American Journal of Epidemiology

Vol. 183, No. 2
DOI: 10.1093/aje/kwv168
Advance Access publication:
December 10, 2015

## Original Contribution

# Estimating the Time-Varying Joint Effects of Obesity and Smoking on All-Cause Mortality Using Marginal Structural Models

**Hailey R. Banack* and Jay S. Kaufman**

* Correspondence to Hailey R. Banack, Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, 1020 Pine Avenue West Montreal, Quebec, Canada H3A 1A2 (e-mail: hailey.banack@mail.mcgill.ca).

*Initially submitted February 10, 2015; accepted for publication June 22, 2015.*

Obesity and smoking are independently associated with a higher mortality risk, but previous studies have reported conflicting results about the relationship between these 2 time-varying exposures. Using prospective longitudinal data (1987–2007) from the Atherosclerosis Risk in Communities Study, our objective in the present study was to estimate the joint effects of obesity and smoking on all-cause mortality and investigate whether there were additive or multiplicative interactions. We fit a joint marginal structural Poisson model to account for time-varying confounding affected by prior exposure to obesity and smoking. The incidence rate ratios from the joint model were 2.00 (95% confidence interval (CI): 1.79, 2.24) for the effect of smoking on mortality among nonobese persons, 1.31 (95% CI: 1.13, 1.51) for the effect of obesity on mortality among nonsmokers, and 1.97 (95% CI: 1.73, 2.22) for the joint effect of smoking and obesity on mortality. The negative product term from the exponential model revealed a submultiplicative interaction between obesity and smoking ($\beta = -0.28$, 95% CI: −0.45, −0.11; $P < 0.001$). The relative excess risk of interaction was −0.34 (95% CI: −0.60, −0.07), indicating the presence of subadditive interaction. These results provide important information for epidemiologists, clinicians, and public health practitioners about the harmful impact of smoking and obesity.

interaction; marginal structural model; obesity; smoking

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; IPTW, inverse probability of treatment weight; IRR, incidence rate ratio; RERI, relative excess risk of interaction.

Epidemiologic evidence has demonstrated that both smoking and obesity are independently associated with a higher risk of cardiovascular disease (CVD) and mortality in the general population (1–4). Smoking and obesity are strongly associated with the development of cardiometabolic risk factors and numerous noncardiac conditions, such as asthma and cancer (1, 5–7). The interaction between these 2 risk factors is especially relevant because obesity and smoking are among the top causes of preventable death in the United States (7). The consequences of smoking and obesity extend beyond individual health effects because they are responsible for significant direct and indirect health care costs (8). Although smoking rates are declining in the general population, the prevalence of obesity is increasing at such a rapid rate that it might be responsible for a decline in life expectancy in the 21st century (9, 10).

Interestingly, there is a negative correlation between smoking and obesity. Smokers tend to have lower body weights than do nonsmokers, potentially because smoking increases the metabolic rate and acts as an appetite suppressant (11). The nature of the relationship between obesity and smoking has been the subject of a longstanding debate (12, 13). Previous studies have reported conflicting results about whether the risk of all-cause mortality differs by obesity status among smokers and nonsmokers. In a large study of American adults, Berrington de Gonzalez et al. (3) reported that the shape of the relationship between body mass index (BMI) and mortality risk changed significantly when current or former smokers were excluded from the analyses. In additional studies, investigators have demonstrated that the relationship between obesity and mortality risk differs among smokers and nonsmokers. Adams et al. (4) reported a hazard ratio of mortality of

1.00 (95% confidence interval (CI): 0.93, 1.08) among obese current smokers and 1.39 (95% CI: 1.28, 1.51) among obese nonsmokers. Ma et al. (14) reported hazard ratios of 3.58 (95% CI: 3.08, 4.16), 1.98 (95% CI: 1.75, 2.23), and 1.66 (95% CI: 1.44, 1.90) among obese middle-aged (45–64 years) current, former, and never smokers, respectively. However, in a large meta-analysis, the Diverse Studies in Populations Collaborative Group found no evidence of an interaction between BMI and smoking on the multiplicative scale (15).

