Original article

Using marginal structural models to estimate the relationship between neighborhood poverty and alcohol use and misuse: the CARDIA study

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Abstract

Previous studies on the relationship between neighborhood disadvantage and alcohol use/misuse have often controlled for individual characteristics on the causal pathway, such as income, potentially underestimating the relationship between disadvantage and alcohol consumption. We used data from the Coronary Artery Risk Development in Young Adults study of 5115 adults aged 18-30 at baseline and interviewed seven times between 1985 and 2006. We estimated marginal structural models using inverse-probability-of-treatment-and-censoring-(IPTC)-weights to assess the association between point-in-time/cumulative exposure to neighborhood poverty (pov_{neigh} was the proportion of census tract residents living in poverty) and alcohol use/binging after accounting for time-dependent confounders including income, education, and occupation. In the weighted model, a one-unit increase in pov_{neigh} at the prior examination was associated with a 62% increase in the odds of binging (OR: 1.62; 95% CI: 1.00, 2.64); the estimate from a standard generalized estimating equations model controlling for baseline and time-varying covariates was: 1.44 (95%CI: 0.91, 2.28). The IPTC-weighted estimate of the relative increase in the number of weekly drinks in the past year associated with cumulative pov_{neigh} was 2.87 (95% CI 1.10, 7.46); the estimate from a standard model was 1.69 (95% CI: 1.08, 2.65). Under certain conditions, traditional regression methods underestimate the magnitude of the association between time-varying exposures and outcomes. Cumulative and point-in-time measures of neighborhood poverty are important predictors of alcohol consumption.

To date, several studies have reported that alcohol abuse and dependence, as well as other risk behaviors, cluster in contexts of poverty, residential instability and social isolation (1-5). The vast majority of these studies are cross sectional and therefore do not allow us to establish temporal sequencing among the characteristics of the residential context and alcohol use and misuse. Establishing such temporal sequencing is helpful in causal reasoning. The question remains whether such multi-level associations are actually due to the influence of neighborhood contextual characteristics on health outcomes such as alcohol abuse, or whether they merely reflect the selection of individuals with similar socioeconomic characteristics into the same types of neighborhoods. Longitudinal studies that follow people and neighborhoods over time are needed to better estimate the nature of the association of neighborhood conditions on alcohol use.

A major analytic challenge in longitudinal studies with a time-dependent exposure is that certain time-varying covariates may be confounders that are also affected by prior exposures, and are thus in the causal pathway between the exposure of interest and the outcome. Most studies of neighborhood associations with alcohol use attempt to tightly control for individual-level socioeconomic position because it may be causally related to the type of neighborhood a person can afford to live in as well as to the person's use of alcohol. At the same time, the neighborhood socioeconomic environment may condition the types of income-generating opportunities a person can obtain (5). Thus individual socioeconomic status could be simultaneously a confounder and a mediator of the neighborhood effect, because it may be affected by prior neighborhood conditions and also may affect the types of neighborhoods that persons subsequently move into (6). Under these conditions, traditional regression analytic techniques yield biased estimates of the neighborhood effect of interest, even if that effect is causal. By controlling for the individual-level composition of neighborhoods to address individual selection into neighborhoods, we run the risk of also controlling for individual-level mediators of earlier neighborhood characteristics and underestimating the impact that long-term cumulative neighborhood

exposure has on health outcomes; at the same time unadjusted estimates are confounded by individual-level characteristics related to selection of persons into neighborhoods (7).

A marginal structural model (MSM) describes the marginal relationship between a time-varying exposure such as neighborhood poverty and alcohol use. Formally, an MSM for repeated measures is a parametric regression model relating any possible exposure history up to time t, to the corresponding counterfactual outcome at time t. MSMs are particularly useful in the presence of time-dependent covariates that may be simultaneously confounders and intermediate variables in the causal pathway between the exposure of interest and the outcome, as is the case with individual income (8, 14, 15)). They are also useful in the case of loss-to-follow-up in longitudinal studies, as they allow us to account for differential loss to follow-up.

The parameters of an MSM can be estimated in an unbiased manner with Inverse-Probability-of-Treatment-and-Censoring Weighting (IPTCW). Briefly, IPTCWs involve a product of two sets of weights: the inverse-probability-of-treatment weights (IPTWs) and the inverse-probability-of-censoring weights (IPCWs). IPTW calculates, at each time point, the probability of an individual receiving the exposure they actually received, conditional on the person's observed stable and time-varying covariates and their exposure and outcome history up to the previous time point. Individuals are weighted by the inverse of the probability in order to create a "pseudopopulation" consisting of a number of copies of each subject equal to the subject's IPTW value. People who are most unrepresented in exposure assignment are given proportionally higher weights, while individuals who are highly represented in exposure assignment are given proportionately lower weights, so that it is possible to obtain a comparable population in terms of stable and time-varying confounders across levels of the exposure. By using weighting to create a pseudopopulation that is balanced in the time-varying covariates across levels of the exposure at each time point, it then becomes possible to estimate the unconfounded association between the exposure and outcome without conditioning on the covariate through its inclusion as a predictor in the outcome model. A detailed example illustrating how weighting creates an unbiased "pseudopopulation" is provided in

Supplemental Digital Content 1. Similarly, by re-weighting each uncensored person-time by the second set of weights corresponding to the inverse conditional probability of being uncensored given the past, it becomes possible to assess the relationship between the exposure of interest and the outcome as if, contrary to fact, all subjects had remained uncensored, rather than having followed their observed censoring history.

Using data from a population-based longitudinal study of young adults, we investigated the association of neighborhood poverty with two types of alcohol-related outcomes: 1) frequency of alcohol consumption and 2) binging. These outcomes capture two important aspects of alcohol consumption: the gradient of consumption from use to abuse (i.e. frequency of alcohol consumption), and the extreme end of consumption, which is very heavy alcohol use (i.e. binging). These two types of alcohol-related behavior may present contrasting etiologies (7) and could be differentially related to neighborhood conditions. Notably, features of the neighborhood environment associated with poverty may have a stronger impact on heavy alcohol consumption, such as binging, than on the overall consumption gradient. Taking advantage of rich longitudinal data with repeated measures of neighborhood conditions, alcohol use and individual-level characteristics we used MSMs to estimate the relationship between cumulative and point-in-time pov_{neigh} and alcohol use behaviors after appropriately accounting for time-dependent confounders that are also affected by prior exposure, and are thus in the causal pathway between the exposure and the outcome, as well as for loss-to-follow-up.

Methods

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a cohort study of cardiovascular risk factors among young adults (9). The sample consists of 5115 adults aged 18-30 at baseline (1985-86). Participants were recruited through telephone contact from community lists in Birmingham, AL; Chicago, IL; and Minneapolis, MN; as well as from membership in a prepaid health plan in Oakland, CA. Investigators aimed to recruit nearly equal numbers of black and white people, men and women, persons <25 and ≥ 25 years of age, and persons with high school education or less and

persons with more than a high school education. Respondents were interviewed seven times between 1985 and 2006: at baseline (1985-86), year 2 (1987-88), year 5 (1990-91), year 7 (1992-93), year 10 (1995-96), year 15 (2000-01) and year 20 (2005-06). Cohort retention at year 20 was 69.4% of the original sample and 72% of survivors.

The outcomes of interest included the following: 1) frequency of alcohol consumption, operationalized as the number of glasses of wine, beer and liquor consumed per week in the past year; and 2) binging, operationalized as having consumed 5 or more drinks as the largest number of drinks per day in the past month. Alcohol consumption and binging were measured at each follow-up visit (from baseline through year 20).

Pov_{neigh}, defined as the proportion of residents living in poverty in the neighborhood (census tract) of the participant, was the main exposure of interest. The Census Bureau uses a set of money income thresholds that vary by family size and age composition to determine who is in poverty. If a family's total pre-tax money income is less than the family's threshold, then that family is considered in poverty. For example, the poverty threshold for one person in 2007 was $10,590 in income. The official poverty thresholds are updated for inflation using Consumer Price Index. This measure is highly correlated with many aspects of a disadvantaged neighborhood (10), and it offers advantages in terms of variable construction, as it is easy to log-transform into a normally-distributed measure which is convenient for calculation of the IPTW weights necessary to fit MSMs. Census tracts were used as proxies for neighborhoods and participant addresses were geocoded at years 0, 7, 10, and 15 to identify census tract of residence. Pov_{neigh} was appended to individual-level data at baseline and each geocoded follow-up time using the closest decennial US Census. For baseline we used the 1980 Census, for years 7 and 10 we used the 1990 Census, and for year 15 we used the 2000 Census. Data for years 2 and 5 were estimated by linear interpolation from Census data for years 1980 and 1990.

