding on the association of BMI with all-cause and cause-specific mortality.

Research Methods and Procedures: Data from two large prospective studies were used. One (a community-based cohort) included 8327 women and 7017 men who resided in two Scottish towns at the time of the baseline assessment in 1972–1976; the other (an occupational cohort) included 4016 men working in the central belt of Scotland at the time of the baseline assessment in 1970–1973. Participants in both cohorts were ages 45 to 64 years at baseline; the follow-up period was 28 to 34 years.

Results: In age-adjusted analyses that did not take account of reverse causality or smoking, there was no association between being overweight (BMI 25 to <30 kg/m^2) and mortality, and weak to modest associations between obesity (BMI ≥ 30 kg/m^2) and mortality. There was a strong association between smoking and *lower* BMI in women and men in both cohorts (all $p < 0.0001$). Among never-smokers and with the first 5 years of deaths removed, overweight was associated with an increase in all-cause mortality (relative risk ranging from 1.12 to 1.38), and obesity was associated with a doubling of risk in men in both cohorts (relative risk, 2.10 and 1.96, respectively) and a 60% increase in women (relative risk, 1.56). In both never-smokers and current smokers, being overweight or obese was associated with important increases in the risk of cardiovascular disease.

Discussion: These findings demonstrate that with appropriate control for smoking and reverse causality, both overweight and obesity are associated with important increases in all-cause and cause-specific mortality, and in particular with cardiovascular disease mortality.

Key words: BMI, cardiovascular disease, epidemiology, mortality, smoking

Introduction

There is debate and confusion about the health impact of being overweight and obese (1–6). A recent review suggested that the current obesity epidemic would halt, and possibly reverse, the consistent increase in life expectancy that has been seen in developed countries during the past few years (1). Around the same time, publication of a prospective study based on three waves of the U.S. National Health and Nutrition Examination Survey (NHANES)[1] reported that being overweight (BMI 25 to <30 kg/m^2) was actually associated with a slightly decreased risk of mortality compared with being of normal weight (BMI 18.5 to <20 kg/m^2) (2). Furthermore, the estimated excess deaths associated with overweight and obesity in that study were considerably lower than reports from previous U.S. cohort studies (3–5), and there was evidence that the association of obesity with mortality decreased over time with repeated waves of the survey. The authors of the NHANES study suggested that the discrepancy between their results and those of previous studies might be related to recent improvements in treatment for the major metabolic complica-

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[1] Nonstandard abbreviation: NHANES, National Health and Nutrition Examination Survey.

tions of overweight and obesity (diabetes, hypertension, and dyslipidemia) and that, as a consequence of this treatment, the impact of overweight and obesity had decreased over time (2). However, it is also plausible that the reason for the weaker effect in more recent surveys was that they had a shorter length of follow-up and were, therefore, more prone to the effects of reverse causality (6). In a systematic review published in 2003, 49 studies were identified in which the relative risk of overweight compared with "normal" weight varied from 0.6 to 1.59 (7). The authors noted that it was not possible to formally combine the results in a meta-analysis because of variations in population characteristics, co-variables included in the analyses, and the cut-off points for BMI used to define overweight and normal weight (7).

The results of the recent NHANES publication received widespread publicity in the popular press in both the United Kingdom and the United States, with headlines such as "Fat vs. fiction: The moral panic about the obesity epidemic was always hard to swallow, says Vivienne Parry. Now, a new study says we may have been wrong all along" (*The Guardian*, June 16, 2005). Public health guidance from national and international policy makers who aim to reduce the obesity epidemic and its health risks is currently being undermined by publications that question whether being overweight or obese is associated with important levels of increased mortality or health risks (8–10). Thus, there is a need to clarify the unbiased effects of overweight and obesity on mortality.

