Cardio-metabolic risk and cognitive decline: the role of socioeconomic status in childhood and adulthood

Socioeconomic conditions in childhood predict cognitive functioning in later life. It remains unclear however, whether poor childhood socioeconomic status (SES) also predicts the acceleration of cognitive decline. One proposed pathway is via cardio-metabolic risk, which has been linked to both childhood SES and the earlier onset of cognitive impairment. Using data from the Health and Retirement Study (N = 9449), we examine the impact of childhood SES on trajectories of cognitive function over 6 years, and test whether it operates through increased cardio-metabolic risk and adult socioeconomic position. We find that higher childhood SES leads to slower cognitive decline, partially due to a lower levels of cardio-metabolic risk. However, these pathways operate entirely through adult socioeconomic attainment. The results have important implications for future trends in cognitive population health within the context of growing social inequality and reduced social mobility.

INTRODUCTION

A growing body of research is dedicated to understanding the life course processes that shape population health. Studies tracing individuals from childhood to late life have established that the social environment in early life plays an important role in morbidity and mortality (Blane et al. 1996; Blane, Netuveli and Stone 2007; Haas 2007; Hayward and Gorman 2004). Aging studies consistently show that circumstances in childhood, such as early-life illness and socioeconomic environment, predict the timing of chronic disease onset, physical limitations (Haas 2008; Haas, Oi and Zhou 2017; Luo and Waite 2005), and death (Smith et al. 1997).

Likewise, socioeconomic resources of parents (childhood SES) have been shown to shape children's trajectories of cognitive development (Heckman 2006; Paxson and Schady 2007) and ultimately, their later-life cognitive functioning. Emerging evidence suggests that being deprived of socioeconomic resources in childhood increases the risk of exposure to malnutrition, psychological distress/trauma, and environmental hazards, all of which are thought to irreversibly predispose individuals to experience accelerated cognitive decline in later life (Greenfield and Moorman 2018).

To illustrate the central aims of this study we must first draw a distinction between two central theoretical concepts–*preserved differentiation*, and the *differential preservation*, of cognitive functioning (Finkel et al. 2009). Preserved differentiation, in this context, refers to the phenomenon in which those who were socioeconomically disadvantaged in childhood experience worse cognitive function in early life relative to their more advantaged peers, and that this gap in cognition persists in similar magnitude throughout the life course. For instance, the material and psychosocial conditions under which early physical, neurocognitive, and psychosocial development occurs mold the central nervous system in fundamental ways that persist over the

life course. An early childhood environment that is not conducive to healthy development may result in permanent physiological and neurocognitive developmental deficits (Cynader and Frost 1999; Hertzman 1999).

Differential preservation, on the other hand, implies that greater childhood socioeconomic resources provide opportunities for cognitive growth and buffer against acute and chronic stressors that negatively affect cognition throughout the life course. As a result, cognitive performance between the more and less advantaged widens with age. The stress-buffering effect of childhood SES is also likely to manifest physiologically, so that those who are deprived of resources exhibit more cumulative damage to the body. One indicator of such damage that has been fairly well characterized is cardio-metabolic dysregulation (Blane et al. 1996; McEwen 2000). A high level of cardio-metabolic dysregulation reflects greater "wear and tear" on the body, manifesting in a variety of cardiovascular morbidities, including atherosclerosis – the build-up of plaque on the arterial lining resulting from hyperglycemia, and chronic inflammation (Blane et al. 1996; Elovainio et al. 2011). These correlates of cardio-metabolic risk have been shown to impair the retention of cognitive functioning in later life (Schmitz et al. 2018). However, it remains unclear the extent to which childhood SES differentiates late-life cardio-metabolic risk when socioeconomic attainment that individuals achieve themselves as adults is accounted for (i.e., adult SES). Childhood and adult SES are independent determinants of cardio-metabolic risk (Elovainio et al. 2011). If the buffering role of childhood SES against stress is cumulative, then childhood SES should predict late-life cardio-metabolic risk and consequently contribute to the differential preservation of cognition, regardless of adult SES.