Baseline independent variables included age, sex, race/ethnicity and marital status. Time-varying covariates included low family income (defined as earning <=$24,999 in the past year), less than

secondary education (having <12 years of education), and having a non-managerial or professional occupational status (defined according to the Census occupation codes). Additional time-varying covariates included the existence of any children or stepchildren of the respondent, home ownership (defined as: owned vs. not owned). Finally, we used the Center for Epidemiological Studies depression scale (11) to measure depression symptoms: we classified respondents as having depressive symptoms if they scored 16 or higher.

Interpolation was used to predict covariate values in cases where a scale had, by design, not been measured at one time point but had been measured at a time point before and after; in cases where a variable had not been measured in the first two time points of the study, the respondent was assigned the covariate value from the third examination. Observations that had missing values on the key covariates of interest (and the covariates had actually been measured at that examination point) were deleted.

Statistical methods

Testing whether time-varying covariates acted as confounders and mediators

We first examined whether the time-varying covariates of interest in our data could be both confounders and mediators in the causal pathway between pov_{neigh} and alcohol use/misuse (directed acyclic graph presented below). This was a necessary precondition for MSMs to be a useful model. We tested whether: a) the main time-varying covariates of interest, low income, non-professional/managerial occupations and low education were longitudinally associated with later pov_{neigh} (i.e. covariates could act as a selector into neighborhood poverty); b) pov_{neigh} predicted the main time-varying covariates of interest (i.e. whether time-varying covariates fulfilled the first requirement to be mediators of the pov_{neigh} - binging and pov_{neigh} - frequency of alcohol use relationships); and c) the time-varying covariates were associated with alcohol frequency of use/binging, independently of pov_{neigh} (i.e. the second condition necessary for the covariates to be confounders or mediators of the pov_{neigh} -alcohol use relationship). Details about these analyses can be found in Supplemental Digital Content 2.

Outcome models

Once the preconditions for marginal structural models were established, marginal structural logistic regression models for repeated binary measures were used to model the odds of binging, while marginal structural mean regressions with a log link were used to model the repeated counts of drinks consumed per week in the past year. As the intraclass correlation coefficient indicated that only 1-2% of the variation in the alcohol use outcomes occurred between neighborhoods and a large proportion of the tracts had only one person per tract by year 10, we did not incorporate a random effect to account for correlation of persons within neighborhoods in either set of models (12, 13).

We estimated three types of models: 1) a series of baseline adjusted models estimating the association between lagged pov_{neigh} ($pov_{neigh,cum\_t-1,i}$ refers to cumulative pov_{neigh} up to the prior exam, that is the sum of pov_{neigh} across examinations, divided by the number of examinations the respondent had participated in; $pov_{neigh,t-1,i}$ refers to pov_{neigh} in the prior exam) and each of the two alcohol risk behaviors after adjusting for baseline covariates (for parsimony *t-1* will refer to the prior examination, which actually took place 2-5 years prior to the current examination; *i* refers to individual; μ_{it} refers to the average number of drinks consumed per week in the past year, Y_{it} is a binary indicator of binging in the previous month at time t, and V_i refers to a vector of baseline covariates):

$$P(Y_{it}=1)=\beta_0+\beta_1 pov_{neigh,cum\_t-1,i}+B'V_i \quad (1a)$$
$$P(Y_{it}=1)=\beta_0+\beta_1 pov_{neigh,t-1,i}+B'V_i \quad (1b)$$
$$\log(\mu_{it})=\beta_0+\beta_1 pov_{neigh,cum\_t-1,i}+B'V_i \quad (1c)$$
$$\log(\mu_{it})=\beta_0+\beta_1 pov_{neigh,t-1,i}+B'V_i \quad (1d)$$

2) a series of models further adjusting for a vector of time-varying covariates (L_{it}) at t-2 (to ensure they were measured prior to the measurement of pov_{neigh} at t-1) and a vector of baseline covariates (V_i) using traditional regression methods;

$$P(Y_{it}=1)=\beta_0+\beta_1 pov_{neigh,cum\_t-1,i}+\Pi'L_{t-2i}+B'V_i \quad (2a)$$
$$P(Y_{it}=1)=\beta_0+\beta_1 pov_{neigh,t-1,i}+\Pi'L_{t-2i}+B'V_i \quad (2b)$$
$$\log(\mu_{it})=\beta_0+\beta_1 pov_{neigh,cum\_t-1,i}+\Pi'L_{t-2i}+B'V_i \quad (2c)$$
$$\log(\mu_{it})=\beta_0+\beta_1 pov_{neigh,t-1,i}+\Pi'L_{t-2i}+B'V_i \quad (2d)$$

and 3) a series of marginal structural models for the counterfactual outcomes $Y_{it}\left(\overline{pov_{neigh}}(t-1)\right)$ and $\mu_{it}\left(\overline{pov_{neigh}}(t-1)\right)$, corresponding to person i's binging (Y_{it}) or consumption (μ_{it}) status at time t, given that he or she been exposed to a history of poverty level $\overline{pov_{neigh}}(t-1)$ up to time t-1.

$$P(Y_{it}\left(\overline{pov_{neigh,cum}}(t-1)\right)=1)=\gamma_0+\gamma_1 pov_{neigh,cum\_t-1,i}+\Omega' \mathrm{V}_i \quad (3a)$$

$$P(Y_{it}\left(\overline{pov_{neigh}}(t-1)\right)=1)=\gamma_0+\gamma_1 pov_{neigh,t-1,i}+\Omega' \mathrm{V}_i \quad (3b)$$

$$\log(\mu_{it}\left(\overline{pov_{neigh,cum}}(t-1)\right))=\gamma_0+\gamma_1 pov_{neigh,cum\_t-1,i}+\Omega' \mathrm{V}_i \quad (3c)$$

$$\log(\mu_{it}\left(\overline{pov_{neigh}}(t-1)\right))=\gamma_0+\gamma_1 pov_{neigh,t-1,i}+\Omega' \mathrm{V}_i \quad (3d)$$

We used two alternative measures of poverty in order to test whether accumulated pov_{neigh} had a different relationship with subsequent alcohol use than exposure to poverty at a single point in time.

Weights estimation methods

The CARDIA data presented a concern of time-dependent confounders in the causal pathway between the main exposure and outcomes of interest: income, occupation and education confounded the association between pov_{neigh} and alcohol use and were also in the causal pathway. It also had loss to follow up over time: we classified a respondent as "censored" the first time he/she skipped an examination or failed to respond to the alcohol outcome of interest. Under these definitions of "censoring", by the seventh follow-up, almost half of the sample had been censored. MSM parameters were thus estimated by inverse-probability-of-treatment-and-censoring weights (IPTCWs).

The MSM approach involved fitting models described in equations (3a-d), using IPTCW weights to account for time dependent confounding and loss-to-follow-up. These models were fit to all respondents who had complete data on $\overline{L}$.

As described above, weights for respondents were formed by the product of two factors, one corresponding to the probability density of receiving the exposure (pov_{neigh}) history the respondent did indeed receive, and the other corresponding to the probability of remaining uncensored. As these two sets of weights were unknown, we estimated them based on the observed data using simple parametric models. The exposure history weight up to time *t,* was defined as:

$$sw_i(t) = \prod_{t=0}^{t} \frac{f(Pov_{neigh}(t) = pov_{neigh,i}(t) \left| \overline{C}(t-1) = 0, \overline{Pov_{neigh}}(t-1) = \overline{pov}_{neigh,i}(t-1), V = v_i \right.)}{f(Pov_{neigh}(t) = pov_{neigh,i}(t) \left| \overline{C}(t-1) = 0, \overline{Pov_{neigh}}(t-1) = \overline{pov}_{neigh,i}(t-1), \overline{L}(t-1) = \overline{l}_i(t-1), V = v_i \right.)}$$

Here C (t-1) refers to censoring at the prior wave. The numerator is estimated to stabilize the weight and ensure it is normally distributed around a mean of 1. If the weight were estimated simply as an inverse of the conditional density of exposure, and the time-varying confounders were strongly associated with the exposure, $f(Pov_{neigh}(t) = pov_{neigh,i}(t) \left| \overline{C}(t-1) = 0, \overline{Pov_{neigh}}(t-1) = \overline{pov}_{neigh,i}(t-1), \overline{L}(t-1) = \overline{l}_i(t-1), V = v_i \right.)$ would vary markedly between subjects, resulting in very large weights for a few respondents. Such subjects would contribute many copies of themselves to the pseudopopulation, and would thus have a large influence in the weighted analyses. To avoid this, Robins (8) suggests using the stabilized weights where the numerator is the density of exposure, conditional on past exposure history and baseline covariates, and the denominator is the density of exposure, conditional on past exposure history and both baseline and time-varying covariates.

