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Review

The obesity paradox: Understanding the effect of obesity on mortality among individuals with cardiovascular disease



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ABSTRACT

Objective. To discuss possible explanations for the obesity paradox and explore whether the paradox can be attributed to a form of selection bias known as collider stratification bias.

Method. The paper is divided into three parts. First, possible explanations for the obesity paradox are reviewed. Second, a simulated example is provided to describe collider stratification bias and how it could generate the obesity paradox. Finally, an example is provided using data from 17,636 participants in the US National and Nutrition Examination Survey (NHANES III). Generalized linear models were fit to assess the effect of obesity on mortality both in the general population and among individuals with diagnosed cardiovascular disease (CVD). Additionally, results from a bias analysis are presented.

Results. In the general population, the adjusted risk ratio relating obesity and all-cause mortality was 1.24 (95% CI 1.11, 1.39). Adjusted risk ratios comparing obese and non-obese among individuals with and without CVD were 0.79 (95% CI 0.68, 0.91) and 1.30 (95% CI = 1.12, 1.50), indicating that obesity has a protective association among individuals with CVD.

Conclusion. Results demonstrate that collider stratification bias is one plausible explanation for the obesity paradox. After conditioning on CVD status in the design or analysis, obesity can appear protective among individuals with CVD.

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Introduction

Over the past three decades, the prevalence of obesity has increased substantially in North America (Flegal et al., 2010). A recent study by Flegal and colleagues highlighted that over one third of American adults (36%) are obese and more than two thirds (69%) are overweight (Flegal

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et al., 2012). In the general population, obesity is associated with an increased risk of death (Adams et al., 2006; Calle et al., 2003; Flegal et al., 2013). An analysis of data from nineteen pooled studies reported all-cause mortality hazard ratios of 1.44 (95% CI 1.38, 1.50) for grade I obesity (BMI 30 to 34.9 kg/m²), 1.88 (95% CI 1.77, 2.00) for grade II obesity (BMI 35 to 39.9 kg/m²), and 2.51 (95% CI 2.30, 2.73) for grade III obesity (BMI ≥ 40 kg/m²) relative to normal weight individuals (Berrington de Gonzalez et al., 2010).

Despite the known association between obesity and mortality in the general population, there have been conflicting reports about the relationship between obesity and mortality among individuals with cardiovascular disease (CVD). Numerous authors have reported that obesity confers a survival advantage in patients with CVD, a phenomenon known as the “obesity paradox” (McAuley and Blair, 2011; Romero-Corral et al., 2006). Among individuals with CVD, studies have reported that obese patients have improved short- and long-term survival, measured by all-cause mortality, relative to normal weight counterparts. Evidence of the obesity paradox has been found among patients with many types of cardiovascular disease, including coronary heart disease, myocardial infarction, hypertension, atrial fibrillation, and heart failure (Angerås et al., 2013; Badheka et al., 2010; Bucholz et al., 2012; Curtis et al., 2005; Lavie et al., 2009a, 2009b; Nigam et al., 2006; Oreopoulos et al., 2008a, 2008b; Uretsky et al., 2007). As well, the obesity paradox has been documented among cardiac surgery patients, such as those who have undergone percutaneous coronary intervention, heart valve surgery, and coronary artery bypass surgery (Gruberg et al., 2002; Oreopoulos et al., 2008a, 2008b; Sarno et al., 2011; Vaduganathan et al., 2012; van der Boon et al., 2013). The obesity paradox has also been reported in patients with other types of chronic disease, including diabetes, cancer, renal disease, and chronic obstructive pulmonary disease (McAuley and Blair, 2011). Several hypotheses have been suggested to explain this phenomenon (Chrysant and Chrysant, 2013; Dixon and Lambert, 2013).

