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Accounting for bias due to selective attrition: The example of smoking and cognitive decline

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Abstract

Background—Selective attrition may introduce bias into analyses of the determinants of cognitive decline. This is a concern especially for risk factors, such as smoking, that strongly influence mortality and drop-out. Using inverse-probability-of-attrition weights (IPAWs), we examined the influence of selective attrition on the estimated association of current smoking (versus never smoking) with cognitive decline.

Methods—Chicago Health and Aging Project participants (n=3,713), aged 65–109, who were current smokers or never-smokers underwent cognitive assessments up to 5 times at 3-year intervals. We used pooled logistic regression to fit predictive models of attrition due to death or study drop-out across the follow-up waves. With these models, we computed inverse-probability-of-attrition weights for each observation. We fit unweighted and weighted, multivariable-adjusted generalized-estimating-equation models, contrasting rates of change in cognitive scores in current versus never-smokers. Estimates are expressed as rates of change in z-score per decade.

Results—Over the 12 years of follow-up, smokers had higher mortality than never-smokers (hazard ratio= 1.93 [95% confidence interval= 1.67 to 2.23]). Higher previous cognitive score was associated with increased likelihood of survival and continued participation. In unweighted analyses, current smokers' cognitive scores declined 0.11 standard units per decade more rapidly than never-smokers' (95% CI= −0.20 to −0.02). Weighting to account for attrition yielded estimates that were 56%–86% larger, with smokers' estimated 10-year rate of decline up to 0.20 units faster than never smokers' (95% CI= −0.36 to −0.04).

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Conclusions—Estimates of smoking's effects on cognitive decline may be underestimated due to differential attrition. Analyses that weight for the inverse probability of attrition help - for this attrition.

Decline in cognitive function is a common occurrence with aging and the hallmark manifestation of dementia.[1–2] Few modifiable risk factors for cognitive decline and dementia have been identified.[3] This may be due in part to the particular methodological challenges that affect longitudinal studies of cognitive aging and other late-life health outcomes. One important challenge is selection bias from selective mortality or other forms of attrition that occur after study enrollment. These selection processes will bias estimates of a risk factor's association with an outcome if selection is influenced by both the risk factor and the outcome or, alternatively, by determinants of the risk factor and the outcome (Figure A).[4] Although selection bias is a concern in all longitudinal studies of aging-related outcomes, it is especially relevant in studies of cognitive decline, because impaired cognition strongly predicts morbidity,[5–8] mortality,[9–10] and attrition after study enrollment.[11–13] Studies of risk factors that are themselves associated with substantial morbidity and mortality, such as smoking, are especially vulnerable to bias due to selective attrition (Figure B).[4, 14]

Smoking is thought to increase risk of cognitive decline and dementia in older age, mainly through its well-established vascular effects, although some data suggest potential benefits of nicotine.[15–17] Findings from previous longitudinal studies of smoking and cognitive decline have been mixed.[15, 18–26] As is typical in longitudinal studies of older adults, many of these studies over the course of follow-up lost a substantial proportion of their baseline populations—often more than 20%—to attrition. Among five studies reporting on attrition in relation to smoking and cognition,[18, 20, 24–26] three reported that attrition was associated with smoking, cognition or both.[18, 24, 26] Given the strong impact of smoking on morbidity and mortality—smokers have 2–3 times the mortality rate of never-smokers[27]—and its overall association with study attrition,[13] previous studies may have underestimated the adverse relation of smoking to cognitive decline. To our knowledge, no prior studies have quantified and corrected for the potential influence of selective attrition on the estimated relation of smoking to cognitive decline.

Until recently, epidemiologists have had few accessible tools for addressing differential attrition.[28] A common approach in regression models of the association between an exposure and outcome of interest is to include terms for factors that predict attrition. This approach is unsatisfactory, because some predictors may be influenced by the exposure, and adjustment for such post-exposure variables is generally known to bias effect estimates.[4] For example, although prior cognitive function is a strong predictor of both attrition and future cognitive decline, adjusting for baseline or intermediate measurements of cognitive function could produce estimates that are substantially inflated if the exposure is associated with baseline cognitive score (eFigure 1, http://links.lww.com).[29] Robins, Hernán, Cole and others[30–31] have developed an inverse-probability-weighting approach to "correct" analyses for differential attrition, based on observed covariate history. This approach allows for use of information on potential intermediates and previous cognitive function while avoiding the pitfalls of conventional adjustment for these variables.