To estimate $f(Pov_{neigh}(t) = pov_{neigh,i}(t) \left| \overline{C}(t-1) = 0, \overline{Pov_{neigh}}(t-1) = \overline{pov}_{neigh,i}(t-1), V = v_i \right.)$ in the numerator of the treatment weights and $f(Pov_{neigh}(t) = pov_{neigh,i}(t) \left| \overline{C}(t-1) = 0, \overline{Pov_{neigh}}(t-1) = \overline{pov}_{neigh,i}(t-1), \overline{L}(t-1) = \overline{l}_i(t-1), V = v_i \right.)$ in the denominator of the treatment weights, we accounted for highly skewed exposure data by using a log-normal density with mean ($\ln \hat{a}_{ti} = \alpha_{0ti} + \alpha_1 \ln pov_{neigh,t-1,i} + \alpha_2 t_{ti} + B' \mathrm{V}_i + e_i$) and variance ($\log[(\ln pov_{neigh,ti} - \ln \hat{pov}_{neigh,ti})^2] = \gamma_{0ti} + \gamma_1 \ln pov_{neigh,t-1,i} + \gamma_2 t_{ti} + B' \mathrm{V}_i$) for the numerator, and a log-normal model with mean ($\ln \hat{pov}_{neigh,ti} = \alpha_{0ti} + \alpha_1 \ln pov_{neigh,t-1,i} + \alpha_2 t_{ti} + \Pi' \mathrm{L}_{t-1i} + B' \mathrm{V}_i + e_i$) and variance ($\log[(\ln pov_{neigh,ti} - \ln \hat{pov}_{neigh,ti})^2] = \gamma_{0ti} + \gamma_1 \ln pov_{neigh,t-1,i} + \gamma_2 t_{ti} + \Pi' \mathrm{L}_{t-1i} + B' \mathrm{V}_i$) to model the denominator. Point estimates of the unknown parameters (α_{0ti}, α_1, α_2, B', Π', γ_{0ti}, γ_1, γ_2) were obtained by pooled linear regression for both mean models, and by pooled log-linear regression of estimated squared-residuals for both variance models. These regression estimates and their predicted values were obtained

using SAS PROC GENMOD (17). A sample program is included in Supplemental Digital Content 3 (SAS program). These predicted values were in turn used to construct the treatment weights based on the log-normal density assumption.

To construct the corresponding censoring weights, we defined the censoring indicator *C(t)* to be 1 if a subject missed an interview or failed to respond to the questions about the outcome of interest by time *t* and *C(t) = 0* otherwise. Censoring weights were defined as

$$sw_i^{\pm}(t) = \prod_{t=0}^{t} \frac{pr(C(t)=0 \mid \overline{C}(t-1)=0, \overline{Pov_{neigh}}(t-1) = \overline{pov}_{neigh,i}(t-1), V=v_i)}{pr(C(t)=0 \mid \overline{C}(t-1)=0, \overline{Pov_{neigh}}(t-1) = \overline{pov}_{neigh,i}(t-1), \overline{L}(t-1) = \bar{l}_i(t-1), V=v_i)}$$

and estimated as in Hernan et al (15), details are omitted.

The final marginal structural model was estimated using SAS PROC GENMOD (17), which allowed us to estimate confidence intervals using "robust" methods. The software treats the weights as fixed instead of estimated, and provides conservative intervals guaranteed to give at least a 95 percent coverage probability (15, 16).

Results

Table 1 presents basic means and frequencies for the variables used in the analysis, by year of measurement. 46.7% of the sample was censored by examination 7 of the study. Study respondents were on average 24.83 years of age at baseline, 45.51% male and 51.55% black and 48.45% white. The proportion of respondents who binged decreased from 24.83% to 14.63% throughout the study, while the mean number of drinks consumed per week in the past year remained constant throughout the study years. Moreover, the mean pov_{neigh} decreased from 24.00% to 11.00%. In parallel, the proportion who were low income decreased from 42.30% to 25.41% during the study.

The preconditions for MSMs to provide an advantage over standard models were met. Having a low income, less than high school education and a longer exposure to non-professional/managerial positions were all positively associated with later $\ln(pov_{neigh})$. Moreover, an increase in the proportion of residents in pov_{neigh} was prospectively associated with higher odds of having a low income, having less

than high school education and with having a non-professional or managerial degree. The magnitude of the correlation between pov_{neigh} also decreased from 0.98 to 0.22 over time. Tables are included in Supplemental Digital Content 2 (Tables A1-A3) and explained in greater detail.

Outcome models: crude, traditional and marginal structural models

Table 2 shows results of crude, traditional, and MSM estimates of associations of pov_{neigh} with the alcohol use outcome measures. As seen in Table 2, we estimated the log odds of binging over the twenty years of the study for nine repeated-measures marginal logistic models for the response $P(Y_{binge} = 1)_{it}$: first using cumulative poverty up to t-1 as the predictor, then using the proportion of poverty at t-1 as the predictor of interest. For each of these functional forms, the first model was unweighted and crude. The second model was unweighted and adjusted for both the baseline regressors and the same time-varying regressors as those used in the linear model for the denominator of $s_{wi.}$ The third model used IPTC weights and adjusted for the baseline regressors.

The first set of columns presents results for cumulative pov_{neigh} up to t-1. Results for the weighted model indicate that each unit increase in cumulative pov_{neigh} up to t-1 is associated with a 59% increase in the odds of binging but confidence intervals were wide (OR 1.59 (95 % CI: 0.81, 3.12)). The corresponding estimate from the standard (unweighted) GEE regression model that included baseline and time-varying covariates as regressors was 1.45 (95 % CI: 0.79, 2.69). The second set of columns presents results for the statistical effect of pov_{neigh} at t-1 on binging: in the weighted model, a one-unit increase in the proportion of residents living in poverty was associated with a 62% increase in the odds of binging (OR: 1.62; 95% CI: 1.00, 2.64). The standard regression model estimated a smaller association between poverty and binging: 1.44 (95%CI: 0.91, 2.28).

Table 3 shows the estimated difference in the average count of drinks consumed per week in the past year for three series of repeated measures Poisson models for the alcohol frequency response, represented as log (μ_{it}). The weighted model indicated that in neighborhoods with a one unit increase in cumulative pov_{neigh} up to t-1, respondents were likely to consume an average of 2.87 times more drinks

per week in the year (95% CI: 1.10, 7.46), while the corresponding estimate from the standard GEE model was 1.69 (95% CI: 1.08, 2.65). If we were to depart from the average weekly drinking rate at the first interview, such an estimate might mean a shift from an average weekly consumption of 4.82 drinks to 13.83 drinks per week. For exposure 2 (pov_{neigh} at *t*-1), the estimate of the ratio of weekly drinks per unit increase in pov_{neigh} at *t*-1from the weighted model was 0.93 (95% CI: 0.43, 2.01) but the estimate from the standard GEE model was 1.32 (95% CI: 0.96, 1.83).

Conclusion

Using marginal structural logistic and Poisson models, we found that greater cumulative and point-in-time poverty exposure were associated with increased odds of binging after adjustment for baseline and time-varying confounders, although the confidence intervals were wide in the case of cumulative poverty. Associations were stronger in weighted than in standard models. Cumulative exposure to neighborhood poverty was also associated with an increased rate of weekly alcohol consumption with associations being stronger for the MSM estimate than for standard models. Exposure to neighborhood poverty at time of the previous examination was associated with a slightly higher weekly rate of drinking alcohol in standard models. In weighted models, an inverse association existed between lagged poverty and the number of drinks consumed per week, although this association was not statistically significant.