Physiological explanations for the obesity paradox

Physiological explanations emphasize the biological advantages of excess fat stores during periods of illness. Body fat may act to decrease oxidative stress and inflammation, reduce levels of B-type natriuretic peptide, and improve secretion of amino acids and adipokines, potentially improving survival among obese individuals (Dixon and Lambert, 2013). Certain hormones and cytokines, such as leptin and tumor necrosis factor alpha, have been suggested as possible moderators of the relationship between obesity, cardiovascular events, and mortality (Lavie et al., 2009a, 2009b; Oreopoulos et al., 2008a, 2008b). As well, in certain catabolic CVD states, such as congestive heart failure, loss of muscle, bone, and fat mass is an indicator of more severe disease (Oreopoulos et al., 2011). Obese individuals may tolerate weight loss better than non-obese individuals due to higher metabolic reserves and body fat, resulting in improved prognosis and survival (Oreopoulos et al., 2008a, 2008b; Wacholder, 2013). Similarly, other authors have advocated the development of frailty, a syndrome defined by unintentional weight loss, exhaustion, weakness, and low physical capacity, as a possible explanation for the higher mortality risk in low-BMI older adults (Fried et al., 2001; Strandberg et al., 2009, 2013). Although these hypotheses are plausible, further evidence is required from animal models and clinical studies to determine whether there is any underlying biologic explanation for the observed paradoxical relationship.

Methodological explanations for the obesity paradox

There are also a number of hypothesized methodological explanations for the obesity paradox. Firstly, using BMI to define obesity has been identified as a possible design flaw. Authors suggest that BMI does not correspond to the same degree of adiposity in individuals of

different height, nor does it account for body composition or the location of adipose tissue (i.e., visceral vs. subcutaneous fat), or differentiate between fat mass and muscle mass (Kopelman, 2000; Lavie et al., 2013; Oreopoulos et al., 2011; Rothman, 2008). It has been suggested that using alternative measures of adiposity such as waist circumference, waist to hip ratio, sum of skinfold thickness, or percent body fat could resolve the paradoxical association between obesity and mortality among individuals with CVD (Flegal et al., 2008; Lavie et al., 2013; Vina et al., 2013). However, researchers have demonstrated that waist circumference and waist to hip ratio are highly correlated with BMI and all have been shown to produce comparable estimates (Flegal et al., 2008; Vazquez et al., 2007). In adult men and women (aged ≥ 20 years), the correlation between waist circumference and BMI has been reported to range from 0.85 to 0.94 and the correlation between percent body fat and BMI ranges from 0.72 to 0.84 (Flegal et al., 2008). Lavie and colleagues have reported finding evidence of the obesity paradox among individuals with CVD regardless of the measure of adiposity used (De Schutter et al., 2013; Lavie et al., 2003, 2009a, 2009b, 2011, 2012). Due to the high correlation between these measures, changing from BMI to an alternate adiposity index is unlikely to substantially alter the observed relations. Another issue related to the use of BMI is the concept of metabolically benign obesity, where individuals who are defined as obese according to BMI cut points have healthy metabolic profiles and may not be at an increased risk of mortality. Obese individuals with healthy metabolic profiles may be at a lower risk of mortality than non-obese individuals with many risk factors such as dyslipidemia or hypertension (Janssen, 2005; Kramer et al., 2013; Ortega et al., 2013).

Other methodologic explanations for the protective association between obesity and mortality among individuals with CVD suggest that it may be the result of inappropriate study designs or poor control of important confounding variables. Recent longitudinal research has highlighted the need to consider obesity as a time-varying exposure and account for changes in weight status over the lifespan to understand the true obesity–mortality relationship (Ferreira and Stehouwer, 2012; Strandberg et al., 2013).

Cigarette smoking has been cited as one possible confounding variable (Cooper, 2008; Durazo-Arvizu and Cooper, 2008; McAuley and Blair, 2011). However, analytic evidence suggests that controlling for smoking has a minimal effect on the BMI–mortality association and omitting smokers leaves results qualitatively unchanged (Durazo-Arvizu and Cooper, 2008; The BMI in Diverse Populations Collaborative Group, 1999). Comparing the BMI associated with minimum mortality in models adjusted and not adjusted for smoking demonstrates that smoking may not be a strong confounder in the general population. Adjusting for smoking, the BMI associated with minimum mortality was 24.3 kg/m² while not adjusting for smoking resulted in a BMI of minimum mortality of 25.0 kg/m² (Durazo-Arvizu and Cooper, 2008). However, recent research has suggested that smoking may act as a strong confounder of the obesity–mortality relationship among individuals with CVD (Preston and Stokes, in press).