To test this idea, the current study examines the extent to which childhood SES differentiates the rate of cognitive decline through cardio-metabolic risk, while accounting for

adult SES. We acknowledge that the linkage between socioeconomic deprivation and cardio-metabolic risk is one of many pathways suggested by the cumulative stress framework that considers childhood adversity as an irreversible cause of accelerated cognitive decline in late life (Greenfield and Moorman 2018). Nevertheless, the focus on cardio-metabolic risk is well-grounded in the emerging literature linking childhood adversity to biomarkers that collectively measure cardio-metabolic risk in adulthood (Suglia et al. 2018). The present study also serves as an empirical revisit to the NIH's consensus statement that "childhood socioeconomic status or cognitive milieu does not appear to strongly influence cognitive decline later in life" (Daviglus et al. 2010: 10).

BACKGROUND

In the literature, three theoretical frameworks have been described to link childhood conditions to later life health and cognitive functioning. The first is the *critical/sensitive period* framework, which posits that early childhood is a period of life in which critical neurocognitive developmental processes occur. During this critical/sensitive period, adverse exposures such as psychological distress/trauma and socioeconomic deprivation may irreversibly affect critical cognitive developmental outcomes such as hippocampal size (Ben-Shlomo, Cooper and Kuh 2016; Cynader and Frost 1999; Daviglus et al. 2010). In addition, early-life material deprivation is thought to irreversibly predispose individuals to physiologic dysregulation, for example by chronically elevating the secretion of stress hormones (Barker 2007; Hackman, Farah and Meaney 2010).

The second framework focuses on the *accumulation of (dis)advantage* from childhood across the life course (Seeman et al. 2004). In the accumulation framework, salubrious inputs and noxious risks deriving from social, environmental, and behavioral exposures are thought to accumulate over the life course. Under such accumulation processes the cognitive benefits of

early life socioeconomic advantage may be further magnified by subsequent socioeconomic advantage in adulthood. Conversely, the deleterious effects of early life deprivation may be either further compounded by hindered socio-economic attainment or rectified by upward social mobility in adulthood.

The third framework conceptualizes childhood SES as a *pathway* mechanism that shapes subsequent socioeconomic conditions in adulthood, which in turn determine later cognitive health. In this framework childhood SES matters largely because it acts as a primary pathway through which parents pass on their socioeconomic position, from which children derive adult cognitive reserves and other characteristics that buffer against cognitive decline. For example, highly educated parents are better able to provide opportunities for their offspring to develop their cognitive abilities and robust cognitive health (Harrison et al. 2015). Familial resources further facilitate educational attainment and other forms of human capital accumulation in adolescence and early adulthood (Currie 2009). The income and occupational resources that individuals gain as returns to human capital investment serve as buffers against the accumulation of stress. Lower occupational statuses, for instance, tend to involve less cognitive stimulation while posing greater stress due to limited autonomy and control (Finkel et al. 2009).

These frameworks jointly illustrate the potential roles of childhood SES in preserved differentiation and differential preservation of cognition. First, as a critical/sensitive period effect, childhood SES may create an initial gap in cognition between the more and less advantaged that persists from childhood onward (preserved differentiation) (Hertzman 1999). Second, childhood SES may further contribute to the widening of that gap (differential preservation) over time via the cumulative effect it has in buffering stress across the life course (e.g. accumulation of (dis)advantage)(Stern 2012). Third, childhood SES structures the central

pathway of socioeconomic attainment that determines the level of adult socioeconomic resources critical to the development of cognitive reserve, resulting in differential preservation of cognitive function (Whalley et al. 2004).