Previous studies have reported contradictory evidence on the relationship between neighborhood socioeconomic conditions and drinking. Some studies have found strong relationships between neighborhood socioeconomic conditions and drinking (4, 5, 18-21): for instance, residing in disadvantaged neighborhoods was associated with increased likelihood that adolescents were offered various kinds of substances (18) and that they developed heavy drinking patterns (4, 5, 20), while other studies found that neighborhoods had limited or no impact on alcohol use (22, 23), and others still found a positive association between neighborhood resource levels and the risk of alcohol/substance use and abuse (24-26). The contradictory evidence provided by these studies remains limited by the cross-

sectional study design, which provides no information to control for the potential of reverse selection by substance users into low-income neighborhoods. Moreover, prior studies focused on either level of alcohol use or extreme forms of consumption such as binging, but did not compare the relative association of neighborhood disadvantage with the two different forms of use.

To the knowledge of the authors, only three studies used a longitudinal design to investigate the influence of neighborhood resources on alcohol use and abuse (27-29). Of these, two found a significant positive relationship between neighborhood disadvantage on alcohol abuse (27, 28): one referred to the Yonkers Project, a quasi-experimental residential mobility study which concerned the random allocation of families from high-poverty neighborhoods to publicly funded houses in middle-class neighborhoods, and found that two years after moving, the families who had moved reported less alcohol abuse (28), while another followed 206 Caucasian men who had been recruited for alcoholism and were followed up for twelve years, and found that residency in more disadvantaged neighborhoods at baseline predicted more alcoholic symptoms twelve years later (27). The present work extends the findings of these previous studies by comparing the effects of long-term vs. acute exposure to neighborhood poverty on trajectories of alcohol use and abuse in a population-based sample of young adults over twenty years. While recent exposure to poverty was associated with binging but not with the number of drinks consumed per week, accumulated experiences of poverty had a positive relationship with both binging and number of drinks consumed after controlling for time invariant and time varying confounders.

The present work also makes a methodological contribution to the literature, as it investigates a key limitation proposed to pervade longitudinal studies: the need to address confounding bias by appropriately controlling for time-dependent covariates that are simultaneously confounders and intermediate variables in the causal pathway between the exposure of interest and the outcome. With IPTCW weights, one can create a pseudo population where there is no confounding by the measured covariates, and we can thus more closely approach a causal interpretation. To the knowledge of the authors, only one study has as of yet investigated the use of marginal structural models as a method to

address this problem in longitudinal multi-level studies of neighborhood effects. Sampson et al. (30) found comparable results with a marginal structural model as with a propensity score matching of individuals, which did not address the problem of simultaneous mediation and confounding by time-varying covariates.

Initial exploratory analyses of our data indicated that the pre-requisites to make marginal structural models necessary were fulfilled. First, the main exposure of interest, the rate of neighborhood poverty, was relatively variable over time. Second, the time-varying covariates of interest, income, education and occupation, both predicted neighborhood poverty and determined alcohol use (acting as confounders) and were also predicted by neighborhood poverty (acting as mediators).

Weighted models consistently yielded stronger estimates of the association of cumulative poverty with binging and alcohol consumption levels than unweighted models. The weighted model also produced a stronger estimate of the association of point-in-time poverty with binging. Unweighted models may be biased towards the null because they included time-varying confounders, such as low income and low education, which were affected by prior levels of cumulative poverty, in the outcome models (31, 32). Including time-dependent covariates that were in the causal pathway into the regression model could have partialed out some of the variability associated with the exposure of interest, thus impeding an assessment of the direct relationship between neighborhood poverty and alcohol use. In contrast, marginal structural models used weighting to address confounding by time-varying covariates that were also outcomes of the exposure of interest, and thus obviated the need to "overcontrol" for potential mediators in the final outcome models. These findings are consistent with prior work on marginal structural models (15, 33-36), which, in the context of simultaneous time-varying confounding and mediation, have found stronger associations between a time-varying exposure and an outcome in weighted than in unweighted models.

These results should be taken in concert with the following limitations. Marginal structural models do not, by themselves, address all issues of causal inference. First, they can only control for observed and measured time-varying confounders, so that unmeasured characteristics may still generate bias in the

relationship of interest (35). However, the concerted attempt to incorporate an extensive set of factors that may contribute to neighborhood selection, including income, education, occupation and mental health status, reduces this concern. Second, they do not address other key aspects of causal inference, such as the biological plausibility of the relationship or replication. Marginal structural models do, however, allow us to approximate consistency with a causal model in the case of observational data with time-varying exposures and confounders. Third, the absence of some geocodes and the absence of certain measures at some study time points necessitated interpolation of the level of exposure as well as some of the covariates at selected time points, which may have led to exposure misclassification and biased the exposure-outcome effect estimates in either direction. Certain measures, such as depression symptom levels, home ownership and income, had to be extrapolated for the first two time points, since they had not been measured at those points of time. However, a sensitivity analysis using only data from the third to the seventh time points, when these key time-varying covariates had been measured, did not produce substantively different results. We thus decided to use all seven time points, in order to maximize power. Fourth, as our main exposure was proportion of residents in poverty, a one-unit shift meant a 100% shift in poverty, which is a large extrapolation. Actual differences in alcohol use and binging levels may be smaller. Finally, the analysis is based on the assumption that dropout was ignorable, conditional on observed covariates. Participants were censored at their first missing outcome measure. A sensitivity analysis conducted with respondents classified as "censored" once they missed an interview, rather than the first time they failed to respond to the outcome measure, provided similar estimates.

This is one of the first longitudinal studies to provide evidence about the effect of point-in-time and accumulated neighborhood poverty on alcohol use. The study highlights the need to consider the impact of short- vs. long-term exposure to poverty on alcohol use and other associated behavioral outcomes: while consistent exposure to higher rates of poverty was associated with higher levels of drinking, short-term exposure to poverty was only associated with an extreme form of alcohol use--binging. The study also illustrates how the careful use of analytic methods such as marginal structural

models provide an opportunity to obtain estimates of the relationship between neighborhood socioeconomic conditions and health that are consistent with a causal framework, in the context of an observational study with time-varying confounders that are affected by prior levels of the exposure of interest.

Supplemental Digital Content:

Supplemental Digital Content 1: Illustration of IPTW weight estimation (text providing an example to illustrate how IPTCW weights are estimated)

Supplemental Digital Content 2*:* Testing whether time-varying covariates acted as confounders and mediators (text and 3 tables describing the analysis of preconditions that make MSM models useful)

Supplemental Digital Content 3: Sample SAS program to estimate IPTCW weights and an MSM model

1. Boardman JD, Finch BK, Ellison CG, et al. Neighborhood disadvantage, stress, and drug use among adults. J Health Soc Behav 2001;42:151-65.

2. Duncan SC, Duncan TE, Strycker LA. A Multilevel Analysis of Neighborhood Context and Youth Alcohol and Drug Problems. Prevention Science 2002;3:125-33.

3. Freisthler B, Lascala EA, Gruenewald PJ, et al. An examination of drug activity: Effects of neighborhood social organization on the development of drug distribution systems. Subst Use Misuse 2005;40:671-86.

4. Jones-Webb R, Snowden L, Herd D, et al. Alcohol-related problems among black, Hispanic and white men: the contribution of neighborhood poverty. 1997;v58:p539(7).

5. Karvonen S, Rimpela AH. Urban small area variation in adolescents' health behaviour. Social Science & Medicine 1997;45:1089-98.

6. Sampson RJ, Sharkey P, Raudenbush SW. Durable effects of concentrated disadvantage on verbal ability among African-American children. Proceedings of the National Academy of Sciences of the United States of America 2007;105:845-52.

7. Galea S, Ahern J, Vlahov D. Contextual determinants of drug use risk behavior: a theoretic framework. J Urban Health 2003;80:50-8.

8. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000;11:550-60.

9. Friedman GD, Cutter GR, Donahue RP, et al. Cardia: study design, recruitment, and some characteristics of the examined subjects. Journal of Clinical Epidemiology 1988;41:1105-16.