A third methodologic explanation is reverse causality. In this context, reverse causality refers to the hypothesis that pre-existing illness results in unintended weight loss and higher mortality among lower BMI groups, making obesity appears protective (Flanders and Augustad, 2008; Flegal et al., 2011; Lawlor et al., 2006; Stevens et al., 2001). As a result, a lower BMI category is composed of a disproportionate number of sicker people at high risk of mortality (Flegal et al., 2011). It is suggested that this form of bias may shift estimates toward the null, or potentially past the null, making obesity appears protective (Flegal et al., 2011; Stevens et al., 2001). However, several studies have reported that the risk of mortality does not change substantially or systematically across BMI categories after excluding individuals with a history of cancer, CVD, or those who died early in the follow-up period (Allison et al., 1999a, 1999b; Flegal et al., 2007; Greenberg, 2006; Orpana et al., 2010). Stevens and colleagues reported that excluding participants who died in the first four years of follow-up resulted in a change in

effect of less than 1% (Stevens et al., 2002). A meta-analysis and simulation study by Allison and colleagues reached a similar conclusion (Allison et al., 1997, 1999a, 1999b).

An alternative explanation

An additional methodologic explanation is that it is due in whole or in part to a form of selection bias known as collider stratification bias (Banack and Kaufman, 2013; Lajous et al., 2014). Selection bias occurs when exposure and disease both affect inclusion into the analysis. In other words, it occurs as the result of conditioning on a common effect of exposure and outcome (Hernán et al., 2004). Conditioning can occur at the study design or analysis stage and may occur through restriction, regression adjustment, or stratification (Cole et al., 2010). Published examples of the obesity paradox among those with CVD are often conditioned on CVD status by restricting cohort entry to those who have an established form of CVD at baseline. For example, in cohort studies that restrict enrollment to individuals who have heart failure, have experienced a myocardial infarction, or have coronary heart disease, the protective association observed within this diseased stratum may not be causal, in the sense that there is no diseased individual whose risk is lowered by being obese rather than by not being obese, even though the obese has lower average risk in those observed to have the disease.

Numerous authors have demonstrated that conditioning on a variable affected by exposure and outcome can introduce a spurious association between exposure and outcome and can even reverse the direction of association, making a harmful exposure appears protective (Cole et al., 2010; Hernán et al., 2004; Hernández-Díaz et al., 2006; Lajous et al., 2014; Rothman et al., 2008). Fig. 1 is a causal diagram representing the basic structure of collider stratification bias applied to the obesity paradox scenario. Obesity is associated with the development of CVD, and CVD is a known predictor of mortality. Obesity has been shown to directly influence mortality risk (Flegal et al., 2013). Fig. 1 also depicts unmeasured common causes (U) of CVD and mortality. It is possible to conceive many unmeasured common causes of the CVD–mortality relationship, such as genetic, physiologic, and behavioral factors (Kopelman, 2000). In the language of causal diagrams, CVD is known as a collider and a rectangular box is placed around this variable to indicate that the obesity paradox results from studies have conditioned on CVD (Cole et al., 2010). This explains why this selection bias is also known as collider stratification bias, since the bias occurs due to stratification on a collider. Conditioning on a variable affected by exposure and outcome will generally distort the relationship between obesity and mortality, potentially producing the obesity paradox (Hernán et al., 2004; Hernández-Díaz et al., 2006).

Fig. 1 can be used to provide a hypothetical explanation for the paradox. For the purpose of this example, we will use a genetic factor such as APOE-ε4 as the unmeasured (U) variable, since APOE-ε4 is known to influence both CVD and mortality and genetic variants are often unmeasured in epidemiologic and clinical research (Eichner et al., 2002; Ewbank, 2007; Song et al., 2004). In obese individuals, those with established CVD may have developed the disease because they are obese or due to genetic factors. However, in non-obese individuals, more individuals with CVD must have the disease because of genetic factors. As a result, since CVD is caused by obesity, when an effect estimate

is calculated within levels of CVD, being obese with CVD makes it less likely the person has APOE-ε4 (U), while among those without CVD, being non-obese makes it more likely the person has APOE-ε4 (U). Stratification on CVD therefore induces an association between obesity and APOE-ε4 that distorts the true causal obesity–mortality relationship in the population. This can produce the apparent protective effect of obesity on mortality known as the “obesity paradox” (Banack and Kaufman, 2013). The purpose of this paper is to quantitatively examine whether collider stratification bias is one plausible explanation for the obesity paradox among individuals with CVD.