The Current Evidence

Over the past two decades research has investigated the role of socioeconomic resources over the life course in shaping later life cognitive health trajectories. Consistent with preserved differentiation, prior research suggests a positive correlation between childhood SES and late-life cognitive functioning, particularly related to short-term/long-term memory (Greenfield and Moorman 2018; Luo and Waite 2005; Lyu 2015; Zhang et al.,2017). This correlation has been found across multiple international contexts (Forstmeier et al. 2012; Greenfield and Moorman 2018; Horvat et al. 2014; Zhang et al.,2017). Furthermore, consistent with a pathways framework this literature shows that a substantial portion of childhood effects, in some case nearly 70%, is accounted for by adult SES (Forstmeier et al. 2012; Horvat et al. 2014; Zhang et al. 2017). There is also consistent empirical support for accumulation processes associated with trajectories of SES over the life course such that those who occupy low social positions in both childhood and adulthood are particularly at risk (Lynch, Kaplan and Shema 1997; Lyu 2015). Regardless of whether it may be partially mediated or moderated by adult SES, childhood SES predicts the level of cognitive performance assessed by various measures.

Evidence for the contribution of childhood SES to differential preservation–that the gap in cognitive function expands over time–remains conflicted. The NIH's consensus statement issued in 2010, reports that childhood SES does not have any influence on the subsequent rate of decline of cognitive function after baseline (Daviglus et al. 2010). This has largely been confirmed by subsequent studies (Greenfield and Moorman 2018; Lyu 2015; Staff et al. 2012).

However, Lyu and Burr (2016) found some evidence that those with more educated mothers experienced slower declines in cognitive functioning. Studies that examined childhood SES as part of a larger life course socioeconomic trajectory have similarly yielded mixed results vis-à-vis the rate of cognitive decline (Staff et al. 2012).

The inconsistent evidence on the differential preservation of cognitive functioning by childhood SES is surprising, given the well-established consensus that childhood adversity threatens the integrity of cardio-metabolic systems in late life (Suglia et al. 2018). Adverse circumstances in childhood such as acute physical/psychological/sexual trauma, neglect, economic hardships, and maltreatment in particular, are associated with risk of obesity, diabetes, and cardiovascular disease (Hemmingsson, Johansson and Reynisdottir 2014; McLaughlin et al. 2015). Those early insults are thought to biologically "program" the body in such ways that permanently elevate the activity level of cardio-metabolic systems (e.g. heart-rate, blood pressure, blood glucose, lipid metabolism) resulting in long-term wear and tear and dysregulation of these systems (Ben-Shlomo, Cooper and Kuh 2016). Psychological distress, for instance, induces hyperactivity of the Hypothalamic-Pituitary-Adrenal Axis (HPA), which leaves cardio-vascular markers through the elevation of immunological/endocrine responses, potentially over a long term (McLaughlin et al. 2015). Furthermore, cardio-metabolic risk and hyperactivity of the HPA axis are known predictors of cognitive impairment (O'brien et al. 1996).

With limited buffers against those cardio-metabolic risks, it is likely that childhood socioeconomic deprivation would irreversibly increase the rate of late-life cognitive decline. However, as reviewed above, empirical support for this claim is scarce and contradictory. One possible explanation for this contradiction is that cardio-metabolic mechanisms of cognitive decline are driven by more proximal factors such as adult SES. A vast body of research has

identified a clear and consistent link between adult SES and cardio-metabolic risk/dysregulation (Kelli, Kassas and Lattouf 2015). Nevertheless, we are not aware of any existing research investigating the link between childhood SES and cognitive decline with the aim of testing cardio-metabolic risk as a specific pathway, while simultaneously accounting for adult SES.

The Present Study and Hypotheses

The present study seeks to better understand the role of childhood SES in the differential preservation of cognitive functioning and has three objectives. We operationalize differential preservation as different rates of decline in cognitive functioning. First, we aim to confirm that higher childhood SES is cumulatively beneficial in preserving cognitive functioning. Second, we explore the extent to which the influence of childhood SES on the rate of cognitive decline can be attributed to varying levels of cardio-metabolic risk observed in later life. Finally, we test if those direct and indirect pathways linking childhood SES and cognitive decline operate independently of adult SES.

Hypotheses

Based on the discussion above we offer three hypotheses.