Inverse-probability-weighting methods should be particularly relevant to longitudinal studies of aging-related health outcomes, given the high rates of attrition that are common in this research. We used inverse-probability-of-attrition weighting (IPAW) to examine the influence of attrition-related selection bias on the estimated association between smoking and cognitive decline. We first developed models of the probability of continuing in the study—i.e., remaining alive and not lost to follow-up—and from these models, we

computed predicted probabilities of continuation for each observation. For greater specificity, we distinguished between attrition due to mortality and attrition due to other causes (study drop-out), which is often related to frail health.[12–13] We then used these probabilities to compute analytical weights that are in inverse proportion to the probability of remaining alive and in the study. Observations with characteristics associated with a lower probability of continuation, e.g., physical frailty, were assigned larger weights, thereby "compensating" for the underrepresentation of these types of observations in the observed follow-up data. We then applied the weights to our analyses of the association between smoking and cognitive decline.

We hypothesized that, compared with never-smokers, persons who were current smokers at baseline would experience faster cognitive decline during 12 years of follow-up. Further, we anticipated that the association between current smoking and cognitive change would be larger after accounting for selective mortality and non-death-related drop-out. Because the evaluation of former smoking and cognitive decline entails additional complexities (e.g., accounting for determinants of cessation), we assessed only the contrast between current and never smoking in this analysis.

METHODS

Study population

We conducted our analyses using data from participants in the ongoing Chicago Health and Aging Project.[32] The first wave of recruitment began in 1993 with a door-to-door census of residents living in three geographically defined neighborhoods on the south side of Chicago. Of 8501 adults aged 65 years and older who were identified in this recruitment wave, 1655 declined to participate, 439 died and 249 moved before an in-person assessment could be conducted. This left 6158 participants in the cohort, 18 of whom did not report their smoking status. We focused our analyses on the 3768 participants who, upon enrollment, reported that they were current smokers or that they had never smoked. Of these participants, 55 (1.5%) were missing data on key covariates used for the computation of weights or for the analytical regression models, leaving 3713 persons (891 smokers and 2822 never smokers) for our primary analyses. Participants undergo in-home assessments every three years, and those in our analyses contributed 10,096 observations over five assessment cycles. Information on time-varying covariates was missing for 11 observations, leaving 10,085 observations for our analyses. Some participants returned to the study after skipping a cycle (279, 9.5% of those censored); we classified these participants as permanently censored upon their first missed cycle, effectively treating drop-out as permanent. This permitted fewer assumptions in estimating inverse-probability-of-attrition (IPA) weights (see: Attrition weight estimation, below).

Smoking assessment

At their baseline interviews, participants were asked: "Do you smoke cigarettes now?," and "Did you ever smoke cigarettes regularly?". We defined never-smokers as participants who responded "no" to both questions. We defined current smokers as participants who responded affirmatively to the first question. We used baseline smoking status as the exposure of interest, although over the course of follow-up, a small fraction of never smokers (0.7%) reported smoking, and about 35% of current smokers reported quitting.

Cognitive assessment

Participants underwent cognitive assessments at each in-home visit. This assessment consisted of four tests of cognitive function: immediate and delayed recall of 12 ideas in the East Boston story, measures of episodic memory[33]; the oral version of the Symbol Digit

Modalities Test, which measures perceptual speed by giving the participants 90 seconds to identify as many digit-symbol matches as possible [34]; and the Mini-Mental State Examination a measure of global cognition.[35] Because the four individual measures are highly correlated, we computed a composite measure of global cognition by first converting the raw scores from each test to *z* scores, using the baseline mean and standard deviation (SD) in the population, and then averaging the *z* scores.[36]

Covariate assessment

We used information on both baseline and time-updated covariates. Baseline covariates included self-reported race and ethnicity (assessed with the US census question on race and ethnicity and categorized as African-American or non-Hispanic white) and number of years of completed formal schooling. Time-updated covariates (assessed at baseline and re-assessed at each interview) were all self-reported via structured interview and included usual alcohol intake; self-rated health; diagnosis of heart attack, stroke, diabetes, and high blood pressure; physical disability via the Nagi score[37] (ability to perform basic upper and lower extremity functions, where a lower score indicates greater disability); and a composite measure of social networks, where a higher score indicates a more highly populated network.[38]

Analytic approach

Attrition weight estimation—To account for potentially informative attrition in our analyses, we estimated weights to apply to each observation in models of smoking and cognitive decline. For each wave of visits contributing to our analysis, the weights were based on the inverse of the wave-specific probability of being observed at that wave, and thus of being alive and uncensored at that wave. The intuition behind these weights is that respondents with characteristics similar to the observations missing due to attrition are up-weighted in the analyses of smoking and cognitive decline, so as to represent their original contribution as well as their missing contributions. Because determinants of death may differ from determinants of study drop-out for other reasons, we separately modeled attrition due to death and attrition by other causes.

For each of the two sources of attrition, we first developed separate models of not being censored over the course of follow-up.[31] For each planned assessment, let C_{ikr} indicate whether person *i* is no longer in the study by wave *k* for reason *r*, where *r* is either death (*r*=1) or loss to follow-up (*r*=2). Each weight represents the reciprocal of individual *i*'s probability of remaining both alive and in the study at wave *k*. We classified a death as occurring at wave *k* if the participant died between waves *k−1* and *k*, so that for such an individual, $C_{ik1} - C_{i(k-1)1}=1$.