Analysis

The following section will provide two examples of how collider stratification bias can produce an apparently protective effect of obesity on mortality among individuals with CVD. The first is a fictitious example intended to provide a demonstration of how the paradox occurs using simple, easy-to-follow, hand calculations. The second example uses data from the Third US National Health and Nutrition Examination Survey (NHANES III) to provide a real-life example of the obesity paradox using multivariate regression analysis.

Example 1

The data for this analysis are intended to emulate a population based study of 1350 adults aged 30–50 years. The exposure, obesity, was measured at baseline. It is a binary variable with two levels: BMI < 30 kg/m² and BMI ≥ 30 kg/m². The outcome variable, mortality, was measured 15 years later. Table 1 summarizes the data from this fictitious study. The crude risk ratio (RR) comparing the risk of mortality among obese individuals compared with the risk among non-obese individuals is (200 / 750) / (100 / 600) = 1.63.

Participants were considered to have CVD if they had a physician-diagnosed report of coronary heart disease, acute coronary syndrome, congestive heart failure, or stroke. Tables 2 and 3 depict the same exposure and outcome information as in Table 1, but are stratified by CVD status (CVD yes/no). Among individuals with CVD, the risk ratio for obesity and mortality is equal to (45 / 130) / (30 / 65) = 0.75, while among individuals with no CVD, the risk ratio is (155 / 615) / (70 / 535) = 1.92. The causal diagram in Fig. 1 and the numeric example in Tables 1–3 illustrate the bias produced by conditioning on a common effect of exposure and outcome. Table 1 presents the unconditional (marginal) effect of obesity on mortality in the entire population. Obese individuals have a 63% greater mortality risk compared with non-obese individuals over 15 years of follow-up. However, since CVD is a cause of obesity, and there are unmeasured common causes of CVD and mortality, when the risk ratio is calculated within levels of CVD, the association between obesity and mortality is reversed and obesity appears protective among those with CVD. As previously discussed, many studies of the obesity–mortality relationship among individuals with CVD are conditioned on having CVD (through restriction at study entry), which amounts to only examining the obesity–mortality relationship in Table 2, while ignoring Tables 1 and 3.

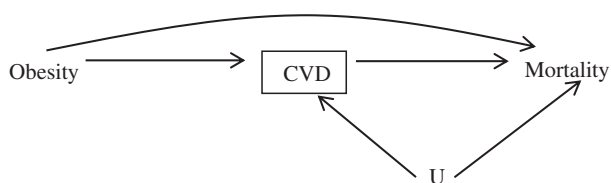


Fig. 1. Directed acyclic graph representing causal relations between obesity, cardiovascular disease, mortality, and unmeasured factor(s) U.

Table 1
The relationship between obesity and mortality.

Exposure (obesity)	Outcome (mortality)	Total		
		Dead	Alive	
Obese (BMI ≥ 30 kg/m ²)		200	550	750
Non-obese (BMI < 30 kg/m ²)		100	500	600

Table 2
The relationship between obesity and mortality among individuals with CVD.

Exposure (obesity)		Outcome (mortality)		Total
		Dead	Alive	
		Yes (BMI < 30 kg/m ²)	45	85
No (BMI ≥ 30 kg/m ²)	30	35	65	

Example 2

The second example uses real data from NHANES III (1988–1994), a nationally representative cross-sectional survey of civilians in the United States (National Center for Health Statistics, 1997). Participation includes completion of a standardized in-home interview including demographic, socioeconomic, and health-related questions and a physical examination at a mobile examination center administered by trained staff. Although the survey recruits participants of all ages, the present analysis will include data from 17,636 participants between 20 and 80 years of age. The US National Centre for Health Statistics has linked NHANES III data to mortality data up to December 31, 2006 in the National Death Index (NDI). Record linkage is performed by a probabilistic match between NHANES and NDI death certificate records (National Center for Health Statistics, 2009). Similar to the previous example, and Fig. 1, the outcome variable in this analysis is all-cause mortality and the exposure variable is obesity as previously defined. CVD is measured in NHANES III by several self-report questions (e.g., has a doctor or health professional ever told you that you had a heart attack?). Participants reporting having coronary heart disease, congestive heart failure, stroke, or heart attack are classified as having CVD for this analysis.