Hypothesis 1: Higher childhood SES leads to a slower rate of cognitive decline.

Hypothesis 2: Cardio-metabolic risk partially, but not entirely, accounts for the effects of childhood SES.

Hypothesis 3: The direct pathway between childhood SES and the rate of cognitive decline and the indirect pathway through cardio-metabolic markers, remain after adjustment for adult SES.

DATA AND METHODS

This study draws data from multiple waves of the Health and Retirement Study (HRS), one of the longest running longitudinal studies of aging in the United States. The first wave of participants was recruited in 1992 with follow-up surveys conducted biannually. Starting in 2006 and onward, the HRS administered an enhanced module to a representative subsample of respondents (Crimmins et al. 2013). This module collected blood and saliva samples which were used to assay the participants' cholesterol, blood sugar, C-Reactive Protein (CRP), and Cystatin C. In addition, the module measured their blood pressure, waist circumference, as well as their physical performance (i.e., grip strength and timed walk).

The analytic sample was drawn from this subsample of 16,438 individuals who had biomarkers collected in 2006 and the subsequent follow-ups (2010 and 2014). We further constrained our analysis to the 9,449 individuals whose cognitive functioning was assessed at least once in 2006 or later. This restriction was necessary to ensure that the baseline assessment of cognitive functioning and cardio-metabolic risk were observed for everyone in the study sample, and that all biomarkers were measured *prior* to any subsequent change in cognitive functioning[1].

Taking advantage of the longitudinal data collected by HRS, we pooled 23,893 observations of cognitive performance among the study sample of 9,449 HRS participants. Each member of the study sample contributed as many observations as were available, so long as those were collected in 2006 or later. As the most recent wave of HRS was collected in 2014, the maximum number of observations per respondent is four. We ordered and denoted observations for each respondent by the number of years elapsed since the baseline at two-year intervals, up to six years.

Cognitive Function

The HRS uses a modified version of the Telephone Interview for Cognitive Status (TICS-M)(Brandt, Spencer and Folstein 1988). The TICS questionnaire has been used extensively by large-scale surveys as a composite measure of general cognitive functioning (Clair et al. 2011). Over the phone, respondents were administered 10-word immediate and delayed recall tests, a serial 7s subtraction test, a counting backwards test, an object naming test to assess language, and recall of the date and president and vice-president to assess working memory, attention and processing speed, language, and temporal orientation, respectively (Crimmins et al. 2011). For a review of the validity, reliability, and methodological limitations of TICS, see Lachman and Spiro (2002). The number of correct answers to TICS items quantifies individual cognitive performance on a scale from 0 to 35. All TICS items were standardized and the scoring was harmonized across waves.

Cardio-Metabolic Risk Index (CM Index)

The analysis utilizes nine markers of cardio-metabolic risk: glycated hemoglobin (HbA1c), Low-Density Lipoproteins (LDL), High-Density Lipoproteins (HDL), C-Reactive Protein (CRP), Cystatin C, systolic & diastolic blood pressure, pulse, and waist circumference. Using these biomarkers, we constructed an index of cardio-metabolic risk. For each biomarker, we determined a threshold by estimating the 75^{th} percentile value based on the total HRS sample rather than the analytic sample in order to ensure it is representative of the US population. One exception is HDL, to which the 25th percentile threshold was applied. The estimated thresholds for the biomarkers are listed in Table 1. For a given biomarker, an individual was assigned a value of 1 if their parameter exceeded the threshold (or lower for HDL) and 0 if not. The index was then calculated by summing across the markers and ranges between 0 and 9 [2].

High levels of HbA1c, Cystatin C, blood pressure, pulse, and central adiposity collectively represent the manifestation of irregularities in cardio-metabolism (Schmitz et al. 2018). High CRP is a marker of inflammation, and its chronic elevation indicates vascular morbidities such as atherosclerosis (Ridker, Wilson and Grundy 2004), and is an independent predictor of cardio-metabolic dysfunction (den Engelsen et al. 2012). High LDL cholesterol, is reflective of cardio-vascular risk in the combination of low HDL cholesterol (Rizzo et al. 2008). We therefore included both lipid measures[3].