Assessment of the statistical interaction between 2 exposure variables requires the inclusion of a product term in the regression model. Statistical interaction corresponds to effect measure modification, which is an examination of whether a primary exposure of interest is modified by another covariate. Causal interaction considers both factors as potentially manipulated exposures and corresponds to the assessment of effect measure modification only in the absence of unmeasured confounding (16). Interaction can be assessed on either the additive or multiplicative scale (17). In a linear regression model, the slope coefficient for the product term indicates deviation from exact additivity (additive interaction), whereas in an exponential regression model, the slope coefficient for the product term indicates deviation from exact multiplicativity (multiplicative interaction) (17, 18). For an in-depth discussion of the scale dependence of interaction, we refer readers to VanderWeele (19).

Additive interaction, also referred to as biologic interaction or public health interaction, implies that the number of deaths caused by the combination of obesity and smoking is greater (or less) than the sum number of deaths that would be caused independently by either exposure (18, 20). Additive interaction is considered most relevant for public health purposes (20). Multiplicative interaction indicates that the product of the joint effects of obesity and smoking is greater (or less) than the product of the 2 exposures individually (18, 20). To the best of our knowledge, there has been no study to date in which the possibility of additive interaction between these 2 variables has been explored.

There is an inherent methodological challenge when attempting to study the relationship among obesity, smoking, and mortality. Consider Figure 1, a causal diagram for the effect of obesity and smoking on all-cause mortality. Smoking and obesity are both time-varying exposures and are subject to time-varying confounding. It is well known that smoking and obesity are associated with a higher risk of CVD (1, 6, 21). Although exposures to obesity and smoking increase the risk of CVD, having CVD decreases the likelihood of being obese or a smoker at a later time point. For individuals with established CVD, clinical guidelines recommend weight loss and smoking cessation for risk reduction and to prevent recurrent events (22). At visits 2, 3 and 4, obesity and smoking status are affected by prior obesity and smoking status, as well as CVD status. It is not possible to estimate the causal effect of obesity and smoking on mortality using standard regression analysis. Failing to adjust for CVD status will result in a biased effect estimate, yet adjustment for CVD status also results in biased estimates (23, 24). Any form of conditioning on CVD status will induce the same form of bias (23). This methodological dilemma has been well described by Hernán et al. (23), Cole and Hernán (25), and Robins et al. (26).

Inverse probability weighting and marginal structural models are some of the analytic tools used to avoid the bias that can occur with standard adjustment of a time-varying confounder affected by prior exposure (25, 26). Because there are 2 exposures of interest, unbiased estimation of the effect of obesity and smoking on mortality requires the use of joint marginal structural models (27–29). Our objective in the present study was to estimate the joint effects of obesity and smoking on mortality and to locate these joint effects on the continuum of interaction in relation to additive and multiplicative benchmarks.

## METHODS

### Study population

We used data from the Atherosclerosis Risk in Communities (ARIC) Study. The ARIC Study is a prospective cohort study from 4 communities in the United States (30). At baseline, 15,792 men and women 45–64 years old were selected from the communities by probability sampling. The study consisted of 4 in-person cohort examinations and annual follow-up telephone interviews (30). Each cohort examination included the administration of questionnaires and a standardized physical examination (30).

### Outcome ascertainment

All-cause mortality was ascertained through annual follow-up interviews by telephone, hospital surveillance, and review of the National Death Index (31, 32). Participants were followed from the date of the first ARIC Study visit until death or administrative censoring on December 31, 2007.

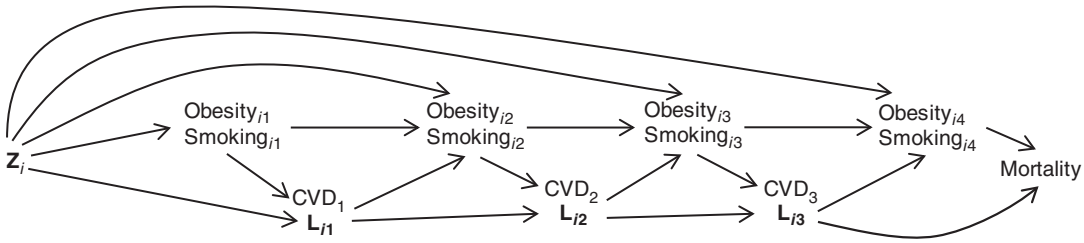


**Figure 1.** Directed acyclic graph for the effect of obesity and smoking on all-cause mortality. $\mathbf{Z}_i$ is a vector of baseline covariates; $\mathbf{L}_{i1}$, $\mathbf{L}_{i2}$, and $\mathbf{L}_{i3}$ represent vectors of time-varying covariates for individual *i* at cohort visits 1, 2, and 3, respectively. CVD, cardiovascular disease.