For each wave of follow-up, we modeled and estimated via pooled logistic regression[30] the probability of being alive in that wave, conditional on remaining alive and uncensored in the previous wave. We separately modeled the probability that such a living and previously uncensored participant remained uncensored. To specify the models, we defined a set of variables *L*, some of which varied over time, we thought likely to influence death or censoring and also affect cognitive function: age, race (African American versus white), sex (male versus female), education (0–8 years, 9–12 years [referent], 13–16 years, 17–30 years), alcohol consumption at the previous visit (none [referent], up to 1 drink/day, >1 drink/day), social network score at the previous visit, cognitive activity at the previous visit, disability score at the previous visit, self-rated health at the previous visit (per unit worsening in rating), chronic cardiovascular conditions, diabetes, global cognitive score at the previous visit, and smoking status (current versus never). We estimated models that included as predictors: the baseline time-constant covariates in *L*, smoking status (X_i), and

the most recent prior values of the time-varying covariates ($L_{i(k-1)}$), including past measurements of cognitive function. We explored weighting models including additional variables representing the history of the time-varying covariates (e.g., $\bar{L}_{i(k-1)} = (L_{i0}, \ldots, L_{i(k-1)})$), but these covariates did not predict censorship or death independently of $L_{i(k-1)}$, and so were dropped from the model. Together, these models were used to calculate the cumulative probability of surviving up to a given follow-up wave and of participating in the assessment at that wave. Weights were applied at the level of observations within individuals, such that for each person-wave contribution to our analysis at wave j, the weight was the inverse of the probability of the conjunction of these two events. These weights can be obtained by the simple product formula:

$$wt_{ij}=\prod_{k=0}^{j}\frac{1}{\widehat{\Pr}[C_{ik1}=0 \mid C_{i(k-1)1}=0, C_{i(k-1)2}=0, X_i, \bar{L}_{i(k-1)}]\widehat{\Pr}[C_{ik2}=0 \mid C_{i(k-1)2}=0, C_{ik1}=0, X_i, \bar{L}_{i(k-1)}]} \quad [1]$$

Implicit to the models we estimated is the Markov assumption that an individual's probability of contributing to the analysis at wave k, and thus of being alive and uncensored at wave k, depends on his or her history of the collection of time-varying covariates $\bar{L}_{i(k-1)}$ only through its most recent value $L_{i(k-1)}$. Such an assumption may be relaxed by incorporating additional lagged covariate values, or a user-specified function of such values (e.g., $\text{cum}(\bar{L}_{i(k-1)}) = L_{i0} + \ldots + L_{i(k-1)}$) as potential predictors in the weight models. To optimize the fit of our attrition models, we explored several functional forms of time, including as a continuous variable and as a set of cycle indicators. We also evaluated several potentially important cross-products, including cognitive score with smoking and time with cognitive score, smoking and age. We used the same set of covariates in the death and drop-out models, selecting the final covariate set (shown in Table 1), as the set that contained variables with modest-to-strong associations with attrition and for which there were minimal missing data.

We present model-based 95% confidence intervals (CIs) for the hazard ratios (HRs) relating each covariate to censoring, under the assumption that the pooled logistic regressions correctly model the hazard of continuation in the study given the entire history of covariates.[39] We used the Bayesian information criterion as an indicator of global goodness of fit. To describe each models' ability to discriminate those who were from those who were not censored, we computed the discordance percentage and the *c*-statistic. We used the Hosmer-Lemeshow test to describe each model's calibration across a range of observed risks.[40–41]

From the combination of the two cause-specific models, we computed IPA weights according to Equation 1. These are also called non-stabilized weights because, as the reciprocal of a probability, they are guaranteed to be greater than 1 for contributing observations, and may potentially be very large for a person with a small probability of staying alive and uncensored. As a potential remedy, we also computed wave-specific stabilized IPA weights by multiplying the individual's non-stabilized weight at that wave by the conditional probability of remaining alive and uncensored up to that wave given a subset of baseline covariates V_i (a subset of L_{i0}) and smoking status. Thus, as the ratio of two probabilities, we generally expect this stabilization to reduce the undue influence of a highly variable non-stabilized weight, and therefore to result in confidence intervals that are narrower than those in analyses using non-stabilized, potentially highly variable weights.