Childhood SES

Three measures of childhood SES are used: mother's education, father's education, and the main occupation of the father or main breadwinner. Parental education was measured as years of completed schooling. Three-digit census occupational codes for respondents and their father/main breadwinner were matched to the level of cognitive demands associated with each occupation using the Occupational Information Network (O*Net). O*Net data is widely used in cognitive research to assess the cognitive demands of occupations (Andel et al. 2015; Forstmeier et al. 2012). O*Net assesses a number of abilities including oral expression, written expression, oral comprehension, written comprehension, deductive reasoning, inductive reasoning, fluency of ideas, originality, problem sensitivity, information ordering, and category flexibility. Score for each ability domain range from 0 to 100–the occupation requires the highest possible level of a given ability. We constructed a composite rating for each occupation by averaging the 12 ability domain scores. The composite ratings were matched to respondent's and their parent's occupation. Following prior research, we then transformed the composite rating into a z-score (based on the total HRS sample) (Andel et al. 2015).

Adult SES

Adult SES was captured using four measures: household income, wealth, cognitive demands of longest-held occupation, and educational attainment. Total household income and wealth represent the sum of the respondent's and spouse's total income/assets from all sources. These were then adjusted for inflation and household size and log transformed. Cognitive demands of longest held occupation was derived as described above, based on the longest-held occupation they reported to the HRS. Educational attainment was measured as years of completed schooling. We utilize the earliest available financial information, if possible, prior to 2006 when their biomarkers were first measured. Approximately 9% of the study sample participated in the 2006 HRS for the first time.

Controls

The analysis also includes controls for age at first observation, race/ethnicity, and sex. Age was centered on the sample mean. Race/ethnicity was measured in four categories: non-Hispanic whites, non-Hispanic blacks, Hispanics and others. Descriptive statistics for the sample are provided in Table 1. The mean age was 70.8. 69.7% of the sample identified as non-Hispanic white, 11.3% as Hispanic, 16.5% as non-Hispanic black, and 2.4% as other. 56.7% of the sample were women.

[table 1 here]

Analytic plan

We used a structural equation framework to estimate latent growth curve models of cognitive function (Muthén 2004). Structural equation models consist of measurement and structural components (Kline 2004). The measurement component statistically links the observed measures to the latent constructs that they measure. The structural component is composed of multiple equations that relate the latent constructs to other variables of interest. Figure 1 presents a path

diagram of the model. Four variables in ovals represent latent constructs, childhood SES, adult SES, and the intercept and slope of cognitive trajectories, based on the corresponding set of observed measures. The latent constructs, childhood SES and adult SES, were each estimated with a one-factor CFA model.

[figure 1 here]

The latent growth curve component of the model in which the TICS score (*Y*) for individual *i* at time *t* can be expressed as

$$Y_{it} = \eta_{\alpha i} + \lambda_t \eta_{\beta i} + \varepsilon_{it} \quad (1)$$

where $\eta_{\alpha i}$ and $\eta_{\beta i}$ respectively represent the intercept and slope for individual *i* and ε_{it} are individual and time-specific random errors. The observed TICS score at the baseline is Y_{i0}, and TICS score at the subsequent time points are denoted as $Y_{i2,}$ $Y_{i4,}$ and Y_{i6}. The individual intercepts are latent components expressed as the sum of the overall mean score at the baseline (μ_α) and their individual deviation from it ($\zeta_{\alpha i}$) ($\eta_{\alpha i} = \mu_\alpha + \zeta_{\alpha i}$). Individual slopes can be expressed as a function of the average change in the TICS score over time (μ_β) and the individual deviation ($\zeta_{\beta i}$) ($\eta_{\beta i} = \mu_\beta + \zeta_{\beta i}$). In a linear growth model λ_t would be set to [0, 2, 4, 6], corresponding to factor loadings for 4 observation periods starting at time 0 and then at two-year intervals. However, rather than a linear model we estimated a freely-specified model in which λ_t = [0, *, *, *, 1]. In this model, * represents estimated (i.e., free rather than fixed) factor loadings corresponding to the proportion of total change occurring by each observation point (i.e., t = 0, 2 , 4 , and 6), and $\eta_{\beta I}$ represents a general shape factor of total change over the period rather than an annual rate of change. The advantage of this specification is that it does not impose a particular functional form (e.g. linear, quadratic) on trajectories of cognition at the individual or population level, and the model fit was better with the freely-specified model over linear/curvilinear models. This is