### Exposure measurement

There are 2 time-varying exposures of interest: obesity and smoking. Both exposures were measured at all 4 ARIC Study visits (1987, 1990, 1993, and 1996). BMI is an index of weight-for-height calculated as weight in kilograms divided by the square of height in meters. Obesity is defined as a BMI greater than 30 (8). Height and weight were measured by trained staff using standard protocols developed by the ARIC Study investigators (33).

The second exposure of interest, cigarette smoking status, was modeled as a dichotomous variable based on participant self-report. Smoking status was modeled using 2 alternate classifications: 1) ever smokers versus never smokers and 2) current smokers versus nonsmokers. Participants were categorized as current smokers at a particular cohort visit if they answered yes to the question "Do you currently smoke cigarettes?" and were considered current nonsmokers if they responded no. Participants were considered to be never smokers if they reported not being a current smoker nor having ever smoked 400 cigarettes. The category of ever smokers consisted of individuals who were current or former smokers (i.e., individuals who reported being current smokers or reported having smoked more than 400 cigarettes in their lifetimes). Analytic results based on the second characterization of smoking status (current smokers vs. nonsmokers) are available in Web Table 1 (available at http://aje.oxfordjournals.org/).

### Covariate measurement

We considered both baseline and time-varying confounders in our analyses. Baseline covariates included age, race, sex, number of years of education completed, and smoking history. Time-varying covariates were assessed at each cohort visit and included current alcohol drinking status, CVD status, diabetes status, and physical activity level (34).

### Statistical analysis

To examine the obesity-mortality relationship among smokers and nonsmokers, we used 2 unweighted, stratified Poisson regression models. These models were stratified by smoking status to explore whether the obesity-mortality relationship differs between ever smokers and never smokers. We then fit a crude regression model and a standard adjusted Poisson regression model. Finally, we fit a joint marginal structural model to estimate the joint effects of obesity and smoking on all-cause mortality. Fitting this model is a 2-step process.

### Step 1: fitting inverse probability of treatment weights

Inverse probability of treatment weights (IPTWs) were used to create a weighted sample in which exposure assignment is unconfounded by measured covariates, similar to a randomized controlled trial (25, 35). The IPTWs are the inverse of the probability of being exposed (or unexposed) at each cohort visit. Using pooled logistic regression, we fit stabilized IPTWs for obesity [$W^{X1}_{(t)}$] and smoking [$W^{X2}_{(t)}$], as follows:

$$SW^{X1}{}_{(t)} = \prod_{k=0}^{j} \frac{f\left[X_1(k_{(m)}) | X_1(k_{(m-1)}), \overline{X}_2(k_{(m)}), \mathbf{Z}_1, \overline{C}_{i(k(m))=0}\right]}{f\left[X_1(k_{(m)}) | X_1(k_{(m-1)}), \overline{X}_2(k_{(m)}), \overline{\boldsymbol{L}}_1(k_{(m-1)}), \overline{C}_{i(k(m))=0}\right]}$$

and

$$SW^{X2}{}_{(t)} = \prod_{k=0}^{j} \frac{f\left[X_2(k_{(m)}) | X_2(k_{(m-1)}), \overline{X}_1(k_{(m-1)}), \mathbf{Z}_2, \overline{C}_{i(k(m))=0}\right]}{f\left[X_2(k_{(m)}) | X_2(k_{(m-1)}), \overline{X}_1(k_{(m-1)}), \overline{\boldsymbol{L}}_2(k_{(m-1)}), \overline{C}_{i(k(m))=0}\right]}.$$