Under our assumptions, both non-stabilized and stabilized weights give unbiased effect estimates, provided V_i is entered into the regression model relating smoking to cognitive function over time, and thus effect estimates conditional on V_i are reported in both analyses.[42] Applying stabilized weights does not adjust for the covariates V_i that were used in the estimation of the numerator of the model. It is instead necessary to include the V_i as regression covariates in the primary analytic model. The stabilized weight for an individual's contribution to wave j is thus given by:

$$stwt_{ij}=\prod_{k=0}^{j}\frac{\widehat{\Pr}[C_{ik1}=0\,|\,C_{i(k-1)1}=0, C_{i(k-1)2}=0, X_i, V_i]\widehat{\Pr}[C_{ik2}=0\,|\,C_{i(k-1)2}=0, C_{ik1}=0, X_i, V_i]}{\widehat{\Pr}[C_{ik1}=0\,|\,C_{i(k-1)1}=0, C_{i(k-1)2}=0, X_i, \overline{L}_{i(k-1)}]\widehat{\Pr}[C_{ik2}=0\,|\,C_{i(k-1)2}=0, C_{ik1}=0, X_i, \overline{L}_{i(k-1)}]} \quad [2]$$

Similar to the denominators, we obtained estimates of the numerators via pooled logistic regression analysis in which V consisted of baseline age, sex, race, education, baseline alcohol consumption, and baseline smoking status.

Several assumptions underlie the IPA weight estimation. First, we assume that the attrition process follows an ignorability assumption that states that the conditional probability of remaining alive and in the study in the next wave, given that one has survived and remained uncensored up to the current wave, does not further depend on one's future cognitive function, given past observed covariates and cognitive measurements.[43] In addition, throughout we make the standard positivity assumption[43] that for any given wave of the study, and any possible realization of the covariates, smoking status and past cognitive function up to the current wave, there is a positive probability that an individual with that observed history remains alive and in the study in the next wave, given that he or she is alive and uncensored in the current wave.

It is important to note that had attrition been jointly independent of time-varying correlates of cognitive function, then a standard unweighted GEE analysis would have produced valid statistical inferences about the effects of smoking on cognitive function. Remarkably, under the above assumptions of the attrition process's ignorability and positivity, given the observed time-varying correlates of cognitive function, our analytic approach corrects for selection bias due to attrition, to the extent that it recovers the effect of smoking on cognitive function (possibly conditional on a subset of baseline variables) one would have obtained using a standard GEE analysis, had attrition been jointly independent of all time-varying predictors of cognitive function (possibly conditional on a subset of variables).

Analyses of smoking and cognitive decline—We evaluated the association between current smoking at baseline and cognitive decline using unweighted and IPA-weighted generalized estimating equations (GEE) regression models,[39] with working exchangeable correlation matrix, in which we estimated the difference between current and never smokers in rates of decline in global cognitive score. In all models, we regressed the global score on the set of predictors V_i, by including main effect terms for age, sex, race, education (4 categories, described previously), baseline alcohol intake (3 categories, described previously), smoking status, time (years, continuous), and the cross-products of each covariate with time. These analyses included data from all eligible person-wave contributions from participants who had a baseline cognitive score.

For comparison, we fitted unweighted models as well as models that weighted observations using the two sets of IPA-weighted estimates (non-stabilized weights and stabilized weights). Our primary hypothesis on the relation of smoking to cognitive decline was assessed with the cross-product between smoking and time, that is, the estimated difference between current and never smokers in their rates of cognitive decline. To make the estimates easier to interpret, we multiplied all estimated annual changes and differences in annual change by 10, obtaining estimates of change and differences in change over 10 years. To place these effect estimates in context, we compared them with the average rate of cognitive decline among never smokers, represented in the main effect term for time, and leaving all other covariates at their referent levels. Supposing that the rate of cognitive decline among never smokers represents "smoking-free cognitive aging," we then estimated "excess years of cognitive aging" (over a 10-year interval) among current smokers by dividing the difference in 10-year change by the annual rate of change among never smokers.

Bootstrapping—Because standard errors from conventional IPA-weighted GEE models can be conservative,[39] we generated bootstrap parameter estimates and standard errors.[44] Using this approach, we repeated the entire set of analyses—from weight estimation to the estimation of the association of smoking with cognitive decline—on each of 1000 bootstrap samples. A given bootstrap estimate of the difference in rate of cognitive change among current smokers versus never smokers was the mean of the 1000 data sets in which individuals' observed histories were sampled with replacement from the original data set. We used the bootstrap standard errors to compute 95% confidence intervals (CIs) for the difference in rate of cognitive change.

Using the bootstrap samples, we formally compared each weighted estimate of the association between smoking and cognitive decline with its unweighted counterpart using a Hausman-type specification test, which tests the null hypothesis that the unweighted estimate is consistent with the weighted estimate (the "consistent" estimator).[45–46] We also compared the estimates as rates of cognitive decline among current smokers as a percentage increase over the rate of decline among never smokers, where the latter rate is the estimate for time.

RESULTS

Of the 3713 participants who had baseline cognitive assessments and nonmissing data on key covariates, 2634 (71%) remained in the sample at the first follow-up, 1722 (46%) remained at the second follow-up, 1274 (34%) remained at the third follow-up, and 756 (20%) remained at the fourth follow-up. Mortality accounted for most (68%) of the attrition.