especially important in the HRS which covers such a wide range of birth cohorts observed at different spans of later life, across which the functional form of cognitive trajectories is likely to vary substantially. We further allow the latent intercept and slope to be correlated.

Estimation is accomplished via Full Information Maximum Likelihood (FIML), using Mplus 6.12. Not all individuals in the sample have cognition measured at all observation points. FIML takes advantage of all available information, thus allowing those individuals with missing information to be retained and contribute to the estimation. Similar to the logic of imputation (Oi 2017), the FIML estimation for missing cases was aided by variables that predict missing values but are not included in the main analysis. These variables included time-varying measures of widowhood, retirement/employment status, activities of daily living, whether their mother/father is alive, and family care giving obligations, all of which are linked to late-life cognitive functioning (Insler 2014). The results were robust to the selection of auxiliary variables.

This modeling strategy is particularly advantageous in testing our hypotheses, as it enables us to directly test the effects of covariates on the rate of cognitive decline, while accounting for between-individual differences in cognitive performance at the baseline (Nexø, Meng and Borg 2016). As mentioned above the latent-variable time-centered rather than age-centered approach that we adopt also offers more flexible options to model change over time.

Coefficients predicting the latent constructs were used to test the hypotheses, represented by arrows drawn between Childhood SES, adult SES, and the cardio-metabolic risk (CM) index, the intercept and slope in Figure 1. The first hypothesis specifies a positive path coefficient of childhood SES predicting the slope (Childhood SES → Slope): a higher level of childhood SES leads to a smaller loss of cognitive functioning over time. The second hypothesis refers to a chain that begins with the negative association between Childhood SES and the CM index, and

then leads to another negative association between the CM index and the slope (Childhood SES → CM index → Slope). These specifications imply that the direct association between Childhood SES and the slope is partially mediated through the CM index. Finally, the third hypothesis is evaluated by examining if these two hypotheses hold even after incorporating adult SES.

RESULTS

Table 2 shows the results from three separate measurement models for childhood SES, adult SES, CFA loadings for education, the intercept, and slope. The far-right column presents the number of observations for each measure. Missingess is particularly severe for the cognitive scores measured for the third and fourth time (t = 4 and 6), indicating that less than a half of the sample did not have their cognitive functioning assessed more than twice.

[table 2 here]

All fit indices are within a satisfactory range (above 0.9 for CFI and TFL, and below 0.05 for RMSEA), indicating that these models fit the data well (Kline 2014). Similarly, all standard loadings, which can be interpreted as correlation coefficients, are above the threshold of 0.4. Beginning with childhood SES, the factor loadings from the one-factor CFA model show that this underlying concept is strongly correlated with its measurements, mother's education, father's education, and the breadwinner's occupation, with standardized loadings of 0.805, 0.792, and 0.521, respectively. In the adult SES model, the standardized coefficients adult SES are 0.487, 0.431, 0.871, 0.561 for logged income, total asset, education, occupational status of the longest-held job. The bottom pane presents the measurement model of the TICS growth curve. In the estimation of the intercept, the unstandardized factor loading is set to 1 for each measurement, because the baseline is fixed across time. The unstandardized factor loadings for

the slope indicate cumulative proportional change at each observation point, so that λ_t = [0, 0.331, 0.725, 1], where t = 0, 2, 4, and 6, respectively.