Two sources of bias are likely to be particularly important in studies assessing the association of BMI with future health outcomes. First, reverse causality may weaken any true association (11). To avoid the impact of reverse causality, large prospective studies, starting in youth or middle age (when individuals are less likely to have chronic diseases) and with a long period of follow-up that enables exclusion of deaths in the early period of follow-up (which might be due to pre-existing undiagnosed disease) are required (11), although there is some evidence that this approach does not have marked effects on the relative impact of BMI on mortality (12,13). In addition to excluding early deaths, reverse causality could also be assessed by comparing effects in occupational cohorts, where the healthy worker effect would reduce the likelihood of reverse causality compared with those in general population cohorts.

Second, smoking is an important confounder that might mask any true effect of overweight or obesity (11). This is because smoking is associated with lower BMI and is strongly associated with many of the health outcomes—diabetes, cardiovascular disease, and respiratory disease—that are likely to be increased in those who are overweight and obese. If smoking is strongly associated with reduced BMI, simple adjustment for smoking in multivariable models may be insufficient to fully control for its effects, as there will inevitably be measurement error (for example, current smokers defining themselves as past smokers). One way to get around this problem is to examine the effect of BMI on mortality only in those defining themselves as never-smokers, because current smokers are less likely to define themselves as such, particularly in groups where smoking is the norm. A number of studies have examined the association of BMI with mortality stratified by smoking status (14–21) but have found inconsistent results. These inconsistencies may be related to the small sample size of some studies once stratified by smoking status and the fact that several of these studies have used self-reported weight and height to determine BMI, which is known to be reported with systematic errors (2).

In light of the recent debate about the true association of overweight and obesity with future mortality, the aim of this study was to determine the unbiased association of overweight and obesity (based on directly measured weight and height) with all-cause and cause-specific mortality in two large prospective cohort studies (one in a general population and the other in a cohort of working men). Our study had three goals: 1) to examine the effects of reverse causation by comparing effects in a cohort of working men (the Collaborative study) and a cohort from the general population of men (the Renfrew/Paisley cohort). Our hypothesis here is that the effect in the working cohort will be stronger than that in the general population, because the working cohort will contain a lower proportion of individuals who are ill (22); 2) to examine the effects of reverse causality by looking for evidence of "wearing off of selection" (6). If reverse causality is important, then one would anticipate that any health risk associated with being underweight would wear off (reduce) over time with a greater length of follow-up, as those who are underweight because of ill health die in the earlier years; and 3) to examine the effect of masking by smoking by assessing the association of BMI categories with all-cause and cause-specific mortality among never-smokers.

Research Methods and Procedures

Data from the Renfrew/Paisley study and the Collaborative study (both part of the Midspan prospective cohort studies) were used. These studies have been described in detail previously (23, 24). The Renfrew/Paisley study consists of 7049 men and 8353 women who were ages 45 to 64 years (mean age, 54.3 years; standard deviation, 5.58) and who resided in the towns of Renfrew and Paisley, near Glasgow, Scotland, at the time of their baseline assessment in 1972–1976 (23). The response to that study was nearly 80%. The Collaborative study included 6022 men and 1006 women of working age from 27 workplaces in west and central Scotland (24). There were too few women to provide meaningful results, so women in that study are not considered further. The men were ages 45 to 64 years (mean age, 51.7 years; standard deviation, 4.40) at baseline. Baseline

data were collected in 1970–1973 in that study, and the response was 70% for the workplaces for which response rates were available (87% of the sample).

Similar protocols were used in the baseline assessment of both studies. Weight and height were measured using standard procedures (23,24), and these data were used to determine BMI (kg/m^2) and World Health Organization categories: underweight (<18.5 kg/m^2), normal-weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (≥30 kg/m^2). Participants completed a questionnaire that asked about past and present smoking. Social class was allocated according to occupation reported at the time of screening using the United Kingdom Registrar General's classification. Women in the Renfrew/Paisley study who reported being housewives were allocated their husband's social class. Deprivation category of postcode of residence was retrospectively derived (25).

The follow-up period (median, 29 years for the Renfrew/Paisley study and 32 years for the Collaborative study) extended to March 31, 2004. Mortality data are obtained through flagging with the National Health Service Central Register in Edinburgh.