The variables included in our final censoring models are listed in Table 1. In these multivariable-adjusted analyses, the current smoker group, relative to never smokers, experienced substantially increased mortality risk (HR, 1.93; 95% CI, 1.67–2.23), but no difference in other-cause attrition (Table 1). By contrast, higher cognitive score was associated with markedly reduced risk of both mortality and other-cause attrition. Other strong predictors of mortality included older age, being male, white race, greater degree of disability at the previous visit, worse self-rated health at the previous visit, and diabetes at baseline. Those with the lowest level of education had reduced mortality, while those with the highest level of education were least likely to drop out. The estimates in the predictive model for mortality were markedly different in magnitude from those in the predictive model for other-cause attrition.

Inverse probability of attrition weights

Fit statistics for the weighting models and the distribution of the IPA weights are shown in Table 2. The models of non-censoring generally fit the data well, with good to excellent discrimination between those who died or dropped out and those who continued in the study. The models were also well-calibrated in that they generated predicted risks of attrition that generally matched observed risks, although they tended to perform somewhat more poorly at the highest decile of risk (eAppendix: eFigure 2). Weights generated by the model for censoring due to drop-out were fairly narrowly distributed, reflecting, in part, that we were unable to identify strong predictors of this type of attrition to the extent that we did for death-related censoring.

Smoking and cognitive decline

In unweighted analyses, the estimated rate of decline on the cognitive tests among never smokers was 0.53 points (in standard units) over 10 years (Table 3). Current smokers' estimated rate of decline was 0.11 points worse (95% confidence interval [CI], −0.20 to −0.02), on average, resulting in an average rate of decline of 0.64 points over 10 years. With the application of the nonstabilized IPCWs, this difference in rates of cognitive decline increased in magnitude by 56% to −0.17 points (95% CI, −0.31 to −0.02). When we applied the stabilized weights, the difference in rates increased further to −0.20 points over 10 years (95% CI, −0.36 to −0.04), 86% larger than the unweighted estimate. Estimates derived from the application of stabilized weights were slightly more efficient—indicated by the standard error as a fraction of the effect estimate—than those derived from the application of nonstabilized weights. Although the weighted difference estimates were substantially larger than the unweighted estimates, the CIs overlapped substantially, and the Hausman tests did not indicate that the unweighted estimate was significantly different from either the estimates from the analyses using non-stabilized (P=0.3) or stabilized weights (P=0.2).

Notably, weighted analyses also yielded larger estimates of the average rate of change in cognitive score among never smokers, likely because time in the study also predicted attrition. Nonetheless, the correction for attrition had a slightly greater impact on the estimates for current smokers. For example, considering the reference group (75-year-old females with 9–12 years of education and no alcohol use), the unweighted results suggested that smokers' decline over 10 years would be as severe as the decline experienced by a non-smoker over 12.1 years. The weighted results suggested that, over 10 years, the smoker would decline as much as a non-smoker would decline over 12.5 years.

DISCUSSION

In this well-characterized longitudinal study of aging, both smoking and cognitive function were strong predictors of attrition after enrollment. Current smoking was associated with significantly faster rates of cognitive decline in all analyses. The application of IPAWs to these analyses to account for differential attrition patterns yielded estimates that were 56%–86% larger than unweighted estimates. In weighted analyses, estimates of cognitive decline among never smokers increased as well, yet weighting had an even larger impact on estimates of decline among smokers. The Hausman test did not reject at conventional thresholds of statistical significance, indicating we cannot rule out the possibility that the difference in estimates is due to chance variation. Yet the difference in point estimates of the magnitude observed may be considered substantively important. Imprecision in either the weighted or unweighted estimator reduce the statistical power of the Hausman test, so such tests may have insufficient power to reject the null even when point estimates differ substantially.

Differential selection processes distort the joint distribution of smoking and cognitive decline in a study population if cognitive change also influences selection, or if there are other uncontrolled factors that influence both selection and cognitive change. For example, given the lethality of cigarette smoking, smokers who survive may have other beneficial characteristics (e.g., genetic background) that protect them from cognitive decline (eAppendix, eFigure 3). This selection induces an association between the risk factor and cognitive decline, even if there is no true effect. Analyses of the risk factor and cognitive decline will be biased, often toward—but possibly beyond—the null. Our findings may offer some insight into the previously mentioned mixed findings in previous longitudinal studies of smoking and cognitive decline.[15, 19–25] In light of the findings in our own study, it seems plausible that many of these studies may have underestimated the adverse relation of smoking to cognitive decline. It bears mentioning that the use of more sophisticated measures of cognitive aging—such as more elaborate cognitive testing batteries, imaging, and clinical diagnoses–will not resolve biases stemming from differential attrition.