With a cohort of $i$ participants, $X_{1i}(k_{(m)})$ represents individual $i$'s obesity status at time $k(m)$, and $X_{2i}(k_{(m)})$ represents individual $i$'s smoking status at time $k(m)$. The letter $m$ (e.g., $k_{(m)}$) represents sequential cohort measurement time points (visits 1–4). Overbars represent covariate history from the first cohort visit up to time $k(m)$. $\mathbf{L}_{1i}(k_{(m)})$ is a vector containing confounders of the obesity-mortality relationship at time $k(m)$. Similarly, $\mathbf{L}_{2i}(k_{(m)})$ is a vector containing confounders of the smoking-mortality relationship at time $k(m)$. Values of time-varying confounders included in $\mathbf{L}_1$ and $\mathbf{L}_2$ were from the prior cohort visit. $\mathbf{Z}_{1i}$ and $\mathbf{Z}_{2i}$ are a subsets of vectors $\mathbf{L}_{1i}(k_{(m)})$ and $\mathbf{L}_{2i}(k_{(m)})$, respectively, included in the numerator of the weights and containing time-fixed covariates of the obesity-mortality and smoking-mortality relationships measured at study entry. These stabilized weights are a ratio of 2 estimated conditional probabilities, which reduces the likelihood of an extreme weight value (36). Although both unstabilized and stabilized weights will yield unbiased effect estimates, stabilized weights are preferred because they improve statistical efficiency (25, 27). A directed acyclic graph corresponding to the weighting models for obesity and smoking is included in Web Figure 1.

The final stabilized IPTW used in the analysis was created by multiplying the stabilized IPTW for obesity [$SW^{X1}_{(t)}$] and the stabilized IPTW for smoking [$SW^{X2}_{(t)}$] (27), as follows:

$$SW(t) = SW^{X1}{}_{(t)} SW^{X2}{}_{(t)}.$$

### Step 2: joint marginal structural model

We estimated the parameters of a joint Poisson marginal structural model with a robust variance estimator. The number of days between cohort visits was included as an offset term:

$$\log\left(\Pr(Y|X_1, X_2) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 Z.\right.$$

Baseline confounders ($Z$) of the obesity-mortality and smoking-mortality relationships were also included in the final marginal structural model. Assuming no unmeasured confounding, informative censoring, structural positivity violations, or model misspecification, the estimates from this model correspond to the average causal incidence rate ratio, estimating the contrast in average outcomes between exposure groups (25, 27). This is a marginal effect with respect to the time-dependent covariates because it expresses the change in average outcome at the population level if everyone were set to one level of exposure versus if everyone were set to another level (35).

A product term for smoking and obesity was included in the model to examine the possibility of interaction. By including an interaction term in the final model, we were able to estimate 1) the incidence rate ratio (IRR) for obese nonsmokers, 2) the IRR for nonobese smokers, and 3) the IRR for obese smokers, all compared with the reference group of nonobese nonsmokers. The estimates from this model were used to calculate the relative excess risk of interaction (RERI), a measure of the amount of deviation from the expected joint effects on the additive scale (18). The RERI was calculated from the following formula:

$$\begin{aligned}\text{RERI} = {} & \exp(\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2) - \exp(\beta_1 X_1) \\ & - \exp(\beta_2 X_2) + 1.\end{aligned}$$

An RERI equal to zero indicates exact additivity, an RERI greater than zero represents superadditivity, and an RERI less than zero represents subadditivity (18). Confidence intervals for the RERI were estimated using the multivariate delta method.

## RESULTS

Demographic characteristics of the study population are presented in Table 1. There were 3,714 deaths (7.2%) over the 21 years of follow-up. The mean BMI of the study sample was 27.7 at baseline. The proportion of obese individuals in the cohort increased from 28% at the first visit to 35% at the final visit. The proportion of current smokers decreased from 27% at the first visit to 15% at the fourth visit. The prevalence of confounding variables included in the weighting models stayed relatively constant over the follow-up period.

Table 2 contains the IRRs for all-cause mortality by BMI category, comparing ever smokers (current and former smokers) with never smokers. The reference BMI group was the normal-weight BMI category (21.00–23.49). In both smokers and nonsmokers, being underweight (BMI <18.5) was associated with substantially higher mortality rate. Among never smokers, results demonstrated that both overweight and obesity were associated with a higher mortality rate relative to normal weight. Increasing BMI appears harmful for all never smokers. Conversely, among ever smokers, the mortality rate was consistently lower in overweight or obese individuals than in individuals in the normal-weight BMI group. Body weight appears to be protective against mortality for ever smokers with BMI values greater than 23.5 up to 38.5. The results for the BMI-mortality relationship stratified by smoking status demonstrate that the relationship between body weight and mortality differs for ever smokers compared with never smokers.