10. Land KC, McCall PL, Cohen LE. Structural Covariates of Homicide Rates - Are There Any Invariances across Time and Social Space. Am J Sociol 1990;95:922-63.

11. Weissman MM, Sholomskas D, Pottenger M, et al. Assessing depressive symptoms in five psychiatric populations: a validation study. American Journal of Epidemiology 1977;106:203-14.

12. Larsen K, Merlo J. Appropriate assessment of neighborhood effects on individual health: Integrating random and fixed effects in multilevel logistic regression. American Journal of Epidemiology 2005;161:81-8.

13. Merlo J, Yang M, Chaix B, et al. A brief conceptual tutorial on multilevel analysis in social epidemiology: investigating contextual phenomena in different groups of people. Journal of Epidemiology and Community Health 2005;59:729-36.

14. Cole S, Hernan M, Robins J, et al. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. Am Journal of Epidemiology 2003;158:687–94.

15. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 2000;11:561-70.

16. Bodnar LM, Davidian M, Siega-Riz AM, et al. Marginal Structural Models for Analyzing Causal Effects of Time-dependent Treatments: An Application in Perinatal Epidemiology. American Journal of Epidemiology 2004;159:926-34.

17. SAS. SAS/STAT User's Guide. Cary, NC, 1999.

18. Crum RM, LillieBlanton M, Anthony JC. Neighborhood environment and opportunity to use cocaine and other drugs in late childhood and early adolescence. Drug Alcohol Depend 1996;43:155-61.

19. Kulis S, Marsiglia F, Sicotte D, et al. Neighborhod effects on youth substance use in a southwestern city. Sociological Perspectives 2007;50:273-301.

20. Wilson N, Syme SL, Boyce WT, et al. Adolescent alcohol, tobacco, and marijuana use: The influence of neighborhood disorder and hope. Am J Health Promot 2005;20:11-9.

21. Chuang Y, Li Y, Wu Y, et al. A multilevel analysis of neighborhood and individual effects on individual smoking and drinking in Taiwan. BMC Public Health 2007;7.

22. Abdelrahman AI, Rodriguez G, Ryan J, et al. The Epidemiology of Substance Use among Middle School Students: The Impact of School, Familial, Community, and Individual Risk Factors. Journal of Child and Adolescent Substance Use 1998;8:55-75.

23. Allison KW, Crawford I, Leone P, et al. Adolescent Substance Use: Preliminary Examinations of School and Neighborhood Context. Am J Community Psychol 1999;27:111-41.

24. Stockdale S, WElls K, Tang L, et al. The importance of social context: Neighborhood stressors, stress-buffering mechanisms, and alcohol, drug and mental health disorders. Social Science & Medicine 2007;65:1867-81.

25. Ennett ST, Flewelling R, Lindrooth R, et al. School and neighborhood characteristics associated wtih school rates of alcohol, cigarette, and marijuana use. Journal of Health and Social Behavior 1997;38:55-71.

26. S G, Ahern J, Tracy M, et al. Neighborhood income and income distribution and the use of cigarettes, alcohol and marijuana. Am J Prev Med 2007;32:S195-S202.

27. Bu A, Mansour M, Wang J, et al. Alcoholism Effects on Social Migration and Neighborhood Effects on Alcoholism Over the Course of 12 Years. Alcoholism 2007;31:1545-51.

28. Fauth R, Leventhal T, Brooks-Gunn J. Short-term effects of moving from public housing in poor to middle-class neighborhoods on low-income, minority adults' outcomes. Social Science and Medicine 2004;59:2271-84.

29. Hoffman J. The community context of family structure and adolescent drug use. J Marriage Fam 2002;64:314-30.

30. Sampson RJ, Sharkey P, Raudenbush SW. Durable effects of concentrated disadvantage on verbal ability among African-American children. Proc Natl Acad Sci U S A 2008;105:845-52.

31. Cole S, Hernan MA. Fallibility in estimating direct effects. International Journal of Epidemiology 2002;31:163-5.

32. Hernan MA. A structural approach to selection bias. Epidemiology 2004;15:615-25.

33. Cole S, Hernan MA, Margolick J, et al. Marginal Structural Models for Estimating the Effect of Highly Active Antiretroviral Therapy Initiation on CD4 Cell Count. American Journal of Epidemiology 2005 162:471-8.

34. Bodnar L, Davidian M, Siega-Riz A, et al. Marginal Structural Models for Analyzing Causal Effects of Time-dependent Treatments: An Application in Perinatal Epidemiology. American Journal of Epidemiology 2004;159:926-34.

35. Joffe M, Ten Have T, Feldman H, et al. Model Selection, Counfounder Control, and Marginal Structural Models: Review and New Applications. The American Statistician 2004;58:272-9.

36. Bachmann M, Booysen F. Economic causes and effects of AIDS in South African households. AIDS 2006;20:1861-7.

Table 1. Sample characteristics by study examination, CARDIA Study, 1985-2006

	1985-86 (n=5102)		1987-88 (n=4552)		1990-91 (n=4066)		1992-93 (n=3677)		1995-96 (n=3324)		2000-01 (n=2956)		2005-06 (n=2629)	
	Mean/%	(SD)	Mean/%	(SD)	Mean/%	(SD)	Mean/%	(SD)	Mean/%	(SD)	Mean/%	(SD)	Mean/%	(SD)
Outcomes														
Binging	24.83	-	24.35	-	21.65	-	19.49	-	16.96	-	14.73	-	14.63	-
Frequency of consumption (number of glasses per week in past year)	4.82	8.42	4.79	8.56	4.39	8.40	4.45	8.58	4.32	8.43	4.43	10.25	4.56	9.39
Main exposure														
Neighborhood poverty														
Proportion in poverty	0.24	0.13	0.22*	0.12	0.17*	0.12	0.14	0.14	0.12	0.12	0.11	0.11		
Cumulative poverty±	0.23	0.13	0.23*	0.12	0.21*	0.11	0.19	0.10	0.18	0.09	0.17	0.09		
Baseline covariates														
Age	24.76	3.63												
Sex														

Male	45.51	-										
Female	54.49	-										
Race/ethnicity												
Black	51.55	-										
White	48.45	-										
Marital status												
Married	22.19	-										
Divorced/separated	6.65	-										
Widowed	7.12	-										
Never married	63.62	-										
Time-varying covariates												
Low Income (%)	42.30†	-	42.30†	-	42.30	-	38.27	-	33.34	-	25.41	-
Non-professional or managerial occupations (%)	78.12	-	66.41	-	58.96	-	53.43	-	49.66	-	49.66	
Less than high school education (%)	10.03	-	7.57	-	6.15	-	5.75	-	6.29	-	5.00	-
Any children or stepchildren (%)	31.79	-	33.726	-	50.43	-	56.25	-	63.94	-	72.15	-
Home ownership												

Owned (%)	44.97†	-	44.97†	-	44.97	-	51.69	-	56.27	-	68.84	-	
Depression score (CES-D; % above depressive cutoff of 16)	20.37†		20.37†		20.37		20.35*		16.48		12.06		

* Values interpolated from closest available measures; †Variable not measured at these times--value taken from closest available measurement.

± Mean value of poverty, based on measures of poverty at all the time points up to time t.