Our study has some limitations. While we took a detailed approach toward addressing death and drop-out after study enrollment, we did not address attrition prior to enrollment (also known as left truncation). In a study that begins when participants have already reached advanced age, mortality and debilitating morbidity related to smoking and cognitive function have occurred prior to study enrollment, leaving a study population that is already differentially selected. This possibility was highlighted by work complementary to ours, a meta-analysis of cohort studies of smoking and dementia which found that relative risks tended to be smaller—sometimes less than 1.0—for studies whose participants were enrolled at older ages.[47] Left truncation processes that generated our study's population of age-eligible participants may have resulted in conservative estimates of smoking's association with cognitive decline, even from the IPA-weighted analyses. Indeed, in unweighted analyses stratified by age, we observed associations between smoking and cognitive decline that diminished in the oldest age group (eAppendix, eTable 1).

Many individuals who smoked at baseline quit during follow-up, so some people we classified as "smokers" were in fact "former smokers" at the time of later cognitive assessments. If cessation is more likely with poor cognition, then, in general, using baseline smoking status remediates this source of bias. The same tools of inverse probability weighting that we have used here to handle attrition could in principal also be applied to account for time-varying smoking status.[30–31] This extension requires a separate model for the determinants of quitting (or initiating) smoking. Our study also did not evaluate the effect of former smoking at baseline on cognitive decline, because such an evaluation entails far more complex methodological considerations around factors influencing cessation, including those that may be causal intermediates. Our IPA-weighted results were premised on the assumption that, conditional on the covariates, individuals who remained in the study and those who did not were "exchangeable" with respect to cognitive outcomes, and, further, that the censoring models were correctly specified. While the first assumption is not empirically testable, goodness-of-fit tests indicated that our models fit the data adequately. In fact, when we used IPAWs based on attrition models composed of other variables (e.g., time instead of cycle, history of hypertension, cognitive activity, previous cognitive change), we obtained IPA-weighted estimates that were consistent with those we reported here (examples in eAppendix, eTable 2) .

Our study also has several important strengths. The CHAP study has complete data on many variables for most participants, which permitted us to explore a wide range of predictors for our censoring models, and ultimately, to develop models that included many strong censoring predictors. In particular, the censoring models allowed us to consider important information on variables that we would otherwise avoid including in models of smoking and

cognitive decline, specifically, previous cognitive function and potential intermediate factors such as self-rated health and disability. Finally, this study represents one of the first applications of inverse probability weighting to analyses of risk factors for cognitive decline and has demonstrated that accounting for differential attrition may unveil associations that are larger than those obtained from unweighted analyses, particularly when the risk factor of interest is strongly related to mortality.