Ethics approval for our study was granted by the University of Glasgow Medical Faculty Ethics Committee.

Statistical Analysis

To compare studies for this analysis, only the 4021 men ages 45 to 64 years were included from the Collaborative study. The 19 men who took part in both the Collaborative study and the Renfrew/Paisley study were removed from the second (i.e., Renfrew/Paisley) study. Twenty-four Renfrew/Paisley participants and four Collaborative participants who were lost to follow-up were excluded from the study. Fifteen Renfrew/Paisley participants and one Collaborative participant were excluded because of missing BMI data. The analysis was, therefore, based on 7017 Renfrew/Paisley men, 8327 Renfrew/Paisley women, and 4016 Collaborative study men.

Cox's proportional hazards regression models, adjusted for age at screening, were used to calculate relative rates of mortality by BMI categories, with the normal-weight category as the reference. The time variable was from the date of screening to death or to March 31, 2004. One-hundred fifteen Renfrew/Paisley and 29 Collaborative participants who had embarked from the United Kingdom were censored at their date of embarkation. We examined our hypothesis that the effect of BMI varied over time by examining whether there was statistical evidence of an interaction between time (considered as a continuous variable, in days) and BMI (in the four categories used throughout these analyses) in their relationship to mortality. The proportions of never-smokers and current cigarette smokers were calculated for each BMI category using χ^2 tests to assess linear trends. Because the two studies had different start dates, the follow-up periods were different (median, 29 years for the Renfrew/Paisley study and 32 years for the Collaborative study) when we undertook the analyses using the same end of follow-up date (March 31, 2004) for both studies. We cannot change the date at which baseline assessments were conducted, but we did undertake a sensitivity analysis in which we restricted the follow-up time to 28 years for all individuals in both studies. Findings from this sensitivity analysis did not differ from the main analyses (follow-up until March 31, 2004, for everyone) presented here. All main analyses were conducted using SPSS software, version 13.0; SAS software, version 9.1, was used to assess the interaction between time and BMI categories.

Results

In the follow-up period, 5242 Renfrew/Paisley men, 5019 Renfrew/Paisley women, and 2957 Collaborative study men died. Table 1 shows the association of BMI categories with all-cause and cause-specific mortality in the whole cohort. For all-cause mortality, the highest relative risk in men and women was among the underweight compared with the normal-weight group, and those in the overweight category had similar risk to those in the normal-weight category, with a modest increase in risk for those who were obese. In these preliminary analyses, which did not take account of the effects of reverse causality or smoking, the associations of both overweight and obesity with all-cause mortality in the working men (Collaborative study) were stronger than those in the general population study of men (Renfrew/Paisley men) ($p = 0.05$ for the overall interaction term between the two cohorts and the four categories of BMI). The risk of cardiovascular disease deaths was increased in those who were obese compared with those who were of normal weight, but being overweight did not seem to be associated with important increases in risk of death from any cause in these analyses. There was no association with all cancers, but lung cancer deaths and respiratory disease deaths were greatest in those who were underweight, and risk was reduced in those who were overweight or obese compared with those of normal weight.

The effect of being overweight or obese on all-cause mortality did not vary over time in either cohort ($p > 0.2$ for interaction with time since follow-up), but the increased risk of mortality associated with being underweight decreased in the general population (Renfrew/Paisley) cohort in both women ($p = 0.03$ for interaction) and men ($p = 0.05$ for interaction). There were no changes in the associations of BMI with all-cause mortality in the working men's cohort (Collaborative). The association of being overweight with respiratory disease deaths strengthened over time in both women ($p = 0.02$ for interaction) and men ($p = 0.05$ for interaction) in the general population cohort, as did the effect of being obese on respiratory disease deaths for women in the general population cohort ($p = 0.02$ for

Table 1. Age-adjusted relative risk of all-cause and cause-specific mortality by BMI categories among all participants