Table 2. Odds ratios of binging (dependent variable) per unit increase in neighborhood proportion below poverty as estimated from standard models and marginal structural models

	Exposure 1: Cumulative poverty up to t-1									Exposure 2: Poverty at t-1								
	Crude model			Model with traditional adjustment for time-varying covariates[1]			Marginal structural model[2]			Crude model			Model with traditional adjustment for time-varying covariates[1]			Marginal structural model[2]		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Intercept	0.29	0.25	0.34	1.65	0.87	3.14	2.97	1.60	5.52	0.29	0.25	0.33	1.64	0.87	3.09	2.97	1.62	5.45
Baseline covariates																		
Age				1.00	0.98	1.02	0.99	0.97	1.01				1.00	0.98	1.02	0.99	0.97	1.01
Time	0.88	0.86	0.90	0.88	0.85	0.91	0.87	0.84	0.90	0.88	0.86	0.91	0.88	0.85	0.91	0.88	0.85	0.91
Female				0.24	0.21	0.27	0.25	0.21	0.29				0.24	0.21	0.28	0.25	0.21	0.29
Race/ethnicity																		
Black				0.73	0.63	0.85	0.91	0.78	1.06				0.73	0.63	0.85	0.90	0.78	1.05
Marital status (reference: Never married)																		
Married				0.73	0.59	0.90	0.77	0.63	0.95				0.73	0.59	0.90	0.78	0.63	0.95
Widowed				1.36	1.06	1.76	1.33	1.01	1.75				1.36	1.05	1.76	1.33	1.01	1.75
Divorced/separated				1.34	1.01	1.78	1.47	1.10	1.97				1.33	1.00	1.76	1.47	1.10	1.97
Time-varying covariates																		
Cumulative	1.29	0.74	2.25	1.45	0.79	2.69	1.59	0.81	3.12									

poverty lagged by one examination													
Poverty lagged by one examination				1.43	0.92	2.23	1.44	0.91	2.28	1.62	1.00	2.64	
Low income (<$25,000)	1.17	1.03	1.34				1.17	1.03	1.34				
Less than HS education	1.65	1.31	2.09				1.65	1.31	2.09				
Cumulative exposure to nonprofessional/ managerial occupations	1.57	1.27	1.93				1.56	1.27	1.93				
Depression (CESD ≥16)	1.28	1.11	1.48				1.28	1.11	1.49				
Number of children in the household	1.23	1.06	1.42				1.23	1.06	1.42				
Home ownership (reference: owned	1.03	0.90	1.17				1.02	0.90	1.17				

[1] This model was unweighted and adjusted for both the baseline regressors and the same time-varying regressors as those used in the linear model for the denominator of $s_{wi.}$
[2] This model used IPTC weights and adjusted for the baseline regressors.

Table 3. Relative rates of weekly drinks consumed (dependent variable) associated with a unit increase in neighborhood proportion below poverty as estimated from standard models and marginal structural models

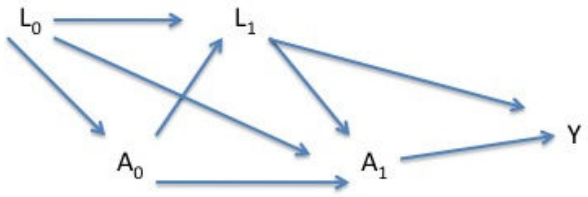
	Exposure 1: Cumulative poverty up to t-1									Exposure 2: Poverty at t-1								
	Crude model			Model with traditional adjustment for time-varying covariates[1]			Marginal structural model[2]			Crude model			Model with traditional adjustment for time-varying covariates[1]			Marginal structural model[2]		
	OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI		OR	95% CI	
Intercept	3.91	3.47	4.41	6.65	3.99	11.09	10.44	5.96	18.29	4.01	3.63	4.42	6.91	4.20	11.37	13.86	7.31	26.29
Baseline covariates																		
Age				1.02	1.01	1.04	1.02	1.00	1.04				1.03	1.01	1.04	1.02	1.00	1.04
Time	1.01	0.99	1.03	1.02	0.99	1.04	1.03	0.98	1.08	1.02	0.99	1.04	1.02	0.99	1.04	1.01	0.99	1.04
Female				0.36	0.33	0.41	0.34	0.29	0.40				0.37	0.33	0.41	0.34	0.29	0.40
Race/ethnicity																		
Black				0.90	0.81	1.01	0.89	0.68	1.18				0.92	0.83	1.03	0.97	0.81	1.16
Marital status (reference: Never married)																		
Married				0.86	0.72	1.03	0.85	0.64	1.11				0.86	0.72	1.02	0.84	0.63	1.11
Widowed				1.25	1.06	1.48	1.15	0.90	1.48				1.25	1.06	1.48	1.14	0.89	1.48
Divorced/separated				1.33	1.04	1.70	1.44	1.05	1.97				1.32	1.03	1.69	1.44	1.06	1.97
Time-varying covariates																		
Cumulative poverty lagged by	1.55	1.00	2.40	1.69	1.08	2.65	2.87	1.10	7.46									

one examination													
Poverty lagged by one examination							1.40	1.00	1.95	1.32	0.96	1.83	0.93	0.43	2.01
Low income (<$25,000)	1.22	1.10	1.35							1.22	1.10	1.36			
Less than HS education	1.64	1.33	2.00							1.64	1.34	2.01			
Cumulative exposure to nonprofessional/ managerial occupations	1.08	0.95	1.23							1.08	0.95	1.23			
Depression (CESD ≥16)	1.21	1.07	1.36							1.21	1.08	1.36			
Number of children in the household	1.08	0.97	1.20							1.08	0.97	1.20			
Home ownership (reference: owned	1.06	0.95	1.18							1.06	0.95	1.17			

[1] This model was unweighted and adjusted for both the baseline regressors and the same time-varying regressors as those used in the linear model for the denominator of $s_{wi.}$
[2] This model used IPTC weights and adjusted for the baseline regressors.

Supplemental Digital Content 1: Illustration of IPTW weight estimation

In the case of non-randomized exposure experienced at a single time point, it is possible to adjust for confounding variables by including them in a regression model. However, when a non-randomized exposure is experienced at multiple time points, covariate adjustment will not work. In the case addressed in this study, imagine the following scenario:



Imagine that L_k denotes a series of confounding variables that exist at time k (in our case, this would be, for example, individual income, education and occupation) and A_k denotes the exposure of interest at time k (i.e. proportion of neighborhood residents with a family income under the poverty threshold). L_1 is affected by exposure A_0—for example, living in a high-poverty neighborhood may limit the type of income-generating and educational opportunities a person can obtain. At the same time, L_1 confounds the relationship between A_1 and Y—that is, individual income, education and occupation influence the level of exposure to a neighborhood with a certain poverty level, and they are also associated with the alcohol use and misuse. In traditional covariate adjustment, if one adjusts for both A_0 and L_1, one is "overadjusting" for a variable in the causal pathway, thus taking away variability associated with the time-varying treatment. However, if one doesn't control for L_1, one ignores potential confounding bias.

The marginal structural model (MSM) is a tool that can be used in the case of time dependent treatments and time-dependent confounders—i.e. observed covariates that are affected by the treatment and relevant to the outcome of interest. MSMs are estimated using Inverse Probability of Treatment Weighting (IPTW). IPTW calculates the probability of an individual receiving the treatment (exposure in a nonrandomized study) they actually received, conditional on their observed stable and time-varying covariates. Individuals are weighted by

the inverse of their probability in order to create a "pseudopopulation" consisting of w_i copies of each subject. People who are most unrepresented in treatment assignment (exposure in a nonrandomized study) are given proportionally higher weights, while individuals who are highly represented in treatment assignment are given proportionately lower weights, so that we can obtain a comparable population in terms of stable and time-varying confounders across levels of the treatment assignment. We can then use the weighted "pseudopopulation" that is balanced in terms of distribution of potential confounders across treatment levels, to estimate the unconfounded relationship between exposure A and outcome Y. By using weighting to address confounding, this approach literally removes time-varying confounders that are in the pathway between the exposure of interest and the outcome, from the dependent side of the equation, and thus avoids the problem of potentially "overcontrolling" for a mediator.

For example, imagine that the distribution of exposure A is imbalanced across the confounder L, so that at L=0, ¾ of the subjects are unexposed to A (A=0) and ¼ are exposed to A (A=1), while at L=1, ¾ of the subjects are exposed to A (A=1) and ¼ are unexposed. If we have 8 subjects (4 at each level of L), and we calculate the probability of A given L, we can conclude that at L=0, 3 of the subjects will have a probability of ¾ of having the exposure A they already have (P (A=0)) and one will have a probability of ¼ of having their own exposure (P (A=1)); in contrast, at L=1, 3 of the subjects will have a probability of ¾ of having A=1, and one will have a probability of ¼ of A=0. Since the IPTW is the inverse of the probability of receiving the treatment they received, given their own covariate history—for those who had L=0 and A=0, the IPTW would be 4/3, while for those who had L=0 and A=1, the IPTW will be 4/1. If, for ease of interpretation, we multiply each of these IPTWs by the relative ratio of the weights (3 to 1), this means that at L=0, the weight for those with A=0 will be 4 and for those with A=1 it will be 12. Using these weights, we will then make 4 copies of each of the three individuals with A=0 (i.e. 3 individuals x 4 copies = 12 "fake individuals" with P (A=0/L=0)), and 12 copies of the 1 individual with A=1 (i.e. 1 individual x 12 copies = 12 "fake individuals" with P(A=1/L=0)). Thus, there would be an equal number of exposed and unexposed individuals at L=0. We can repeat the same process at L=1, so that those with A=1/L=1 would have an IPTW of 4/3 and those with A=0/L=1 would have an IPTW of 4. If we repeated the same process of multiplying by the relative ratio of 3,

we would again end up with 4 copies of each of the three individuals with A=1 (i.e. 3 individuals x 4 copies =12 with P(A=1/L=1)), and 12 copies of the individual with A=0 (i.e. 1 individual x 12 copies = 12 with P(A=1/L=0). In the end, we would thus have, at each level of L, 12 individuals with A=1 and 12 individuals with A=0, and we would have a perfectly balanced distribution of exposure history by covariate history. We then use the weighted "pseudopopulation" to estimate the relationship between exposure A and outcome Y. In this way, inverse probability of weighting addresses a potential imbalance in confounders by exposure history, and thus addresses confounding without introducing the simultaneous confounder and mediator L into the equation estimating the relationship between A and Y.