It is likely that differential selection may influence the findings on other risk factors for cognitive aging, and, more generally, other aging-related outcomes. Risk factors for mortality such as smoking, elevated blood pressure, hypercholesterolemia, diabetes, and socioeconomic position have often been observed to have diminished impact in "older older" adults as compared with "younger older" adults.[48–50] This pattern appears in findings on risk factors of dementia, too, whereby a factor that predicts dementia risk among "younger older" cohorts more weakly predicts dementia risk—or fails to predict dementia risk at all—among "oldest old" adults.[47, 51–55] While some age-dependent patterns have a hypothesized biologic basis,[55–57] determining which patterns are related to selection and to what degree has critical implications for extrapolating study findings to clinical practice and health policy. This study makes an advance in that direction by addressing the influence of differential attrition on the estimated relation between smoking and cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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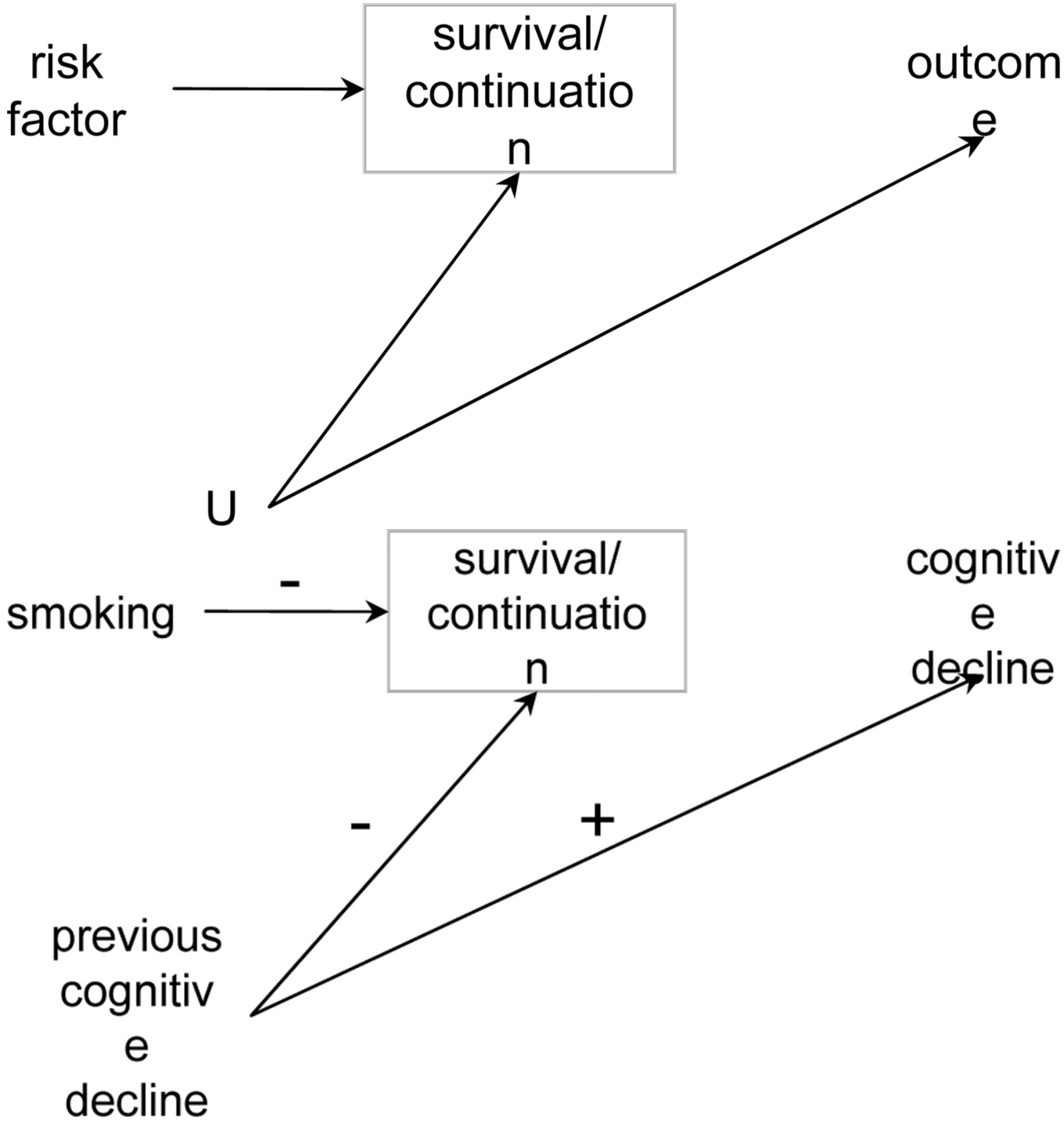

Figure 1.

a. A. Directed acyclic graph (DAG) depicting general causal structure underlying attrition-related selection bias. In this DAG, the risk factor of interest directly influences post-enrollment survival or continuation in the study. The outcome is associated with survival or continuation through its relation to the unmeasured factor, U (e.g., a genetic variant that results in more efficient detoxification). Survival/continuation is a collider on the path between the risk factor and the outcome. Conventional unweighted analyses of

follow-up data are restricted to the group of participants who survive and continue in the study, a form of conditioning indicated by the box around “survival/continuation.” As shown in the DAG, this restriction can induce a spurious association between the risk factor and U, and thus between the risk factor and the outcome, even in the absence of a true causal relation between the two.

B. Directed acyclic graph (DAG) depicting causal structure underlying attrition-related selection bias in the relation of smoking to cognitive decline. This DAG shows that smoking decreases post-enrollment survival or continuation. Cognitive decline over the course of the study is inversely related to survival or continuation through its association with previous cognitive decline. Conventional unweighted analyses of follow-up data are restricted to the group of participants who survive and continue in the study, a form of conditioning indicated by the box around “survival/continuation.” Continuing survivors who smoke will have had less than expected previous cognitive decline, and the restriction to continuing survivors can induce a downward bias in the association between smoking and cognitive decline, resulting in underestimates of harm or overestimates of protection. For an introduction to DAGs, see Glymour MM, Greenland S. Chapter 12: Causal diagrams. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology, Third Edition*. New York: Wolters Kluwer, 2008: 183–209.

Table 1

Baseline characteristics of the study population, and adjusted hazard ratio (HR) and (95% confidence interval) of attrition over five study cycles, estimated from models of continuation.