	Underweight BMI (<18.5 kg/m^2)	Normal BMI (18.5 to <25 kg/m^2)	Overweight BMI (25 to <30 kg/m^2)	Obese BMI (≥30 kg/m^2)
Renfrew/Paisley men				
No.	53	2805	3410	749
All-cause mortality				
No. of deaths	45	2123	2483	591
RR (95% CI)	1.34 (1.00 to 1.81)	1	0.90 (0.85 to 0.95)	1.08 (0.99 to 1.19)
CVD				
No. of deaths	13	968	1307	355
RR (95% CI)	0.85 (0.49 to 1.47)	1	1.04 (0.95 to 1.13)	1.42 (1.26 to 1.61)
CHD				
No. of deaths	9	623	876	246
RR (95% CI)	0.91 (0.47 to 1.75)	1	1.09 (0.98 to 1.20)	1.52 (1.31 to 1.76)
Stroke				
No. of deaths	4	216	275	63
RR (95% CI)	1.21 (0.45 to 3.26)	1	0.97 (0.81 to 1.15)	1.16 (0.88 to 1.54)
Cancer				
No. of deaths	10	655	713	138
RR (95% CI)	0.97 (0.52 to 1.82)	1	0.84 (0.75 to 0.93)	0.82 (0.68 to 0.98)
Lung cancer				
No. of deaths	6	299	259	30
RR (95% CI)	1.26 (0.56 to 2.82)	1	0.67 (0.57 to 0.79)	0.39 (0.27 to 0.56)
All smoking-related cancers				
No. of deaths	7	461	449	81
RR (95% CI)	0.96 (0.45 to 2.02)	1	0.75 (0.66 to 0.86)	0.68 (0.54 to 0.86)
Respiratory disease				
No. of deaths	14	269	194	38
RR (95% CI)	3.37 (1.97 to 5.77)	1	0.55 (0.45 to 0.66)	0.56 (0.40 to 0.78)
Renfrew/Paisley women				
No.	189	3824	3061	1253
All-cause mortality				
No. of deaths	144	2177	1804	894
RR (95% CI)	1.80 (1.52 to 2.14)	1	0.97 (0.91 to 1.03)	1.28 (1.18 to 1.38)
CVD				
No. of deaths	57	1024	895	499
RR (95% CI)	1.50 (1.15 to 1.95)	1	1.0 (0.91 to 1.09)	1.48 (1.33 to 1.64)
CHD				
No. of deaths	29	539	489	270
RR (95% CI)	1.43 (0.98 to 2.08)	1	1.06 (0.93 to 1.19)	1.53 (1.32 to 1.78)
Stroke				
No. of deaths	20	344	282	154
RR (95% CI)	1.57 (1.0 to 2.46)	1	0.91 (0.78 to 1.07)	1.32 (1.09 to 1.60)
Cancer				
No. of deaths	38	640	506	206
RR (95% CI)	1.58 (1.14 to 2.20)	1	0.96 (0.85 to 1.08)	1.05 (0.89 to 1.23)

Table 1. (continued)