Demographic and clinical characteristics of the sample are provided in Table 4. Participants with CVD were more likely to be male, of older age, and have less than a high school education compared with those without CVD. Additionally, people with CVD were substantially more likely to have diabetes and hypertension. Using a generalized linear model with a log-link and a binomial distribution, we calculated adjusted risk ratios and 95% confidence intervals for mortality among the total sample as well as among those with and without CVD. Models were adjusted for potential confounders of the obesity–mortality relationship, including gender, age, race, education, and smoking status. The mortality risk ratio comparing obese and non-obese individuals was 1.24 (95% CI 1.11, 1.39) in the total NHANES cohort. The stratum-specific mortality risk ratios comparing obese and non-obese individuals were 0.79 (95% CI 0.68, 0.91) among those with CVD and 1.30 (95% CI 1.12, 1.50) among those without CVD. The stratified results seemingly demonstrate that obese individuals with CVD have a lower mortality risk than non-obese individuals with CVD, apparently illustrating the presence of an obesity paradox. However, the inverse relationship between obesity and mortality may be spurious, caused by stratification on CVD status.

Bias analysis

Bias analysis techniques can be used as sensitivity analyses to understand the magnitude of bias induced by studying a highly selected population drawn from the total cohort. They can be used to quantify the amount of selection bias affecting an estimate of the obesity–mortality

Table 3
The relationship between obesity and mortality among individuals without CVD.

Exposure (obesity)		Outcome (mortality)		Total
		Dead	Alive	
		Yes (BMI < 30 kg/m ²)	155	465
No (BMI ≥ 30 kg/m ²)	70	465	535	

Table 4
Participant characteristics in NHANES III.

	Total sample	CVD	No CVD
Male gender (%)	48.8	56.6	47.6
Mean age, years	42.4	62.2	41.3
Caucasian (%)	75.4	76.6	75.4
High school education	34.5	26.9	34.9
Mean BMI, kg/m ²	26.4	28.5	26.3
Mean waist circumference, cm			
Females	88.3	97.8	87.9
Males	94.7 (±13.6)	101.6	94.3 (±13.5)
Current smoker (%)	29.1	26.2	29.2
Has diabetes (%)	5.06	22.2	4.16
Hypertensive (%)	14.7	36.8	13.5
Mean serum total cholesterol, mmol/L	5.23	5.76	5.21
Mean serum HDL, mmol/L	1.31 (±.40)	1.18	1.32
Mean serum LDL, mmol/L	3.27 (±.99)	3.59	3.25
Mean serum triglycerides, mmol/L	1.60 (±1.4)	2.23	1.57

relationship among individuals who already have CVD compared with an estimate of the obesity–mortality relationship in the total population. To conduct a bias analysis, one must select values for the bias parameters and use those chosen values to calculate the effect estimate that would have been observed in the absence of bias (Lash et al., 2009; Orsini et al., 2008). For selection bias, the bias parameters are known as sampling fractions, representing the probability of selection into the analysis of exposed and unexposed cases and non-cases (Rothman et al., 2008). The cross product of these sampling fractions is the selection bias factor (Kleinbaum et al., 1981; Lash et al., 2009; Rothman et al., 2008). It is simple to correct for selection bias by dividing the biased effect estimate by the selection bias factor if it is known (Lash et al., 2009; Orsini et al., 2008).

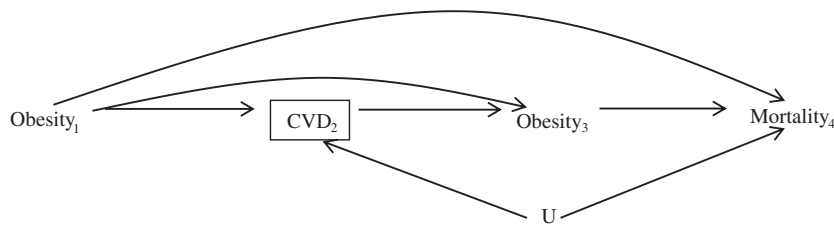
For the purpose of illustrating how to conduct this bias analysis, we use the results presented in example 2 from the NHANES III data set. The results demonstrated that obese individuals with CVD have a lower risk of mortality than non-obese individuals with CVD 0.79 (95% CI 0.68, 0.91). Table 5 presents the results of this bias analysis. When the selection bias factor is equal to 1.0, the distribution of obesity and mortality among those with CVD perfectly represents the distribution of these variables in the total population, and no selection bias is present. However, when the selection bias factor is less than one, the magnitude of bias introduced gets progressively larger. When the selection bias factor is equal to 0.6, the effect of obesity on mortality no longer appears protective, and individuals who are obese are at an increased risk of death relative to non-obese individuals (RR = 1.32 95% CI 1.13, 1.52). Since CVD is selected with a much lower proportion than 60% of the cohort, this bias analysis demonstrates that selection bias can be of sufficient magnitude to reverse the direction of the relationship between exposure and outcome in this example.

