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Using Marginal Structural Models to Estimate the Direct Effect of Adverse Childhood Social Conditions on Onset of Heart Disease, Diabetes, and Stroke

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Abstract

Background—Early-life socioeconomic status (SES) is associated with adult chronic disease, but it is unclear whether this effect is mediated entirely via adult SES or whether there is a direct effect of adverse early-life SES on adult disease. Major challenges in evaluating these alternatives include imprecise measurement of early-life SES and bias in conventional regression methods to assess mediation. In particular, conventional regression approaches to direct effect estimation are biased when there is time-varying confounding of the association between adult SES and chronic disease by chronic disease risk factors.

Methods—First-reported heart disease, diabetes and stroke diagnoses were assessed in a national sample of 9,760 Health and Retirement Study participants followed biennially from 1992 through 2006. Early-life and adult SES measures were derived using exploratory and confirmatory factor analysis. Early-life SES was measured by parental education, father's occupation, region of birth, and childhood rural residence. Adult SES was measured by respondent's education, occupation, labor force status, household income, and household wealth. Using marginal structural models we estimated the direct effect of early-life SES on chronic disease onset that was not mediated by adult SES. Marginal structural models were estimated with stabilized inverse-probability-weighted log-linear models to adjust for risk factors that may have confounded associations between adult SES and chronic disease.

Results—During follow-up, 24%, 18%, and 9% of participants experienced first onset of heart disease, diabetes, and stroke, respectively. Comparing those in the most disadvantaged to the least disadvantaged quartile, early-life SES was associated with CHD (risk ratio=1.30 [95% confidence interval= 1.12–1.51]) and diabetes (1.23 [1.02–1.48]) and marginally associated with stroke via pathways not mediated by adult SES.

Conclusions—Our results suggest that early-life socioeconomic experiences directly influence adult chronic disease outcomes.

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Early-life socioeconomic conditions predict adult cardiovascular disease (CVD); however, the role of adult socioeconomic status (SES) in mediating this relationship remains controversial and persistent socioeconomic inequalities in chronic diseases exist.[1–7] At least three alternative hypotheses linking early-life SES to chronic disease outcomes in later life have been proposed.[1] According to the latent-effects model, early-life SES affects risk for chronic disease independently of adult SES. The effect of early-life SES on chronic disease that is not mediated by adult SES (e.g., if everyone in the population was fixed to a "high" level of adult SES) is defined as the controlled direct effect of early-life SES[8]; direct effects may include physiologic embodiment of socioeconomic disadvantage and attendant exposures through "fetal-programming" (represented by path 1 in Figure 1) and behavioral changes and shifts in chronic disease risk factors (represented by path 2*3 in Figure 1).[9] In contrast, the pathway or social-trajectories model suggests that early-life SES does not directly affect disease risk. Rather, early-life SES is linked to chronic disease in later life through its influence on SES in adulthood (represented by paths 4*5 and 2*6*5 in Figure 1). Finally, the cumulative-exposure model hypothesizes that SES in both early-life and adulthood directly influences disease risk in later life.

Extant research concerning the relation between life-course SES and chronic disease is mixed. Some evidence suggests that early-life SES directly influences CVD, independently of adult SES.[10–13] However, several studies have shown that associations between early-life SES and CVD outcomes were attenuated after adjustment for adult SES and CVD risk factors.[14,15] These inconsistencies may result from methodological challenges in estimating direct effects. For example, greater error in the measurement of early-life relative to adult SES may underestimate the direct effect of early-life SES on chronic disease outcomes.[16] Additionally, conventional regression methods to assess mediation,[17] specifically by regressing a chronic disease outcome on early-life SES, the proposed mediator (i.e., adult SES), and potential confounders and chronic disease risk factors (e.g., body mass index), produces an unbiased estimate of the controlled direct effect of early-life SES only under very specific conditions.[18]

In this study, we aimed to assess whether the effects of early-life SES on adult onset of coronary heart disease (CHD), diabetes, and stroke were mediated by adult SES using data from the US-based Health and Retirement Study. We improved on extant work by using factor analyses to measure SES and applying a marginal structural model to control for adult cardiovascular risk factors. Adult risk factors may confound the association of adult SES and CVD but mediate the effect of early-life SES on adult CVD. Conventional approaches to direct effect estimation are biased when there is time-varying confounding by adult risk factors. However, by handling potential confounding by measured covariates through weighting rather than conditioning on covariates, marginal structural models allow for the identification of direct effects even in settings in which conventional approaches are biased, including when there is a consequence of early-life SES that confounds the association between adult SES and the outcome of interest.[19,20] We compare results from marginal structural models to estimates obtained using the conventional direct effects estimation procedure based on regression adjustment for measured risk factors.[17]

METHODS

Study design

The Health and Retirement Study is a longitudinal, biennial survey of a national sample of US adults born 1931–1941 and their spouses. The study was initiated in 1992, based on a multi-stage area probability sample. The initial response rate was 81% and biennial follow-up interviews (or proxy for decedents) were conducted between the baseline assessments in 1992 and 2006, with wave-to-wave retention rates through 2006 of approximately 90%.[21]

The University of Michigan Health Sciences Human Subjects Committee approved the Health and Retirement Study.