Supplemental Digital Content 2*:* Testing whether time-varying covariates acted as confounders and mediators

We examined whether the time-varying covariates of interest in our data could be both confounders and mediators in the causal pathway between pov_{neigh} and alcohol use/misuse (directed acyclic graph presented below). We tested whether: a) the main time-varying covariates of interest, low income, non-professional/managerial occupations and low education were longitudinally associated with later pov_{neigh} (i.e. covariates could act as a selector into neighborhood poverty); b) pov_{neigh} predicted the main time-varying covariates of interest (i.e. whether time-varying covariates fulfilled the first requirement to be mediators of the pov_{neigh} - binging and pov_{neigh} - frequency of alcohol use relationships); and c) the time-varying covariates were associated with alcohol frequency of use/binging, independently of pov_{neigh} (i.e. the second condition necessary for the covariates to be confounders or mediators of the pov_{neigh} -alcohol use relationship).

In order to test these conditions, we estimated a series of models including: a) repeated measures linear regression models separately estimating the association between lagged income, education and non-professional/managerial status and pov_{neigh}; b) repeated measures marginal logistic regression models separately estimating the association between lagged pov_{neigh} and low income, low education and non-professional/managerial occupational status; c) repeated measures marginal logistic/ negative binomial models estimating the association between lagged pov_{neigh} (estimated separately as cumulative up to *t*-1 and as just poverty at *t*-1), low income, low education, non-professional/managerial occupational status, and alcohol use (frequency of use and binging). We explored several different functional forms of income at the prior examination (continuous income, less than $25,000 of income, cumulative income up to the examination t-1, cumulative income for the two examinations, and cumulative income for the past three examinations), education at the prior examination (continuous years of education, less than high school education, educational categories—less than high school, high school, more than high school) and occupational status at the prior examination (continuous employment codes, non-professional or managerial, cumulative exposure to non-professional or managerial up to examination t-1, cumulative exposure to non-professional/managerial in past two examinations, and cumulative exposure to non-professional/managerial in past three examinations) to

determine which specific functional form best predicted pov_{neigh} –in terms of significance and model fit. Since pov_{neigh} is skewed, $\ln(pov_{neigh})$ was used as the outcome measure in the models that estimated the association between it and lagged income, education and non-professional/managerial status.

An additional precondition for marginal structural models to be useful is that time-varying covariates and the main exposure of interest, in this case pov_{neigh}, actually change over time. We tested this precondition by examining the tracking correlation between reports for the same measure over time; we wanted to see if the magnitude of the correlation between measures of pov_{neigh} at different examination points decreased markedly over time.

Table A1 shows the relationship between income, occupation and education at *t*-1 and $\ln(pov_{neigh})$ at *t*. Comparison of models with different functional forms for income, occupation and education (not shown) indicated that low income, less than high school education and cumulative exposure to non-professional/managerial positions up to *t*-1 were associated with a larger magnitude of change in $\ln(pov_{neigh})$ than their counterparts, and were thus selected as the functional forms for these predictors. Model 4 incorporates all three predictors of $\ln(pov_{neigh})$: having a low income, less than high school education and a longer exposure to non-professional/managerial positions were all positively associated with $\ln(pov_{neigh})$.

Table A2 provides estimates of associations in the other direction: the association between lagged pov_{neigh} and the odds of having low income, less than high school education, and a non-professional/managerial occupation. A 20% increase in the proportion of residents in pov_{neigh} was associated with higher odds of having a low income (OR: 1.32; 95% confidence interval (CI): 1.21,1.45), having less than high school education (OR: 1.32; 95% CI: 1.11,1.57) and with having a non-professional or managerial degree (OR: 1.25; 95% CI: 1.14, 1.37).

Table A3 shows the mean, standard deviation and correlations between neighborhood poverty measures across the six examinations of measurement. The mean proportion of poverty in neighborhoods decreased over the study duration, from 24% to 12% of the population. Moreover, the magnitude of the correlation between pov_{neigh} decreased from 0.98 to 0.22 over time, indicating that the concentration of poverty in the neighborhood did change over time.

Table A1. Parameter estimates and standard errors from mixed linear regression models exploring the relationship between lagged income, occupation and education and dependent variable $\ln(\text{pov}_{\text{neigh}})$ over time: the CARDIA study, 1985-2001

	M1[1]		M2[2]		M3[3]		M4[4]	
Variable	Parameter	SE	Parameter	SE	Parameter	SE	Parameter	SE
Intercept	-0.82***	0.03	-0.75***	0.04	-0.82***	0.04	-0.88***	0.04
Baseline covariates								
Age (years)	0.002	0.001	0.001	0.001	0.002*	0.001	0.003*	0.001
Time	-0.07***	0.004	-0.07***	0.004	-0.07***	0.004	-0.07***	0.004
Female	-0.01	0.01	-0.005	0.01	-0.01	0.01	-0.01	0.01
Race/ethnicity								
Black	0.20***	0.01	0.21***	0.01	0.21***	0.01	0.19***	0.01
Marital status (reference: never married)								
Married	-0.02~	0.01	-0.02*	0.01	-0.02~	0.01	-0.02~	0.01
Widowed	0.004	0.02	0.01	0.02	0.01	0.02	0.01	0.02
Divorced/ separated	0.01	0.02	0.02	0.02	0.01	0.02	0.01	0.02
Time-varying covariates								
Prior $\ln(\text{pov}_{\text{neigh}})$	0.66***	0.01	0.67***	0.01	0.66***	0.01	0.66***	0.01
Prior low income ($\leq$\$24,999)[5]	0.07***	0.01					0.06***	0.01
Prior less than HS education			0.07***	0.02			0.05*	0.02
Prior cumulative occupation[6]					0.07***	0.01	0.04*	0.01
Depression (CESD $\geq$16)[5]	0.04***	0.01	0.04***	0.01	0.04***	0.01	0.04*	0.01
Number of children in the household	0.01	0.01	-0.004	0.01	-0.01	0.01	0.005	0.01
Home ownership (home owned is reference category)[5]	-0.01	0.01	-0.05***	0.01	-0.05***	0.01	0.01	0.01

p-values: ~<.10; *<0.05; ***<0.0001

[1] Mixed linear regression model estimating association between low income and $\ln(\text{pov}_{\text{neigh}})$

[2] Mixed linear regression model estimating association between low education and $\ln(\text{pov}_{\text{neigh}})$

[3] Mixed linear regression model estimating association between cumulative non-professional/managerial occupation and $\ln(\text{pov}_{\text{neigh}})$

[4] Mixed linear regression model estimating association between low income, low education, cumulative non-professional/managerial occupation and $\ln(\text{pov}_{\text{neigh}})$

[5] Values are interpolated for those examination times when the covariate was not measured

[6] Cumulative occupation is defined as cumulative exposure to non-professional or managerial up to examination t-1

Table A2. Odds ratios and 95% confidence intervals estimating the association between lagged $\ln(pov_{neigh})$ and three time-varying dependent variables: low income (<$25,000), less than high school education and non-professional/managerial occupations: the CARDIA study, 1985-2001