Conclusion

The objective of the present paper was to review the obesity paradox and explore whether it can be explained as an example of collider

Table 5
Bias analysis.

Selection bias factor	Corrected RR estimate	Lower 95% CI	Upper 95% CI
0.1	7.9	6.8	9.1
0.2	3.9	3.4	4.638
0.3	2.63	2.27	3.03
0.4	1.98	1.70	2.28
0.5	1.58	1.36	1.82
0.6	1.32	1.13	1.52
0.7	1.13	0.97	1.30
0.8	0.99	0.856	1.14
0.9	0.88	0.76	1.01
1.0	0.79	0.68	0.91



Note: Numeric subscripts denote temporal ordering of measurement of obesity, CVD, and mortality

Fig. 2. Directed acyclic graph depicting longitudinal relationship between obesity, cardiovascular disease, mortality, and unmeasured factor(s) U. Note: Numeric subscripts denote temporal ordering of measurement of obesity, CVD, and mortality.

stratification bias. Both the fictitious example and the NHANES III data suggest that after conditioning on CVD status in the analysis, obesity appears protective among individuals with CVD. Stratifying on CVD status creates an imbalance in the distribution of unmeasured common causes (U) between obese and non-obese individuals.

The bias analysis presented in this paper is a form of sensitivity analysis that illustrates the danger of studying only a highly selected subset of the total cohort, and that the protective effect of obesity on mortality can be explained by a simple selection bias. Correcting for selection bias reverses the protective effect of obesity on mortality among individuals with CVD in the NHANES III cohort. Rather than being a true protective effect of obesity on mortality among individuals with CVD, the obesity paradox could simply be an artifact of improperly conditioning on a variable affected by exposure and sharing common causes with the outcome (a “collider”). It is important to recognize that if this is true, the apparent protective effect of obesity on mortality is spurious even among the strata of individuals who have CVD. That is to say, even if obesity was truly harmful for every single individual in the population, a protective effect in the diseased stratum could be observed through this selection bias alone (Flanders and Klein, 2007). This is because selection distorts the relationship between exposure and outcome in the strata of individuals with CVD. It would be incorrect to claim that the effect of obesity is truly protective among those with CVD but simply does not generalize to the entire population or those without CVD. Although this bias analysis demonstrates that selection bias may explain the obesity paradox, it does not preclude alternate explanations (Glymour and Vittinghoff, 2014). See Appendix A for a discussion of this point, including simulations.

A relevant question for many clinicians, epidemiologists, and public health practitioners is how one should analyze data on the effect of obesity among individuals with prevalent disease, such as CVD. Unfortunately, it is not possible to obtain an unbiased estimate of the effect of obesity on mortality among individuals with CVD without making strong assumptions about the magnitude and sign of the important unmeasured confounders (U) of the CVD–mortality relationship. In addition to these assumptions, to correctly estimate this effect, one would need longitudinal data in which measurement of body weight temporally precedes disease incidence, and in which there is an additional measurement of body weight at some point after disease was diagnosed (Fig. 2). If such data were available, the use of methods developed to study time varying exposures and time varying confounding (e.g. marginal structural models) could provide unbiased estimates of the total and direct effects of obesity on mortality (Robins et al., 2000). However, in most clinical settings, longitudinal data of this nature is not available, and, moreover, it is unlikely that investigators could ever claim to be in a scenario without important unmeasured confounding.

Further research is required to understand the effect of obesity on mortality among individuals with chronic disease under varying plausible assumptions about the magnitude of unmeasured confounding affecting this relationship (VanderWeele, 2010). Additionally, it would be a valuable addition to the literature to explore whether the mechanism responsible for the obesity paradox is the same in different types

of CVD. Through the use of causal diagrams and quantitative examples, the results of this paper provide theoretical and empirical evidence that when the obesity–mortality relationship is subject to unmeasured confounding, the magnitude of collider bias induced is large enough to make an apparently harmful exposure appear protective.