We followed respondents through 2006 for first onset of three chronic disease outcomes: (1) fatal or non-fatal heart disease; (2) diabetes; or (3) fatal or non-fatal stroke. The Health and Retirement Study most commonly learns of the death of a respondent when an interviewer attempts to reach the respondent for a biennial follow-up interview. In these instances, the respondent's spouse or another close family member completes a final (exit) interview. The overall response rate for exit interviews conducted through 2002 was 93 percent, and there is no evidence of systematic bias by demographic groups. The Health and Retirement Study conducts linkages using the Social Security Death Index and the National Death Index to confirm the status, timing, and cause of death for deceased respondents. Further details of the study design and outcomes assessment of the Health and Retirement Study are available elsewhere.[22–24]

Among 9,760 age-eligible Health and Retirement Study participants enrolled in 1992, we excluded 495 (5%) without a follow-up interview between 1994 and 2006. Excluding prevalent cases of each outcome at baseline, we defined three separate samples, comprising 8,318 CHD-free, 8,278 diabetes-free, and 9,055 stroke-free participants.

Measures

For consistency with previous studies, we used standard RAND coding of wealth, income, and other variables, when available.[25]

Chronic disease outcomes—At each wave, participants were asked, "Since we last talked to you, has a doctor told you that you had a heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems?" Diabetes and stroke were similarly assessed. For deceased participants or those unavailable for direct interviews, proxy informants, typically spouses, were interviewed.

Life-course socioeconomic status—We used exploratory and confirmatory factor analyses to estimate the latent construct SES at two stages in the life-course, early-life and adulthood. We selected eight indicators of early-life SES based on retrospective assessment and six indicators of adult SES (eTable 1, http://links.lww.com).[26,27] Exploratory factor analysis with quartimin rotation was used to assess the dimensionality of our SES indicators, resulting in a final two-factor model. Indicators of early-life SES included father's educational attainment (0–7, 8–11, 12, >12 years), mother's educational attainment (0–7, 8–11, 12, >12 years), father's occupation (manual/unskilled service, professional/white collar), birth in the southern US (yes/no), and rural residence during childhood (yes/no); all were assessed retrospectively at baseline with the exception of father's occupation, which was assessed in 1998. Indicators of adult SES included respondent's educational attainment (<high school, high school/GED, some college, college+), respondent's longest job occupation (manual/unskilled service, professional/white collar), respondent's current labor force status (works full-time/part-time/retired, unemployed/disabled/not in labor force), household income (split into quartiles), and household wealth (split into quartiles), all assessed at baseline. We next used confirmatory factor analysis with maximum likelihood estimation to output factor scores for early-life and adult SES. Continuous early-life and adult SES scores were cut into quartiles for analysis. Factor analyses were conducted in Mplus version 5. Further detail concerning the methods used to measure life-course SES is provided in the eAppendix, http://links.lww.com.

Confounders and risk factors—We distinguish between (1) socio-demographic confounders that potentially confound the relation between early-life SES and our outcomes and (2) chronic disease risk factors that potentially confound the relation between adult SES and our outcomes (as shown in the Figure).[28,29] Measured confounders of the relation between early-life SES and our outcomes included baseline age (categorized as 50–52, 53–55, 56–58, or >58), sex, race (dichotomized as black or other), and self-rated childhood health (very good/excellent, good, fair/poor, or unknown/missing). Measured baseline risk factors that potentially confounded the relation between adult SES and our chronic disease outcomes included whether a doctor had ever told the respondent they had high blood pressure (no or yes), body mass index (BMI) (categorized as <25, 25–29.9, or 30+), self-rated health (categorized as excellent, very good, good, fair, or poor), diabetes (no or yes), whether health problems limited the respondent's ability to work (no or yes), current smoking (no or yes), and alcohol consumption (categorized as doesn't drink, <1 drink/day, 1–2 drinks/day, or ≥3 drinks/day). Diabetes was not included as a risk factor in analyses for which diabetes was the outcome.

Statistical analyses

Our goal was to estimate, for individual, the controlled direct effect of early-life SES (A_i) on chronic disease outcomes (Y_i) that was not mediated by adult SES (M_i) after accounting for potential confounding by measured confounders (i.e., birth cohort, sex, race/ethnicity, and self-rated childhood health) and risk-factors (i.e., high blood pressure, BMI, self-rated health, diabetes, functional limitations, current smoking, alcohol consumption), represented by the vectors C_i and R_i, respectively. Here, and throughout, the variables A_i and M_i denote the vectors of indicator functions for the various quartiles of early-life and adult SES, respectively.