	Underweight BMI (<18.5 kg/m^2)	Normal BMI (18.5 to <25 kg/m^2)	Overweight BMI (25 to <30 kg/m^2)	Obese BMI (≥30 kg/m^2)
Lung cancer				
No. of deaths	16	181	88	28
RR (95% CI)	2.38 (1.43 to 3.98)	1	0.60 (0.46 to 0.77)	0.52 (0.35 to 0.77)
All smoking-related cancers				
No. of deaths	23	307	208	69
RR (95% CI)	2.03 (1.33 to 3.09)	1	0.83 (0.70 to 0.99)	0.75 (0.57 to 0.97)
Respiratory disease				
No. of deaths	31	231	151	61
RR (95% CI)	3.85 (2.64 to 5.60)	1	0.75 (0.61 to 0.92)	0.83 (0.62 to 1.10)
Collaborative men				
No.	35	1894	1829	258
All-cause mortality				
No. of deaths	28	1325	1295	209
RR (95% CI)	1.36 (0.94 to 1.98)	1	1.01 (0.94 to 1.09)	1.28 (1.11 to 1.49)
CVD				
No. of deaths	10	624	702	120
RR (95% CI)	1.02 (0.55 to 1.91)	1	1.16 (1.04 to 1.30)	1.55 (1.28 to 1.89)
CHD				
No. of deaths	8	405	463	85
RR (95% CI)	1.23 (0.61 to 2.48)	1	1.18 (1.03 to 1.35)	1.68 (1.33 to 2.12)
Stroke				
No. of deaths	0	141	145	23
RR (95% CI)		1	1.07 (0.85 to 1.35)	1.31 (0.85 to 2.04)
Cancer				
No. of deaths	7	392	356	51
RR (95% CI)	1.14 (0.54 to 2.41)	1	0.94 (0.81 to 1.08)	1.06 (0.79 to 1.42)
Lung cancer				
No. of deaths	2	160	107	18
RR (95% CI)	0.78 (0.19 to 3.14)	1	0.69 (0.54 to 0.88)	0.91 (0.56 to 1.48)
All smoking-related cancers				
No. of deaths	4	255	201	32
RR (95% CI)	0.99 (0.37 to 2.65)	1	0.81 (0.68 to 0.98)	1.02 (0.70 to 1.47)
Respiratory disease				
No. of deaths	8	169	100	6
RR (95% CI)	3.26 (1.61 to 6.64)	1	0.61 (0.48 to 0.79)	0.29 (0.13 to 0.66)

RR, relative risk; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease.

interaction). The association of being overweight with all forms of cancer in the Collaborative cohort increased over time ($p = 0.03$ for interaction). For other cause-specific mortality outcomes, there was no change in the magnitude of association over time.

Table 2 shows the distribution of smoking by BMI category. There was a very strong association of smoking with BMI, such that, among both men and women, nearly 80% of the underweight category were current smokers, whereas just 34% of obese women and 41% to 43% of obese men were current smokers.

Table 3 shows the effects of BMI on all-cause and cause-specific mortality in never-smokers and with the first 5 years of deaths removed. Because of very small numbers, it

Table 2. Association between smoking and BMI category among Renfrew/Paisley and Collaborative Study participants ages 45 to 64 years at screening

	Smoking prevalence by BMI category				
	Underweight	**Normal-weight**	**Overweight**	**Obese**	***p****
Renfrew/Paisley men					
No.	53	2805	3410	749	
No. (%) current smokers	44 (83.0)	1919 (68.4)	1697 (49.8)	321 (42.9)	<0.0001
No. (%) never-smokers	4 (7.5)	364 (13.0)	634 (18.6)	167 (22.3)	<0.0001
Renfrew/Paisley women					
No.	189	3824	3061	1253	
No. (%) current smokers	149 (78.8)	2118 (55.4)	1196 (39.1)	423 (33.8)	<0.0001
No. (%) never-smokers	36 (19.0)	1420 (37.1)	1618 (52.9)	739 (59.0)	<0.0001
Collaborative men					
No.	35	1894	1829	258	
No. (%) current smokers	30 (85.7)	1208 (63.8)	923 (50.5)	106 (41.1)	<0.0001
No. (%) never-smokers	0	214 (11.3)	312 (17.1)	62 (24.0)	<0.0001

* χ^2 test.

was impossible to examine associations with deaths due to lung or smoking-related cancers or respiratory disease in this group of never-smokers. Furthermore, there were too few participants who were never-smokers and underweight to be able to include this BMI category in the analysis. There was a clear increase in risk of all-cause, cardiovascular disease, and all cancer deaths associated with being overweight and obese in both men and women and in both cohorts. The magnitude of the effect of obesity was greater among this group of never-smokers than in the cohort as a whole. The effects of being overweight or obese on cardiovascular disease in all three groups appeared to be largely driven by effects on coronary heart disease, with very little effect on stroke outcomes.