Conflict of interest statement

The authors declare that there are no conflicts of interests.

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Appendix A

Consider two simple scenarios for the true causal mechanism for obesity and mortality. In World A, obesity is always harmful and therefore increases mortality risk for each obese individual in the population. If researchers in World A studied the obesity–mortality relationship by recruiting only individuals with CVD, the resulting stratification on CVD = 1 status would induce collider stratification bias if there were unmeasured common causes of CVD and mortality. These researchers would therefore erroneously report a protective effect of obesity on mortality among individuals with CVD. In World B, obesity is harmful overall for the unstratified (total) population, but is truly beneficial for individuals with CVD. If researchers in World B conducted the same study as those in World A, they could also find a protective effect of obesity on mortality among individuals with CVD, even if there were no unmeasured causes of CVD and mortality, and therefore no collider-stratification. Researchers in both worlds A and B could conduct the bias analysis we describe in this paper, and both could observe that by varying the selection bias factor it is possible to make the apparently protective effect of obesity flip to being harmful in the unselected population. This is because the selection bias correction reweights back to the average effect in the total population. The bias analysis shows that the observed data are entirely consistent with an explanation for the paradox that relies solely on collider stratification bias in a world in which obesity is harmful for all individuals. But the observed data could be consistent with many other scenarios as well. Simple Stata simulations produce data under World A and World B as described above, and demonstrate the reversal of the observed protective effect of obesity in both scenarios.

World A: Simulation with unmeasured confounding (U) of the CVD–mortality relationship

```
clear
set obs 10000
set seed 123456
*generating the distribution of exposure (obese),
outcome (die), intermediate (cvd), and confounder (u)
gen Obese=uniform(>.8
gen u=uniform(>.9
gen cvd=(uniform(>.9 | u==1) if Obese==0
replace cvd=(uniform(>.6 | u==1) if Obese==1
gen die=(uniform(>.9 | u==1) if Obese==0 & cvd==0
replace die=(uniform(>.8 | u==1) if Obese==1 & cvd==0
replace die=(uniform(>.9 | u==1) if Obese==0 & cvd==1
replace die=(uniform(>.8 | u==1) if Obese==1 & cvd==1
cc die Obese, by (cvd)
tab die Obese if cvd==1
tab die Obese
*bias analysis using Episens macro (a Stata add-on)
episens die Obese if cvd==1, st(cc) dpscex(c(338/562))
dpscun(c(842/1516)) dpsnex(c(531/1376)) dpsnun(c(671/
6546))
cc die Obese
```

Results from simulation:

	Odds ratio	95% confidence interval
Total population	1.76	1.57, 1.97
Individuals without CVD	2.31	1.94, 2.74
Individuals with CVD	0.51	0.43, 0.60

Results from bias analysis:

Odds ratio observed from data	0.51 (0.43, 0.60)
Corrected odds ratio	1.76

World B: Simulation with no unmeasured confounding of the CVD–mortality relationship

```
clear
set obs 10000
set seed 123456
*generating the distribution of exposure (obese),
outcome (die), and intermediate (cvd)
gen Obese=uniform(>.8
gen cvd=uniform(>.95 if Obese==0
replace cvd=uniform(>.9 if Obese==1
gen die=uniform(>.95 if Obese==0 & cvd==0
replace die=uniform(>.9 if Obese==1 & cvd==0
replace die=uniform(>.8 if Obese==0 & cvd==1
replace die=uniform(>.9 if Obese==1 & cvd==1
cc die Obese, by (cvd)
tab die Obese if cvd==1
tab die Obese
*bias analysis using Episens macro (a Stata add-on)
episens die Obese if cvd==1, st(cc) dpscex(c(23/189))
dpscun(c(80/464)) dpsnex(c(138/1749)) dpsnun(c(329/
7598))
cc die Obese
```

Results from simulation:

	Odds ratio	95% confidence interval
Total population	1.77	1.48, 2.12
Individuals without CVD	1.95	1.60, 2.36
Individuals with CVD	0.69	0.39, 1.16

Results from bias analysis:

Odds ratio observed from data	0.69 (0.41, 1.14)
Corrected odds ratio	1.77

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