Formally, if we allow $Y_i(a, m)$ to represent the counterfactual outcome Y_i if potentially counter to the fact A_i had been set to a and M_i had been set to m, the controlled direct effect on the risk ratio (RR) scale comparing $A_i = a$ to $A_i = a^*$ for some fixed level $M_i = m$ is defined as

$$RR_i^m(a, a*) = \frac{P[Y_i(a, m)=1]}{P[Y_i(a*, m)=1]}.$$

Although it is often assumed that the effect of A_i on Y_i is homogenous for all levels of M_i, the controlled direct effect of early-life SES may depend on the value to which adult SES is set. As such we tested for interaction between A_i and M_i on Y_i in models estimating direct effects of early-life SES. However, in the absence of such interaction, the controlled direct effect is defined as the effect of early-life SES on the particular chronic disease outcome if adult SES were set to the highest quartile; this effect includes both paths 1 and 2*3 in the Figure, but not paths via adult SES (paths 4*5 or 2*6*5).

We compare two approaches for estimating the direct effect of early-life SES on our outcomes: the conventional regression approach to effect decomposition[17] and the marginal-structural-model approach using inverse probability weights.[19,20] First, we estimated on the RR scale the total effect of early-life SES on chronic disease outcomes, conditional on $C_i = c$,

$$RR_i(a, a*|c) = \frac{P[Y_i(a)=1|C_i=c]}{P[Y_i(a*)=1|C_i=c]},$$

by fitting a log-linear model for each outcome ($Y_i = 1$ if participant reports the outcome during follow-up, 1992–2006) regressedon quartiles of early-life SES (A_i) and the set of confounders(C_i), separately for the three samples comprising CHD-free, diabetes-free, and stroke-free respondents:

$$\log[P(Y_i=1|A_i=a, C_i=c)] = \beta_0 + \beta_1' A_i + \beta_2' C_i. \quad [1]$$

The coefficient β_1 in Model 1 gives an estimate of the total effect of early-life SES provided that the measured confounders suffice to control for confounding between early-life SES and the chronic disease outcomes. Second, we estimated the direct effect of early-life SES on our outcomes using the approach proposed by Baron and Kenny (1986).[17] Specifically, we regressed each outcome Y_i on quartiles of early-life SES (A_i), quartiles of adult SES (M_i), and the set of socio-demographic confounders (C_i), by fitting a log-linear model of the form:

$$\log[P(Y_i=1|A_i=a, M_i=m, C_i=c)] = \beta_0 + \beta_1' A_i + \beta_2' M_i + \beta_3' C_i. \quad [2]$$

The coefficient β_1 in Model 2 gives an estimate of the direct effect of early-life SES not through pathways involving adult SES (paths 1 and 2*3 in the Figure) provided that the measured confounders suffice to control for confounding between (i) early-life SES and the chronic disease outcomes and (ii) adult SES and the chronic disease outcomes. There was no evidence of interaction between C_i and A_i. As such, the coefficient β_1 gives both conditional direct effects and also the marginal direct effect described above. We additionally tested for interaction between early-life and adult SES on the chronic disease outcomes by including cross-product terms between A_i and M_i in Model 2. As seen in eTable 2 (http://links.lww.com), there was not evidence of interaction beyond what would be expected by chance alone for any of our outcomes and the cross-product terms were subsequently omitted.

To compare with prior work in which adult risk factors were controlled, we also fit a log-linear regression model (Model 3) in which adult risk factors (R_i) were included as covariates:

$$\log[P(Y_i=1|A_i=a, M_i=m, C_i=c, R_i=r)] = \beta_0 + \beta_1' A_i + \beta_2' M_i + \beta_3' C_i + \beta_4' R_i. \quad [3]$$

The coefficient β_1 in Model 3 gives an estimate of the direct effect of early-life SES not through pathways involving adult SES or the adult risk factors (path 1 in the Figure) provided that measured confounders and risk factors suffice to control for confounding between (i) early-life SES and the chronic disease outcomes, (ii) adult SES and the chronic disease outcomes and (iii) the adult risk factors and chronic disease outcomes. Note that even under these assumptions this is a different direct effect from that defined above (i.e., it includes only the effect of path 1 in the Figure). There was not consistent evidence of interaction between A_i and M_i in Model 3 (eTable 3, http://links.lww.com) for any of our outcomes and therefore we omitted the cross-product terms.

The controlled direct effect of early-life SES on our outcomes using a marginal structural model (Model 4) was estimated by a stabilized inverse-probability-weighted marginal structural model as described by VanderWeele and Robins et al.[19,20] In brief, we fit a weighted log-linear regression model of the form:

$$\log\left[P\left(Y_i=1|A_i=a, M_i=m\right)\right]=\beta_0+\beta_1^{'}A_i+\beta_2^{'}M_i, \quad [4]$$

excluding a cross-product term between early-life and adult SES because there was not consistent evidence of interaction for any of the outcomes (eTable 4, http://links.lww.com). Potential confounding by the sets of confounders and risk factors was accounted for by fitting the above model with stabilized inverse-probability weights of the form $W=w_i^A * w_i^M$, where