	Low income			Less than high school			Non-professional or managerial occupations		
	M1			M2			M3		
	OR	95% CI		OR	95% CI		OR	95% CI	
Intercept	2.29	1.40	3.73	0.34	0.10	1.24	7.94	5.04	12.50
Baseline covariates									
Age (years)	0.96	0.94	0.97	0.94	0.90	0.98	0.94	0.92	0.95
Time	0.80	0.77	0.82	0.85	0.80	0.91	0.91	0.88	0.93
Female	1.02	0.90	1.14	0.55	0.41	0.72	0.93	0.83	1.04
Race/ethnicity									
Black	1.59	1.39	1.80	1.23	0.88	1.72	2.05	1.82	2.32
Marital status (reference: never married)									
Married	0.44	0.37	0.53	0.96	0.62	1.49	0.89	0.76	1.03
Widowed	0.67	0.53	0.84	0.99	0.55	1.78	0.93	0.76	1.15
Divorced/separated	1.13	0.88	1.43	1.54	0.89	2.65	1.22	0.94	1.58
Time-varying covariates									
Poverty at t-1	4.07	2.60	6.36	3.95	1.66	9.45	3.05	1.94	4.82
Depression (CESD $\geq$16)	1.64	1.44	1.86	1.94	1.49	2.54	1.42	1.25	1.61
Number of children in the household	1.55	1.36	1.76	2.90	2.13	3.96	1.90	1.70	2.13
Home ownership (reference: owned)	0.37	0.33	0.41	0.37	0.27	0.51	0.77	0.69	0.85

Table A3. Correlations between pov_{neigh} at different years of measurement: the CARDIA study, 1985-2001

Year of measurement	pov_{neigh} by year of measurement					
	1985-86	1987-88	1990-91	1992-93	1995-96	2000-01
1985-86	1	0.98	0.67	0.41	0.26	0.22
1987-88	0.98	1	0.75	0.48	0.31	0.25
1990-91	0.67	0.75	1	0.43	0.28	0.19
1992-93	0.41	0.48	0.43	1	0.49	0.3
1995-96	0.26	0.31	0.28	0.49	1	0.27
2000-01	0.22	0.25	0.19	0.3	0.27	1

Supplemental Digital Content 3: Sample SAS program to estimate IPTCW weights and an MSM model

```
/*TREATMENT WEIGHTS*/
/********Program to calculate the numerator of the IPTW weights **********************/
proc reg data=cardia_long;
        where cens=0; /*this means for those respondents who have not been censored*/
        model log_povt=log_prepovt a01age1 time a01sex black married widow divsep ; /*baseline covariates*/
        output out=model1a p=pa0_num r=res0_num; /*here res0_num is the residual*/
run;
/*need to check whether the residual is normally distributed*/
proc univariate data=model1a plot normal;
var res0_num;
run;
/*creating the squared residual from the model output*/
data num_residual;
set model1a;
ressq=res0_num*res0_num;
run;
/*estimating the variance of the residual squared*/
proc genmod data=num_residual;
        where cens=0;
        model ressq=log_prepovt a01age1 time a01sex black married widow divsep  /dist=normal link=log;
        output out=model1b p=pa0_num2 ;/*pa0_num2 is the variance, or σ^2 */
run;
proc sort data=model1a;
```

```
by id time;
proc sort data=model1b;
by id time;
data num_residual2;
merge model1b model1a;
by id time;
/*here we are using the residual and variance to step-by-step estimate the log normal density function*/
residual=ressq/(2*pa0_num2);
exponent=exp(-(residual));
den=1/((sqrt(2*3.14159))*(sqrt(pa0_num2))*povt);
num_prob=den*exponent;
run;
```

/* $\frac{(\ln pov_{neigh,ti} - \ln \hat{pov}_{neigh,ti})^2}{2\sigma^2}$ */

/* $\exp - \left(\frac{(\ln pov_{neigh,ti} - \ln \hat{pov}_{neigh,ti})^2}{2\sigma^2} \right)$ */

/* $\frac{1}{\sqrt{2\pi\sigma^2}\, pov_{neigh,ti}}$ */

/* $\frac{1}{\sqrt{2\pi\sigma^2}\, pov_{neigh,ti}} * \exp - \left(\frac{(\ln pov_{neigh,ti} - \ln \hat{pov}_{neigh,ti})^2}{2\sigma^2} \right)$ */

/*Program to calculate the denominator of the IPTW weights ************************/**

```
proc reg data=cardia_long;
        where cens=0;
        model log_povt=log_prepovt a01age1 time a01sex black married widow divsep
 predrink pst_loinc pst_hs cum_nonprof dep child home ;
        output out=model1b p=pa0_den r=res0_den;
run;
proc univariate data=model1b plot normal;
var res0_den;
```

```
run;
/*creating the squared residual from the model output*/
data den_residual;
set model1b;
ressq=res0_den*res0_den;
run;
/*estimating the variance of the residual squared*/
proc genmod data=den_residual;
        where cens=0;
        model ressq=log_prepovt a01age1 time a01sex black married widow divsep
 predrink pst_loinc pst_hs cum_nonprof dep child home /dist=normal link=log;
        output out=model1b2 p=pa0_den2 ;/*pa0_num2 is the variance, or σ^2 */
run;
proc sort data=model1b;
by id time;
proc sort data=model1b2;
by id time;
data den_residual2;
merge model1b model1b2;
by id time;
residual=ressq/(2*pa0_den2);
```

/* $\frac{\sqrt{\ln pov_{neigh,ti} - \ln \hat{pov}_{neigh,ti}}}{2\sigma^2}$ */

```
exponent=exp(-(residual));
```

/* $\exp -\left(\frac{(\ln pov_{neigh,ti} - \ln \hat{pov}_{neigh,ti})^2}{2\sigma^2} \right)$ */

den=1/((sqrt(2*3.14159))*(sqrt(pa0_den2))*povt); /* $\frac{1}{\sqrt{2\pi\sigma^2}\,pov_{neigh,ti}}$ */

den_prob=den*exponent; /* $\frac{1}{\sqrt{2\pi\sigma^2}\,pov_{neigh,ti}} * \exp{-\left(\frac{(\ln pov_{neigh,ti} - \ln \hat{pov}_{neigh,ti})^2}{2\sigma^2}\right)}$ */

run;

proc univariate data=den_residual2 plot normal;

var stdres den_prob;

run;

/*CENSORING WEIGHTS (IPCW)*/

/*First is the program to estimate the denominator*/

proc logistic descending data=cardia_long;

class a01sex ;

model cens(event='0')=log_prepovt time a01age1 a01sex black married widow divsep;

output out=model1ca p=pc0_num;

run;

/*Second is the program to estimate the denominator*/

proc logistic descending data=cardia_long ;

class a01sex prebinge home;

model cens(event='0')=log_prepovt a01age1 time a01sex black married widow divsep

predrink pst_loinc pst_hs cum_nonprof dep child home ;

output out=model1cb p=pc0_den;

run;

proc sort data=num_residual2;

by id time;

run;

```
proc sort data=den_residual2;
by id time;
run;
proc sort data=model1ca;
by id time;
run;
proc sort data=model1cb;
by id time;
run;
```

/*Here we actually create the final stabilized weights, which are a product of the IPTW and IPCW weights*/

```
data weights;
        merge den_residual2 num_residual2 model1b model1ca model1cb;
        by id time;
        if first.id then do;
        k1_0=1;kc1_0=1;
        k1_w=1;kc1_w=1;
        end;
        retain k1_0 kc1_0 k1_w kc1_w;
        /*inverse probability of censoring weights*/
        kc1_0=kc1_0*pc0_num;
        kc1_w=kc1_0*pc0_den;
        /*inverse probability of treatment weights*/
                        k1_0=k1_0*num_prob;
```

```
                    k1_w=k1_w*den_prob;


        /*stabilized weights*/
        stabwt=(k1_0*kc1_0)/(k1_w*kc1_w);
        run;
```

/*WEIGHTED MSM MODEL*?

```
 /*Here we use the stabilized weights to estimate an MSM model—that is a weighted model estimating the marginal relationship between cumulative poverty at t-1 and the frequency of weekly alcohol use in the past year */
 proc genmod descending data=weights ;
        class id;
        model drink= time cum_povt a01age1 time a01sex black married widow divsep
 /link=log dist=poisson ;
        weight stabwt;
        repeated subject=id/type=ind;
 run;
```