When only current smokers were considered, the effects of overweight and obesity showed similar patterns of association with cardiovascular disease and coronary heart disease to those seen among the never-smokers (Table 4). However, the effects for all-cause mortality were somewhat weaker than among the never-smokers (p for interactions comparing current to never-smokers for the effect of BMI categories on all-cause mortality with first 5 years of deaths removed: Renfrew/Paisley men, $p < 0.0001$; Renfrew/Paisley women, $p = 0.004$; and Collaborative men, $p = 0.14$). This weaker effect of overweight/obesity on all-cause mortality seemed to be attributable to an aggregation of an increased risk of cardiovascular disease deaths but decreased risk of smoking-related and respiratory deaths.

Adjustment for occupational social class and area deprivation category did not substantively alter any of these associations.

Discussion

Our findings demonstrate that reverse causality may result in an underestimation of the effect of obesity on all-cause mortality and that smoking strongly masks the effects of both overweight and obesity on all-cause and cause-specific mortality. This is because of the strong association between smoking and lower BMI and the strong effect of smoking on all-cause, cardiovascular, and cancer mortality. Thus, mortality in those of lower BMI is increased because of their greater likelihood of being smokers and not because lower BMI is unimportant to health. Among healthy never-smokers, overweight was associated with a 12% to 38% increase in all-cause mortality and obesity was associated with a doubling of risk of all-cause mortality in men and a 60% increase in women. Being either overweight or obese was associated with important increases in cardiovascular disease mortality (in particular, from coronary heart disease) and in cancer mortality among never-smokers. Among current smokers, being overweight or obese was also associated with important increases in the risk of cardiovascular disease, but being underweight among current smokers was associated with an increased risk of smoking-related cancers and respiratory disease deaths. This is likely to be related to the effect of smoking on body weight and the negative health effect of smoking, rather than any true benefit of being overweight rather than underweight if one smokes.

A major strength of this study is the size and very long follow-up of the two studies included in this analysis, which means that we were able to make the appropriate exclusions

Table 3. Age-adjusted relative risk of all-cause and cause-specific mortality by BMI categories among restricted groups of never-smokers and with first 5 years of deaths removed

	Normal-weight	Overweight	Obese
Renfrew/Paisley men			
No.	347	605	160
All-cause mortality			
No. of deaths	175	374	117
RR (95% CI)	1	1.38 (1.16 to 1.66)	2.10 (1.66 to 2.66)
CVD			
No. of deaths	100	205	73
RR (95% CI)	1	1.32 (1.04 to 1.68)	2.27 (1.68 to 3.08)
CHD			
No. of deaths	48	132	47
RR (95% CI)	1	1.73 (1.24 to 2.40)	2.84 (1.90 to 4.25)
Stroke			
No. of deaths	38	53	16
RR (95% CI)	1	0.94 (0.62 to 1.43)	1.48 (0.82 to 2.67)
Cancer			
No. of deaths	35	92	23
RR (95% CI)	1	1.68 (1.14 to 2.48)	1.98 (1.17 to 3.37)
Renfrew/Paisley women			
No.	1385	1569	698
All-cause mortality			
No. of deaths	660	849	477
RR (95% CI)	1	1.12 (1.01 to 1.23)	1.56 (1.39 to 1.76)
CVD			
No. of deaths	318	431	278
RR (95% CI)	1	1.15 (1.00 to 1.33)	1.84 (1.56 to 2.16)
CHD			
No. of deaths	155	222	142
RR (95% CI)	1	1.23 (1.00 to 1.51)	1.93 (1.53 to 2.42)
Stroke			
No. of deaths	130	141	95
RR (95% CI)	1	0.90 (0.71 to 1.15)	1.52 (1.16 to 1.98)
Cancer			
No. of deaths	172	226	97
RR (95% CI)	1	1.17 (0.96 to 1.43)	1.26 (0.98 to 1.62)
Collaborative men			
No.	210	307	56
All-cause mortality			
No. of deaths	101	162	39
RR (95% CI)	1	1.23 (0.96 to 1.58)	1.96 (1.35 to 2.84)
CVD			
No. of deaths	53	85	28
RR (95% CI)	1	1.23 (0.87 to 1.73)	2.68 (1.69 to 4.24)
CHD			
No. of deaths	30	49	21
RR (95% CI)	1	1.24 (0.79 to 1.95)	3.38 (1.93 to 5.91)