$$w_i^A=\frac{P(A=a_i)}{P(A=a_i|C=c_i)} \quad [5]$$

and

$$w_i^M=\frac{P(M=m_i|A=a_i)}{P(M=m_i|A=a_i, C=c_i, R=r_i)}. \quad [6]$$

The weight w_i^A accounts for measured confounding of the relation between early-life SES and the chronic disease outcomes and the weight w_i^M accounts for measured confounding of the relation between adult SES and the outcomes. The coefficients β_1 in the final weighted model (Model 4) gives the direct effect of early-life SES not through adult SES pathways provided that (i) the measured confounders suffice to control for confounding between early-life SES and chronic disease outcomes and (ii) the measured confounders, early-life SES, and the adult risk factors suffice to control for confounding between adult SES and chronic disease outcomes. Note that under these assumptions the direct effect β_1 includes the effect of early-life SES through adult risk factor pathways (path 2*3 in the Figure, in addition to path 1), but not through adult SES.

The denominator of w_i^A is the probability of receiving the quartile of early-life SES the individual in fact experienced, conditional on the set of confounders. The denominator of w_i^M is the probability of receiving the quartile of the mediator, adult SES, the individual in fact experienced, conditional on quartiles of early-life SES, confounders, and the set of risk factors. Stabilizing the weights by including probabilities in the numerator results in more efficient estimation.[20] Weights were estimated using multinomial logistic regressions where the response variables for w_i^A and w_i^M were quartiles of SES in early-life and adulthood, respectively. Predicted probabilities for the numerator and denominator were assigned based on the category of actual SES reported and divided to obtain stabilized weights. The distributions of the multiplied weights, *W*, were: (1) Mean=1.00, Range=0.15–10.88, IQR=0.68–1.12 for heart disease; (2) Mean=1.00, Range=0.16–9.88, IQR=0.69–1.13 for diabetes; and (3) Mean=1.00, Range=0.16–10.12, IQR=0.68–1.12 for stroke. See eFigures 2–4 (http://links.lww.com) for histograms and additional statistics describing the distributions of the stabilized weights for each of the outcomes. All analyses were conducted using SAS version 9.1.3. Annotated SAS code for estimating the models described above is provided in the eAppendix (http://links.lww.com).

RESULTS

Characteristics of the total sample and the samples used in analyses for each condition are shown in Table 1. Between baseline and the end of follow-up in 2006 24% of participants experienced first-onset heart disease (1886 non-fatal and 115 fatal events), 18% experienced first-onset diabetes (1461 events), and 8% experienced first-onset stroke (618 non-fatal and 90 fatal events).

Estimates of the total and direct effects of early-life SES on CHD are shown in Table 2. The total effects model (Model 1) indicated that those in the third and fourth most disadvantaged quartiles of early-life SES had, respectively, 12% (RR=1.12 [95% confidence interval (CI)=1.00–1.25]) and 16% (1.16 [1.04–1.30]) increased risk of CHD compared with those in the least disadvantaged quartile of early-life SES. After adjusting for adult SES in Model 2 as in a conventional regression approach, there was a null association between early-life SES and CHD (1.00 [0.87–1.16]), comparing those in the most disadvantaged to least disadvantaged quartile of early-life SES]. Results were essentially unchanged after adjusting for adult risk factors (Model 3). Applying the marginal structural model approach using inverse-probability weights to adjust for adult risk factors (Model 4), those in the third and fourth most disadvantaged quartiles of early-life SES were estimated to have, respectively, 23% (1.23 [1.08–1.40]) and 30% (1.30 [1.12–1.51]) increased risk of CHD compared with those in the least disadvantaged quartile of early-life SES.

Estimates of the total and direct effects of early-life SES on diabetes are shown in Table 3. There was a dose-response association between early-life SES and diabetes (Model 1). Compared with those in the least disadvantaged quartile of early-life SES, those in the second, third, and fourth quartiles had, respectively, 12% (1.12 [0.97–1.29]), 31% (1.31 [1.14–1.51]), and 62% (1.62 [1.41, 1.86]) increased risk of diabetes. The association between early-life SES and diabetes was substantially attenuated after adjustment for adult SES (Model 2) and nearly null after additional adjustment for adult risk factors (Models 3). In the marginal structural model (Model 4), those who experienced the greatest disadvantage in early life showed increased risk of diabetes relative to those in the least disadvantaged quartile (1.23 [1.02–1.48]).

Estimates of the total and direct effects of early-life SES on stroke are shown in Table 4. The total-effects model (Model 1) showed those in the third and fourth most disadvantaged quartiles of early-life SES had, respectively, 37% (1.37 [1.11–1.69]) and 59% (1.59 [1.29–1.95]) increased risk of stroke relative to those in the least disadvantaged quartile. After controlling for adult SES and risk factors using the conventional regression approach (Models 2 and 3), associations between early-life SES and stroke were attenuated and provided no evidence of a direct effect of early-life SES. The associations between early-life SES and stroke using the marginal structural model approach (Model 4) were stronger in magnitude than for the conventional regression approach; for example, the 4th quartile of early-life SES was associated with an RR for stroke of 1.29 (95% CI=0.96–1.72) compared with those in the top quartile.