**Table 1.** Demographic Characteristics of the Cohort by Visit, Atherosclerosis Risk in Communities Study, 1987–1998

| Characteristic | Visit 1, % | Visit 2, % | Visit 3, % | Visit 4, % |
|---|---|---|---|---|
| Obese | 27.8 | 29.1 | 33.3 | 35.1 |
| Current smoker | 26.5 | 22.7 | 17.8 | 15.0 |
| Male sex | 45.4 | 45.2 | 44.9 | 44.8 |
| Age, years[a] | 54.2 (5.7) | 57.1 (5.7) | 60.1 (5.7) | 62.9 (5.7) |
| Black | 26.1 | 23.9 | 22.1 | 21.6 |
| Education level, years | | | | |
| 11 | 24.0 | 21.9 | 20.4 | 19.3 |
| 12–16 | 40.8 | 41.7 | 41.9 | 42.3 |
| 17–21 | 35.2 | 36.4 | 37.3 | 38.4 |
| Current drinker | 56.2 | 56.6 | 52.3 | 49.4 |
| Cardiovascular disease | 5.0 | 8.7 | 9.7 | 12.0 |
| Physical activity[a] | | | | |
| Sport | 2.4 (0.8) | | 2.5 (0.8) | |
| Leisure | 2.4 (0.6) | | 2.3 (0.6) | |
| Occupational | 2.2 (0.9) | | 1.9 (0.9) | |

[a] Values are expressed as mean (standard deviation).

**Table 2.** Incidence Rate Ratios for Mortality by Body Mass Index, Atherosclerosis Risk in Communities Study, 1987–2007

| BMI Category[a] | Ever Smokers ($n < 30,468$) | | Never Smokers ($n < 20,805$) | |
|---|---|---|---|---|
| | IRR | 95% CI | IRR | 95% CI |
| 16.00–18.49 | 1.84 | 1.38, 2.45 | 3.47 | 1.80, 6.68 |
| 18.50–20.99 | 1.39 | 1.16, 1.66 | 1.81 | 1.23, 2.66 |
| 21.00–23.49 | 1.00 | Referent | 1.00 | Referent |
| 23.50–25.99 | 0.85 | 0.75, 0.97 | 1.14 | 0.85, 1.51 |
| 26.00–28.49 | 0.77 | 0.68, 0.88 | 1.06 | 0.80, 1.41 |
| 28.50–30.99 | 0.75 | 0.65, 0.86 | 1.13 | 0.84, 1.51 |
| 31.00–33.49 | 0.84 | 0.72, 0.97 | 1.41 | 1.05, 1.90 |
| 33.50–35.99 | 0.87 | 0.72, 1.04 | 1.73 | 1.26, 2.36 |
| 36.00–38.49 | 0.77 | 0.60, 0.98 | 1.63 | 1.15, 2.30 |
| 38.50–39.99 | 0.97 | 0.74, 1.28 | 1.83 | 1.21, 2.77 |
| >41.00 | 1.09 | 0.87, 1.39 | 2.09 | 1.47, 2.96 |

Abbreviations: BMI, body mass index; CI, confidence interval; IRR, incidence rate ratio.

[a] Weight (kg)/height $(m)^2$.

Table 3 describes the results from the crude, adjusted, and weighted marginal structural models for the joint effect of obesity and smoking on mortality. We verified that the mortality rate remained relatively constant over the follow-up period by examining the visit-specific IRRs for mortality. The stabilized IPTW used in the marginal structural model had a mean of 1.00 and standard deviation of 0.08. The stabilized weights ranged from 0.35 to 1.96. Web Table 2 contains additional information on the stabilized IPTWs. Histograms and boxplots describing the stabilized IPTWs can be found in Web Figures 2 and 3. In the weighted model, the IRR for smoking among the nonobese participants was 2.00 (95% CI: 1.79, 2.24). The IRR for obesity among nonsmokers was 1.31 (95% CI: 1.13, 1.51), and the IRR for the joint effect of smoking and obesity on mortality was 1.97 (95% CI: 1.73, 2.22). The weighted model was additionally adjusted for the baseline covariates age, sex, education level, and race. Standard adjustment for both time-fixed and time-varying covariates resulted in attenuated IRRs for obesity (1.10, 95% CI: 0.97, 1.26) and obesity and smoking combined (1.65, 95% CI: 1.46, 1.85) but a slightly increased risk ratio for smoking alone (2.09, 95% CI: 1.89, 2.32). The coefficients for the product terms from the crude, adjusted, and weighted models were −0.37 (95% CI: −0.52, 0.22), −0.33 (95% CI: −0.48, −0.18), and −0.28 (95% CI: −0.45, −0.11), respectively. The product terms for all 3 models suggested a negative interaction on the multiplicative scale ($P < 0.001$). The RERI estimates were negative for all 3 models, indicating that the interaction between obesity and ever smoking is subadditive.