		Adjusted hazard ratio (95% CI)			
	Mean (SD) or % in population at baseline	Attrition due to death[a]		Attrition due to other causes[b]	
Current smoking, baseline (ref: never)	24%	1.93	(1.67 to 2.23)	0.85	(0.71 to 1.03)
Global cognitive score, per SD, prior	−0.05 (0.91)	0.62	(0.58 to 0.66)	0.78	(0.70 to 0.87)
Age, per year, baseline	75.2 (6.6)	1.07	(1.06 to 1.09)	0.98	(0.97 to 1.00)
Male (ref: Female)	31%	1.81	(1.58 to 2.07)	0.94	(0.81 to 1.10)
African-American (ref: white)	62%	0.78	(0.68 to 0.89)	0.75	(0.63 to 0.89)
Education (years) (ref: 10–12 years)					
0–8	20%	0.83	(0.71 to 0.97)	0.97	(0.78 to 1.20)
13–16	27%	1.11	(0.96 to 1.28)	0.94	(0.79 to 1.12)
17–30	7.7%	1.07	(0.85 to 1.34)	0.67	(0.50 to 0.89)
Social network score[c], per SD, prior	7.6 (6.6)	1.00	(0.99 to 1.01)	0.99	(0.98 to 1.00)
Alcohol intake, drinks/day, prior (ref: none)					
>0 to 1	21%	0.81	(0.70 to 0.94)	1.11	(0.92 to 1.33)
2+	6.2%	1.18	(0.88 to 1.57)	1.10	(0.75 to 1.60)
Nagi disability score[d], per unit, prior	15.8 (5.0)	0.93	(0.91 to 0.94)	1.01	(1.00 to 1.03)
Self-rated health[e], per unit, prior	2.1 (0.9)	1.29	(1.20 to 1.39)	1.02	(0.92 to 1.13)
History of diabetes at baseline	6.5%	1.72	(1.37 to 2.15)	0.77	(0.54 to 1.09)
Previous cycle was the:					
second (first follow-up)	-	1.23	(1.07 to 1.42)	1.35	(1.15 to 1.59)
third (second follow-up)	-	1.25	(1.05 to 1.48)	0.46	(0.34 to 0.62)
fourth (third follow-up)	-	2.53	(2.14 to 3.00)	1.43	(1.10 to 1.85)
Age (baseline)*cycle:					
Age*second cycle	-	1.01	(0.99 to 1.03)	1.01	(0.99 to 1.04)
Age*third cycle	-	1.00	(0.98 to 1.03)	0.97	(0.92 to 1.03)
Age*fourth cycle	-	1.01	(0.99 to 1.04)	1.06	(1.02 to 1.11)

[a] 2011 cases,9347 oversations.

[b] 940 cases, 7334 observations.

[c] Higher score indicates larger social network.

[d] Higher score indicates less disability.

[e] Higher score indicates worse self-rated health.14 persons were missing data on this variable, which we coded as an indicator.

Table 2

Characteristics of attrition models and the weights they generated.[a]

Model:	Fit statistics			Nonstabilized weights[b]		Stabilized weights[b]	
Attrition due to …	**% discordant**	***c* statistic**	**Hosmer-Lemeshow χ^2 test[c], *P* value**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**
Death	21	0.79	0.5	1.4 (1.4)	1–52.5	1.0 (0.4)	0.2–12.9
Non-death cause	38	0.62	0.7	1.2 (0.2)	1–2.8	1.0 (0.05)	0.7–1.5
Combination of death and non-death models	-	-		1.8 (2.4)	1–84.7	1.0 (0.4)	0.2–14.7

[a] Based on the non-bootstrapped analyses.

[b] Models for the weight denominators included terms for baseline smoking status (current vs never), prior global cognitive score, baseline age (years), sex, African American race, education (4 categories), prior social network score, prior alcohol intake, prior Nagi disability score, prior self-rated health, diabetes at baseline, interview cycle, and the cross-product between cycle and age. Models for the numerators (stabilized weights only) included baseline smoking status, baseline age, sex, African American race, and education.

[c] This test had 8 degrees of freedom.

Table 3

Unweighted and weighted multivariable-adjusted[a] difference between current and never smokers in cognitive change over 10 years.

Model	Change in cognitive score over 10 years among never smokers[b]	Difference in cognitive score change over 10 years:current smokers vs never smokers			Increase[d] from the unweighted result	Excess years of cognitive aging among current smokers[e]
		Difference	SE[c]	(95% CI)		
Not weighted	−0.53	−0.11	0.05	(−0.20 to −0.02)	-	2.1
Weighted: non-stabilized weights	−0.70	−0.17	0.07	(−0.31 to −0.02)	56%	2.4
Weighted: stabilized weights	−0.82	−0.20	0.08	(−0.36 to −0.04)	86%	2.5

[a] Adjusted for age, sex, race, education, and alcohol consumption.

[b] Based on the model's parameter estimate for the "time," which is also the average rate of change among never smokers.

[c] SE: standard error.

[d] Increase on an absolute scale, computed from estimates expressed to their nearest 0.001.

[e] Assuming that the rate of cognitive score change among never smokers represents “smoking-free cognitive aging,” we estimated the excess years of cognitive aging within a chronological period of 10 years among current smokers by dividing the difference between smokers’ and never smokers’ change in cognitive score over 10 years by the annual rate of change among never smokers. Estimates are specific to persons with reference group characteristics (except for smoking), specifically, 75-year-old white females with 9–12 years of education and no alcohol consumption.