DISCUSSION

Consistent with several prior studies, we found evidence of a total effect of early-life SES on incidence of CHD, diabetes, and stroke in a sample of 9,760 Health and Retirement Study enrollees.[30–32] In a novel application of marginal structural models, we also found evidence of pathways from early-life SES to each outcome not mediated by adult SES.

Estimating the effect of early-life SES on risk of adult chronic disease via mechanisms other than adult SES raises several methodological issues primarily because early-life SES

strongly influences adult SES. When we used the traditional direct effects estimation approach[17] of regressing chronic disease outcomes on early-life SES and adult SES, we found that estimated effects of early-life SES on our outcomes were attenuated and there was no evidence of a direct effect. The pattern was similar whether or not we additionally adjusted for adult CVD risk factors. However, there are several adult risk factors that may mediate the effect of early-life SES but confound the association of adult SES with our health outcomes (as shown in the Figure). For example, prior work suggests that chronic disease risk factors, including obesity, may lie on the pathway between early-life SES and adult health and also be causally related to adult SES, suggesting these risk factors may operate contemporaneously as mediators of the association between early-life and health, as well as confounders of the association between adult SES and health.[33–35]

When there is a consequence of early-life SES that confounds the association between adult SES and the outcome of interest (if paths 2,3, and 6 in the Figure exist), controlled direct effects cannot be identified using conventional regression approaches, regardless of whether the model is additionally adjusted for adult risk factors.[19] When factors that confound the association between adult SES and chronic disease outcomes are omitted from the regression model, then conditioning on adult SES may induce bias in the estimate of the direct effect of early-life SES due to collider stratification.[36] This bias may have resulted in an underestimation of the direct effect of early-life SES in our analyses, although collider stratification bias could be in either direction. However, adjusting for such chronic disease risk factors in a conventional regression approach blocks measured risk factor pathways linking early-life SES to chronic disease. This would estimate the effect of early-life SES on chronic disease that is not through adult SES and not through the adult risk factors. The marginal structural model circumvents this confounding, and our results suggest that conflicting results in the existing literature might be explained, in part, by different biases that result with and without controlling for adult risk factors using conventional regression approaches.

There are a number of caveats to our study. First, there may be error in the measurement of self-reported SES or health outcomes. Second, we used full-information maximum likelihood to obtain factors scores for early life SES despite the fact that some indicators were missing. This method has been shown to be unbiased and more efficient than other common methods for handling missing data in structural equation modeling.[37] Third, we assume that our parametric regression and marginal structural models were correctly specified and that the consistency assumption holds.[38] Future work should consider alternative estimation approaches for direct effects that rely on weaker modeling assumptions.[39–41] Fourth, marginal structural models and inverse-probability-of-treatment weighting require a positivity assumption that the probabilities in the denominator of the weights are nonzero,[42] and this assumption may be violated if there were negligible levels of social mobility in the Health and Retirement Study sample. However, alternative categorizations of SES did not substantively change our findings. Fifth, use of inverse probability weights does not address unmeasured confounding. We attempted to minimize unmeasured confounding in our study by including measures on recognized potential confounders included in the Health and Retirement Study. However, unmeasured risk factors, including mood disorders, may be caused by early-life SES and potentially confound the association between adult SES and our health outcomes. Alternatively, measured risk factors may be measured with error (e.g., current smoking is an imperfect proxy for smoking history). Sixth, to be included in our sample respondents must survive at least 50 years since birth (to be eligible for the Health and Retirement Study) and not be a prevalent case at baseline; individuals of lower SES are less likely to satisfy these criteria and the exclusion of these individuals may underestimate the true effect of adult SES on health. Seventh, risk factors and adult SES were measured concurrently. Although we

included only those risk factors posited to influence adult SES, there may be a reciprocal relation between these characteristics, and further work should model this association longitudinally.

These caveats considered, our results support the hypothesis that early environmental conditions may have lasting effects on adult health and well-being. However, socioeconomic disadvantage during early-life is a broad construct and a number of mechanisms (encompassed by path 1 in the Figure) may "directly" link early-life SES to adult onset of chronic disease independently of intermediate levels of adult SES and measured risk factors. At the individual level, socioeconomic disadvantage is associated with neuroendocrine and inflammatory processes that may increase risk for chronic disease onset.[43,44] Although most of these studies have been conducted among adults, recent work suggests that socioeconomic disparities in subclinical risk for CVD may be established early in life[45]; whether these risks are explained by behavioral, physiologic, psychologic differences, or some combination of these mechanisms, is unclear. Extending this to a multilevel framework that incorporates family, school, and neighborhood exposures, greater socioeconomic disadvantage in early-life may engender differences in social, physical, or service environments and influence risk for chronic disease directly or indirectly.[46] The application of marginal structural models to longitudinal data and the extension of socioecononomic disdvantage to include place-based factors may help to elucidate the specific mechanisms linking the early-life socioeconomic environment to adult onset of chronic diseases.[47]