## DISCUSSION

Using prospectively collected data from the ARIC Study, we estimated the joint effects of smoking and obesity on all-cause mortality. Smoking and obesity were associated with an increased risk of mortality, both independently and jointly. We found evidence of a significant negative interaction between the 2 exposures on both the additive and multiplicative scales.

The results of the stratified analyses demonstrate that the relationship between body weight and mortality rate differs across strata of smoking status. There is minimal overlap of the confidence intervals of ever smokers and never smokers. The present stratified analysis provides support for the inclusion of an obesity-smoking product term in the main analytic model. It is often recommended that authors stratify on smoking status in analyses of body weight and mortality to completely remove the possibility of confounding by smoking status (4, 37, 38).

However, the stratified analyses that we have presented are intended to caution authors against restricting entry to the analytic cohort based on smoking status. Our results demonstrate that presenting results from only 1 stratum of smoking status rovides a distorted view of the total effect of body weight on mortality. For example, Calle et al. (37) found obese men and women who were healthy never smokers to be at a higher risk of all-cause mortality than obese current or former smokers with a history of chronic disease (heart disease, stroke,

**Table 3.** Incidence Rate Ratios for the Joint Effects of Obesity and Smoking on Mortality Among Men and Women, Atherosclerosis Risk in Communities Study, 1987–2007

| Smoking Status and Obesity Category | Crude Model | | Adjusted Model | | Weighted Model | |
|---|---|---|---|---|---|---|
| | IRR | 95% CI | IRR | 95% CI | IRR | 95% CI |
| Never smoker | | | | | | |
| Nonobese | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Obese | 1.50 | 1.32, 1.70 | 1.10 | 0.97, 1.26 | 1.31 | 1.13, 1.51 |
| Smoker | | | | | | |
| Nonobese | 2.23 | 2.02, 2.45 | 2.09 | 1.89, 2.32 | 2.00 | 1.79, 2.24 |
| Obese | 2.31 | 2.05, 2.56 | 1.65 | 1.46, 1.85 | 1.97 | 1.73, 2.22 |
| *P* value for product term | <0.001 | | <0.001 | | <0.001 | |
| RERI | −0.42 | −0.68, −0.16 | −0.54 | −0.76, −0.31 | −0.34 | −0.60, −0.07 |

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; RERI, relative excess risk of interaction.

cancer, or respiratory disease). Studies that only include never smokers also have poor external validity; the results cannot be generalized to the entire population because it comprises current, former, and never smokers.

The results from the joint marginal structural model provide estimates of the effects of obesity and smoking while accounting for time-varying confounding by CVD and other covariates using IPTWs. As expected, results indicate that both obesity and smoking are associated with a higher mortality rate. These results are consistent with those from previous studies and meta-analyses in which the harmful impact of obesity and smoking has been demonstrated (14, 15, 39). Compared with estimates from the standard adjusted model, estimates from the marginal structural model were 19% higher for obesity ((1.31–1.10)/1.10 = 0.191) and for the joint effect of obesity and smoking ((1.97–1.65)/1.65 = 0.194). It is possible that this result could be attributed to the fact that some of the variables in the standard adjusted model were affected by obesity and shared common causes with the outcome (e.g., CVD) (12, 23, 27). The attenuated results from the adjusted model might also be due to selection bias induced by adjustment of time-varying confounders affected by prior exposure (40).