Table 3. (continued)

	Normal-weight	Overweight	Obese
Stroke			
No. of deaths	19	23	7
RR (95% CI)	1	0.94 (0.51 to 1.72)	2.06 (0.86 to 4.92)
Cancer			
No. of deaths	22	44	6
RR (95% CI)	1	1.52 (0.91 to 2.54)	1.32 (0.53 to 3.26)

RR, relative risk; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease.

to deal with reverse causality and masking by smoking. In addition, we were able to compare an occupation-based cohort with a general population cohort from the same geographic area. However, even with the large numbers in our studies, some of our estimates were imprecise. In part, this was because smoking prevalence was generally very high in both of these cohorts. As the population prevalence of smoking has decreased, contemporary studies will have greater power (because of greater numbers of non-smokers) to assess the true effect of obesity in never-smokers.

We have assumed that the occupational cohort is similar to the population-based cohort with the exception that they are all definitely working, and we further assumed that this means that they are healthier than the general population cohort. Both cohorts are from approximately the same geographic area, and baseline data collection was at a similar time with nearly identical procedures used in the two cohorts for the collection of baseline and follow-up data. It is possible that, among the workers, those with lower BMI and greater fitness may be exposed to the most dangerous jobs compared with those with higher BMI, but this would tend to mean that we have underestimated the difference in effect between the two cohorts. Our results were not markedly changed by adjustment for baseline socioeconomic position and area deprivation, which are related to other potential confounding factors such as diet, alcohol consumption, and physical activity. However, we were unable to adjust for these other potential confounders directly. There is evidence that the effects of physical inactivity and obesity on mortality are independent of each other (7), and it is unlikely that any of these potential confounding factors would alter our conclusions regarding the masking effect of smoking and the effect of reverse causality.

We do not have data on changes in smoking status over time in either study and, therefore, cannot take this into account, but it is appropriate to use smoking status at the time of weight and height assessment when one is concerned with the possibility that smoking masks the association of BMI with health outcomes. Several studies have shown smoking to be inversely associated with BMI, and there is evidence that smoking cessation is associated with increased BMI, but findings from the British Regional Heart Study showed that the health benefits of quitting smoking far outweighed any disbenefit of weight gain (26).

It has been argued that examining associations only among never-smokers is unhelpful, because the results are not generalizable to the whole population (8). There are several counterarguments to this position. First, stratified analyses are the most appropriate way to deal with a potential confounder when it is strongly associated with the main exposure and the outcome and its effects are likely to mask the main association of interest. Second, we found that both being overweight and being obese were importantly associated with increased cardiovascular disease mortality in never-smokers and in current smokers in this study. Therefore, the advice that greater BMI is bad for cardiovascular disease health is applicable to smokers and non-smokers alike. Third, even if effects are more pronounced in never-smokers, these findings are important to a large and growing proportion of the population; as smoking prevalence decreases, the findings will become increasingly important for the whole population. Because the population prevalence of overweight and obesity has increased over the past 30 years in most industrialized countries and continues to increase, whereas, at the same time, smoking prevalence has decreased in these countries, our results suggest that the role of overweight and obesity as major determinants of population health will increase during the coming decades.

In conclusion, we have demonstrated that smoking and reverse causality mask the true effects of overweight and obesity on all-cause and cause-specific mortality. As the population prevalence of smoking decreases and that of overweight and obesity increases, there seems little doubt that overweight and obesity in adults are one of the major public health problems of current times.