In conclusion, our analyses provide evidence for a direct effect of early-life SES on chronic disease in the Health and Retirement Study when using marginal structural models but not when using the conventional regression approach. Most theories of the life-course development of chronic disease suggest an underlying causal structure in which the marginal structural model would identify the causal effect of substantive interest but conventional regression methods for estimating direct effects would not. These results therefore suggest that alternative methods, including marginal structural models, should be explored for estimating direct effects in the context of life-course epidemiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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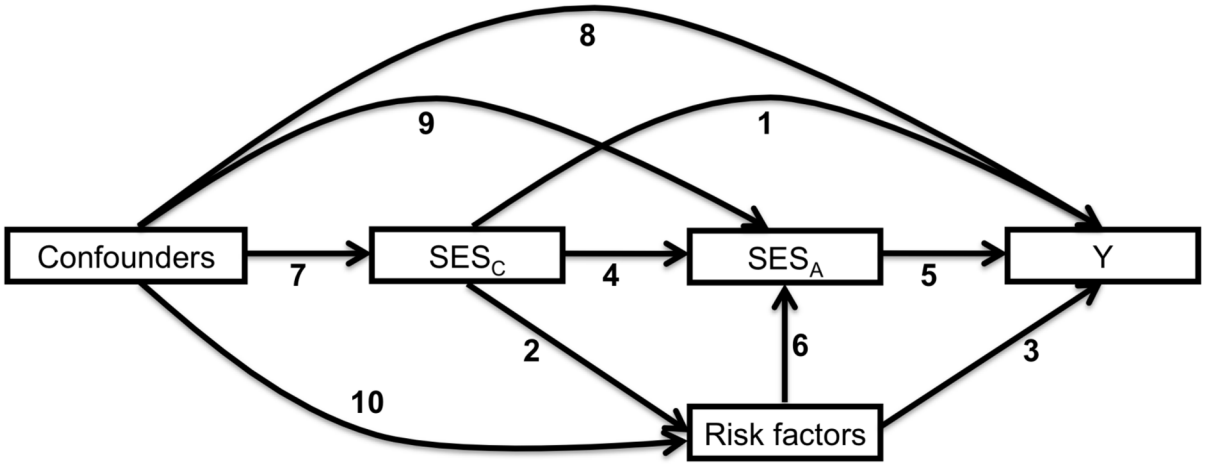

Figure 1.
Causal diagram of the hypothesized effects of early-life (SES_C) and adult SES (SES_A) on chronic disease outcomes (Y) where "confounders" denote potential socio-demographic confounders (i.e., age, race, sex, self-rated childhood health) of the association between early-life SES, adult SES, and the chronic disease outcomes and "risk factors" denote conventional chronic disease risk factors (i.e., high blood pressure, BMI, self-rated health, diabetes, functional limitations, current smoking, alcohol consumption) that may operate contemporaneously as mediators of the association between early-life SES and health and confounders of the association between adult SES and health

Table 1

Descriptive characteristics and bivariate associations between socio-demographic characteristics, risk factors, life-course SES and chronic disease (i.e., heart disease, diabetes, and stroke) outcomes; n=9,760 Health and Retirement Study enrollees followed from 1992–2006

	Total	Heart Disease sample	Diabetes sample	Stroke sample
	No. (% of total)	*No. (% with CHD)*[a]	*No. (% with diabetes)*[a]	*No. (% with stroke)*[a]
Total sample size	9760	8318 (24)[b]	8278 (18)[b]	9055 (8)[b]
Socio-demographic confounders				
Birth cohort/baseline age (years)				
50–52.9	2175 (22)	1910 (21)	1891 (17)	2048 (6)
53–55.9	2757 (28)	2387 (22)	2394 (17)	2560 (6)
56–58.9	2606 (27)	2221 (25)	2188 (19)	2433 (8)
59+	2222 (23)	1800 (29)	1805 (17)	2014 (10)
Race/ethnicity				
White/other	8065 (83)	6906 (24)	6968 (16)	7528 (7)
Black	1695 (17)	1412 (24)	1310 (25)	1527 (12)
Sex				
Male	4594 (47)	3796 (27)	3868 (18)	4210 (9)
Female	5166 (53)	4522 (21)	4410 (17)	4845 (7)
Childhood self-rated health				
Very good/excellent	5861 (60)	5374 (24)	5314 (18)	5747 (7)
Good	1478 (15)	1315 (28)	1307 (22)	1445 (10)
Fair/poor	548 (6)	28.91 (29)	483 (23)	526 (11)
Unknown/missing	1873 (19)	17.28 (17)	1174 (11)	1337 (7)
Risk factors				
High blood pressure				
No	5884 (60)	5247 (20)	5271 (13)	5548 (5)
Yes	3876 (40)	3071 (32)	3007 (25)	3507 (12)
Body mass index (BMI; kg/m^2)				
<25	3419 (35)	2980 (19)	3073 (7)	3181 (7)
25–29.9	4003 (41)	3417 (24)	3415 (18)	3712 (8)
30+	2338 (24)	1921 (31)	1790 (36)	2162 (10)