We also found evidence of a significant interaction on both the additive and multiplicative scales. The Wald *P* values for the obesity-smoking product term were less than 0.001 in all 3 models, demonstrating a departure from exact multiplicativity (20). In the weighted model, the observed joint effect of obesity and smoking was 1.97, whereas the expected product of obesity and smoking under a model of exact multiplicativity would be 2.62. This result differs from that of a previously published pooled analysis of data from 57 prospective studies, in which no evidence of a multiplicative interaction between smoking and obesity was reported (15). There are a number of possible reasons for these differing results. In their pooled analyses, the Diverse Studies in Populations Collaborative Group excluded individuals with CVD ($n < 54{,}347$) and stroke ($n < 4{,}349$) and excluded all deaths in the first 5 years of follow-up to minimize the possibility of confounding due to pre-existing illness (15).

The RERI value for the weighted model was negative, indicating subadditive interaction. This result is consistent with the model of competitive antagonism (41). Competitive antagonism occurs when both exposures have a non-null association with the outcome, but because the exposures effectively compete to cause the outcome, the effect estimate for the exposures together is less than the sum of either exposure considered independently (19, 41, 42). Weinberg (43) used a simple analogy involving duck hunters to explain a situation in which 2 independent exposures compete to cause 1 outcome. Her example demonstrates that the existence of 2 independent exposures does not necessarily lead to exact additivity, because even independent exposures can create joint effects that are mutually antagonistic through competition (43).

A complex issue in the study of obesity and mortality is how to define obesity. We defined obesity as a BMI greater than 30, which is in line with the guidelines of the World Health Organization (8). The definition of obesity as a binary variable based on BMI in the main analyses represents a limitation of the present study. However, the fact that BMI was calculated based on measured height and weight is an important strength. Multiple definitions of adiposity exist in the literature (waist circumference, body fat percentage), and though each definition has its own set of limitations, they all are highly correlated with each other (44). Additionally, authors have raised concerns over the validity of the use of obesity as an exposure in causal analyses (45). It is difficult to interpret the causal effect of an ill-defined exposure like obesity because there is no specified intervention to set obesity or BMI (45). The results of the present study do not apply to any single particular determinant of obesity (i.e., becoming obese due to poor diet and inactivity versus obesity due to genetic or hormonal causes). Another limitation of our results is the use of self-reported smoking status, which might have introduced some misclassification bias into the results. Estimates of smoking prevalence based on self-report are generally lower than estimates based on objective measures, such as cotinine concentration, but only by a small magnitude (46). Reports have indicated that smoking prevalence is 0.3% lower in Canada and 0.6% lower in the United States when based on self-report versus objective measures (46).

There are several important assumptions that must be met to obtain valid estimates from a marginal structural model. We assume that the model was correctly specified, that there was no unmeasured confounding (exchangeability assumption), and that the positivity assumption was satisfied (25). The exchangeability assumption implies that the measured covariates included in the analysis are sufficient to control for confounding bias. We assume that conditioning on the baseline and time-varying covariates included in our analyses is sufficient to control for important confounders of both the obesity-mortality and smoking-mortality relationships. Additionally, as the ARIC Study has a very low proportion of losses to follow-up (<10%), study attrition was assumed to be noninformative for the purpose of the present analysis (47). If informative censoring were a substantial concern, fitting inverse probability of censoring weights is 1 possible option to obtain more valid results.

In summary, our results provide evidence that smoking and obesity are harmful exposures, both independently and jointly. The interdependence of the effects of smoking and obesity on mortality implies that the influence of smoking in the population depends on the presence or absence of obesity, and likewise that the influence of obesity in the population depends on the presence or absence of smoking (20, 48). The stratified models demonstrate the hazards of excluding current and former smokers from analyses of obesity and mortality. In addition, the differing estimates from the standard adjusted model and the marginal structural model provide support for the use of methods specifically designed for time-varying exposures and time-varying confounders in future research.

## ACKNOWLEDGMENTS

Author affiliations: Department of Epidemiology, Biostatistics, and Occupational Health, Faculty of Medicine, McGill University, Montreal, Quebec, Canada (Hailey R. Banack, Jay S. Kaufman).

H.R.B. was supported by a doctoral research award from the Fonds de la Recherche en Sante du Quebec. J.S.K. was supported by the Canada Research Chair program.

This paper was awarded the Tyroler Student Prize Paper Award at the 48th annual meeting of the Society for Epidemiologic Research, June 16–19, 2015, Denver, Colorado.

Conflict of interest: none declared.

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