Table 4. Age-adjusted relative risk of all-cause and cardiovascular disease mortality by BMI categories among restricted groups of current smokers and with first 5 years of deaths removed

	Underweight	Normal-weight	Overweight	Obese
No.	35	1730	1527	282
All-cause mortality				
No. of deaths	30	1387	1172	230
RR (95% CI)	1.09 (0.76–1.57)	1	0.95 (0.88 to 1.02)	1.08 (0.94 to 1.24)
CVD				
No. of deaths	9	592	589	126
RR (95% CI)	0.77 (0.40 to 1.48)	1	1.12 (0.99 to 1.25)	1.39 (1.14 to 1.68)
CHD				
No. of deaths	5	381	382	84
RR (95% CI)	0.67 (0.28 to 1.61)	1	1.12 (0.97 to 1.29)	1.43 (1.13 to 1.81)
Cancer				
No. of deaths	8	477	373	64
RR (95% CI)	0.86 (0.43 to 1.72)	1	0.87 (0.76 to 1.0)	0.87 (0.67 to 1.13)
All smoking-related cancers				
No. of deaths	5	355	266	47
RR (95% CI)	0.71 (0.29–1.72)	1	0.84 (0.72 to 0.98)	0.86 (0.63 to 1.17)
Respiratory disease				
No. of deaths	7	186	98	17
RR (95% CI)	1.85 (0.87 to 3.93)	1	0.60 (0.47 to 0.77)	0.61 (0.37 to 0.99)
Renfrew/Paisley women				
No.	128	2003	1133	404
All-cause mortality				
No. of deaths	98	1230	714	297
RR (95% CI)	1.57 (1.28 to 1.93)	1	0.99 (0.90 to 1.08)	1.24 (1.09 to 1.40)
CVD				
No. of deaths	42	587	351	161
RR (95% CI)	1.40 (1.02 to 1.92)	1	1.01 (0.88 to 1.15)	1.39 (1.16 to 1.65)
CHD				
No. of deaths	20	326	195	94
RR (95% CI)	1.18 (0.75 to 1.86)	1	1.02 (0.85 to 1.22)	1.46 (1.16 to 1.84)
Cancer				
No. of deaths	25	372	199	68
RR (95% CI)	1.30 (0.87 to 1.96)	1	0.93 (0.78 to 1.10)	0.96 (0.74 to 1.24)
All smoking-related cancers				
No. of deaths	18	227	107	32
RR (95% CI)	1.54 (0.95 to 2.49)	1	0.82 (0.65 to 1.03)	0.74 (0.51 to 1.07)
Respiratory disease				
No. of deaths	20	138	80	31
RR (95% CI)	3.05 (1.91 to 4.88)	1	0.97 (0.74 to 1.28)	1.16 (0.79 to 1.72)
Collaborative men				
No.	28	1127	866	95
All-cause mortality				
No. of deaths	22	839	668	80
RR (95% CI)	1.25 (0.82 to 1.90)	1	1.10 (1.0 to 1.22)	1.22 (0.97 to 1.54)

Table 4. (continued)

	Underweight	Normal-weight	Overweight	Obese
CVD				
No. of deaths	9	382	355	43
RR (95% CI)	1.11 (0.57 to 2.15)	1	1.28 (1.11 to 1.48)	1.44 (1.05 to 1.97)
CHD				
No. of deaths	8	252	239	29
RR (95% CI)	1.47 (0.73 to 2.97)	1	1.30 (1.09 to 1.56)	1.46 (1.0 to 2.15)
Cancer				
No. of deaths	6	258	188	24
RR (95% CI)	1.10 (0.49 to 2.46)	1	1.01 (0.83 to 1.22)	1.19 (0.78 to 1.81)
All smoking-related cancers				
No. of deaths	4	182	125	18
RR (95% CI)	1.03 (0.38 to 2.77)	1	0.95 (0.75 to 1.19)	1.26 (0.78 to 2.05)
Respiratory disease				
No. of deaths	6	124	59	3
RR (95% CI)	2.43 (1.07 to 5.52)	1	0.67 (0.49 to 0.91)	0.31 (0.10 to 0.98)

RR, relative risk; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease.

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