	Total	Heart Disease sample	Diabetes sample	Stroke sample
	No. (% of total)	*No. (% with CHD)*[a]	*No. (% with diabetes)*[a]	*No. (% with stroke)*[a]
Self-rated health				
Poor	2119 (22)	2002 (15)	1999 (11)	2037 (4)
Fair	2723 (28)	2506 (22)	2490 (15)	2601 (5)
Good	2711 (28)	2313 (26)	2291 (21)	2535 (9)
Very good	1405 (14)	1031 (36)	1009 (27)	1255 (13)
Excellent	802 (8)	466 (38)	489 (27)	626 (17)
Diabetes				
No	8696 (89)	7542 (22)		8124 (7)
Yes	1064 (11)	776 (41)		931 (17)
Health problems limit work				
No	7645 (79)	6875 (22)	6750 (16)	7259 (6)
Yes	2092 (21)	1433 (35)	1517 (23)	1782 (14)
Current smoker				
No	7084 (73)	6077 (22)	6000 (17)	6602 (7)
Yes	2676 (27)	2241 (28)	2278 (19)	2453 (11)
Alcohol use (drinks/day)				
0	3871 (40)	3210 (26)	3077 (21)	3520 (10)
<1	4346 (45)	3779 (23)	3833 (16)	4101 (6)
1–2	1024 (10)	894 (21)	909 (13)	957 (7)
≥3	520 (5)	435 (25)	459 (14)	477 (10)
Socioeconomic status				
Early-life SES[b]				
Quartile 1 (highest SES)	2443 (25)	2160 (22)	2167 (14)	2298 (6)
Quartile 2	2437 (25)	2104 (23)	2129 (15)	2279 (5)
Quartile 3	2440 (25)	2038 (25)	2063 (18)	2263 (9)
Quartile 4 (lowest SES)	2440 (25)	2016 (26)	1919 (24)	2215 (11)
Continuous factor score mean (SD)	0.00 (2.71)	0.08 (2.72)	0.13 (2.69)	0.04 (2.71)
Adult SE[b]				
Quartile 1 (highest SES)	2444 (25)	2183 (22)	2198 (13)	2321 (5)

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	Total	Heart Disease sample	Diabetes sample	Stroke sample
	No. (% of total)	*No. (% with CHD)*[a]	*No. (% with diabetes)*[a]	*No. (% with stroke)*[a]
Quartile 2	2440 (25)	2130 (24)	2147 (15)	2294 (6)
Quartile 3	2436 (25)	2020 (23)	2040 (18)	2245 (8)
Quartile 4 (lowest SES)	2440 (25)	1985 (28)	1893 (26)	2195 (12)
Continuous factor score mean (SD)	0.00 (1.43)	0.06 (1.43)	0.09 (1.41)	0.03 (1.43)

Abbreviations: SD=standard deviation

[a]No. of participants without each condition in 1992; numbers in parentheses show percent experiencing first onset of condition between 1992 and 2006

[b]Factor scores from confirmatory factor analysis with maximum likelihood estimation, split into quartiles of early-life and adult SES

Table 2

Total effects, conventional regression with and without adjustment for risk factors, and MSM results for heart disease (n=8308)

Life-course socioeconomic status	Total effects (Model 1)[a]		Regression adjustment for adult SES and confounders (Model 2)[b]		Regression adjustment for adult SES, confounders and risk factors Model 3)[c]		Marginal structural model (Model 4)[d]	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Early-life SES[e]								
Quartile 1 (highest SES)[†]	1.00		1.00		1.00		1.00	
Quartile 2	1.01	(0.90–1.13)	0.98	(0.87–1.10)	1.00	(0.87–1.14)	1.05	(0.93–1.18)
Quartile 3	1.12	(1.00–1.25)	1.04	(0.91–1.19)	1.05	(0.91–1.22)	1.23	(1.08–1.40)
Quartile 4 (lowest SES)	1.16	(1.04–1.30)	1.00	(0.87–1.16)	1.02	(0.86–1.21)	1.30	(1.12–1.51)
Adult SES[a]								
Quartile 1 (highest SES)[†]			1.00		1.00		1.00	
Quartile 2			1.09	(0.97–1.22)	0.95	(0.83–1.09)	0.98	(0.87–1.09)
Quartile 3			1.04	(0.91–1.19)	0.83	(0.71–0.97)	0.85	(0.75–0.97)
Quartile 4 (lowest SES)			1.29	(1.11–1.49)	0.87	(0.73–1.05)	0.86	(0.74–1.00)

[a] Adjusted for early-life SES and set of confounders (i.e., birth cohort, sex, race/ethnicity, and self-rated childhood health).

[b] Adjusted for early-life SES, adult SES, and set of confounders (i.e., birth cohort, sex, race/ethnicity, and self-rated childhood health).

[c] Adjusted for early-life SES, adult SES, set of confounders (i.e., birth cohort, sex, race/ethnicity, and self-rated childhood health), and set of risk factors (i.e., high blood pressure, BMI, self-rated health, diabetes, functional limitations, current smoking, alcohol consumption).

[d] Stabilized inverse probability weights used to account for potential confounding by the sets of confounders and risk factors.

[e] Factor scores from confirmatory factor analysis with maximum likelihood estimation, split into quartiles of early-life and adult SES.

[f] Reference cateogy.

Table 3

Total effects, conventional regression with and without adjustment for risk factors, and MSM results for diabetes (n=8267)

Life-course socioeconomic status	Total effects (Model 1)[a]		Regression adjustment for adult SES and confounders (Model 2)[b]		Regression adjustment for adult SES, confounders and risk factors (Model 3)[c]		Marginal structural model (Model 4)[d]	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Early-life SES[e]								
Quartile 1 (highest SES)[†]	1.00		1.00		1.00		1.00	
Quartile 2	1.12	(0.97–1.29)	1.02	(0.87–1.19)	0.99	(0.83–1.17)	1.06	(0.91–1.23)
Quartile 3	1.31	(1.14–1.51)	1.07	(0.90–1.27)	0.99	(0.82–1.19)	1.15	(0.97–1.36)
Quartile 4 (lowest SES)	1.62	(1.41–1.86)	1.17	(0.98–1.41)	1.08	(0.88–1.32)	1.23	(1.02–1.48)
Adult SES[a]								
Quartile 1 (highest SES) [†]			1.00		1.00		1.00	
Quartile 2			1.12	(0.95–1.31)	0.98	(0.83–1.17)	1.02	(0.87–1.18)
Quartile 3			1.27	(1.08–1.51)	1.06	(0.88–1.28)	1.02	(0.86–1.21)
Quartile 4 (lowest SES)			1.64	(1.37–1.98)	1.24	(1.00–1.54)	1.40	(1.17–1.68)

[a] Adjusted for early-life SES and set of confounders (i.e., birth cohort, sex, race/ethnicity, and self-rated childhood health).

[b] Adjusted for early-life SES, adult SES, and set of confounders (i.e., birth cohort, sex, race/ethnicity, and self-rated childhood health).

[c] Adjusted for early-life SES, adult SES, set of confounders (i.e., birth cohort, sex, race/ethnicity, and self-rated childhood health), and set of risk factors (i.e., high blood pressure, BMI, self-rated health, functional limitations, current smoking, alcohol consumption).

[d] Stabilized inverse probability weights used to account for potential confounding by the sets of confounders and risk factors.

[e] Factor scores from confirmatory factor analysis with maximum likelihood estimation, split into quartiles of early-life and adult SES.

[f] Reference category.

Table 4

Total effects, conventional regression with and without adjustment for risk factors, and MSM results for stroke (n=9041)

Life-course socioeconomic status	Total effects (Model 1)[a]		Regression adjustment for adult SES and confounders (Model 2)[b]		Regression adjustment for adult SES, confounders and risk factors (Model 3)[c]		Marginal structural model (Model 4)[d]	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Early-life SES[e]								
Quartile 1 (highest SES)[†]	1.00		1.00		1.00		1.00	
Quartile 2	0.86	(0.68–1.09)	0.71	(0.55–0.91)	0.74	(0.57–0.96)	0.75	(0.57–0.97)
Quartile 3	1.37	(1.11–1.69)	0.91	(0.70–1.18)	0.93	(0.71–1.21)	1.24	(0.95–1.61)
Quartile 4 (lowest SES)	1.59	(1.29–1.95)	0.88	(0.66–1.16)	0.90	(0.67–1.21)	1.29	(0.96–1.72)
Adult SES[a]								
Quartile 1 (highest SES)[†]			1.00		1.00		1.00	
Quartile 2			1.17	(0.91–1.52)	0.98	(0.75–1.28)	0.98	(0.76–1.27)
Quartile 3			1.74	(1.33–2.28)	1.26	(0.95–1.67)	1.28	(0.98–1.68)
Quartile 4 (lowest SES)			2.35	(1.75–3.16)	1.35	(0.98–1.87)	1.49	(1.11–2.00)

[a] Adjusted for early-life SES and set of confounders (i.e., birth cohort, sex, race/ethnicity, and self-rated childhood health).

[b] Adjusted for early-life SES, adult SES, and set of confounders (i.e., birth cohort, sex, race/ethnicity, and self-rated childhood health).

[c] Adjusted for early-life SES, adult SES, set of confounders (i.e., birth cohort, sex, race/ethnicity, and self-rated childhood health), and set of risk factors (i.e., high blood pressure, BMI, self-rated health, diabetes, functional limitations, current smoking, alcohol consumption).

[d] Stabilized inverse probability weights used to account for potential confounding by the sets of confounders and risk factors.

[e] Factor scores from confirmatory factor analysis with maximum likelihood estimation, split into quartiles of early-life and adult SES.

[f] Reference category.