Table 3 represents coefficients in the structural component of the model, including the mean estimates of the intercept and slope, with the upper and lower half sections containing those predicting the intercept and slope, respectively. Recall that the intercept represents the average baseline score (μ_α) and the slope is the average total change in the TICS score for the six-year period (μ_β).

In keeping with the logic of mediation analysis, we constructed four models, with the fourth model presented in Figure 1. All models control for baseline age, sex, and race/ethnicity, and childhood SES. Model 2 adds the CM index, while Model 3 instead includes adult SES. Model 4 (full model) includes childhood, adult SES, and the CM index. Across the four models, the variables included explain 30.6%-49.6% of the variance in the intercept and 46.7-49.7% of variation in the slope.

Beginning with Model 1, the estimates from the slope equation show that when all the covariates are at the value of 0 (e.g., a baseline age of 70), the average cognitive decline over 6 years is -1.701. The intercept is largely dependent on individual age at baseline. Individuals who were older at the baseline experience greater cognitive decline over the period, by 0.178 per one-year increase in age. Childhood SES positively influences the level of cognitive performance at the first observation; a one-standard deviation increase in childhood SES increases the baseline score by 0.407. In addition, childhood SES is also associated with cognitive decline, a one standard deviation increase in childhood SES lowers the rate of decline by 0.097. None of the other variables significantly predicts the slope.

[table 3 here]

Model 2 shows the estimates after including the CM index. The CM index itself is associated with both the intercept and slope in the expected direction: higher cardio-metabolic dysregulation is associated with a lower baseline TICS score and a stronger negative change over time. The positive coefficient of childhood SES predicting the slope is reduced from 0.097 in Model 1 to 0.086 in Model 2, (a nearly 10% reduction) though remains statistically significant.

When adult SES is alternatively added to the model (Model 3), the effect of childhood SES on the slope is reduced substantially from 0.097 to 0.027, and is no longer statistically significant. Similarly, childhood SES is no longer predictive of baseline cognitive score. Adult SES is significantly associated with both the intercept and slope; one standard deviation increase in Adult SES increases the baseline cognitive score by 1.002, and reduces cognitive decline by 0.114. The mediation of the coefficient for childhood SES through adult SES is nearly 73%.

To visualize how childhood SES contributes to the differentiation of cognitive trajectories, Figure 2 plots predicted age-specific TICS score over the six-year period based on the estimates from Models 1, 2, and 3. Trajectories are plotted for the mean respondent at baseline (age 70 and all covariates except childhood SES held to their baseline means). As discussed above, the slope of this latent growth model is freely specified, meaning that change in the TICS score is not linear or curvilinear but rather expressed as the proportion of the overall change (i.e., the slope) at each observation point (t = 0, 2, 4, 6). In other words, the model cannot extrapolate change beyond the 6 year-period. These plotted TICS scores represent aging trajectories between 70 and 76 for two groups: those with high childhood SES (2 standard deviations above the mean) and low childhood SES (2 standard deviations below the mean). Childhood SES estimated by CFA analysis follows the normal distribution. Thus, those with "high" childhood SES are nearly the 95th percentile of the distribution, and "low" childhood SES

means about the 5th percentile. Models 1 and 2 show that those with high childhood SES score significantly higher than those with low childhood SES at the baseline and also the former experience a slower rate of cognitive decline than the latter. However, no such differentiation is observed in Model 3 that holds adult SES at the same level for both groups.

[figure 2 here]

In the presence of both the CM index and adult SES (Model 4), childhood SES is not significantly associated with the intercept or slope. The results from Model 3 show that adult SES alone, without the CM index, mediates the significance of childhood SES in the intercept and slope. We tested the significance of all potential mediating pathways including those that do not involve adult SES, based on the Model 4 estimates.

The direct effect of childhood SES on the slope is 0.034. Total indirect effects involving childhood SES and the CM index amount to 0.063. Among all possible paths, there are two that are statistically significant at the p-value of 0.004 and 0.001, respectively: childhood SES → adult SES → slope (0.049), and childhood SES → adult SES → CM index → slope (0.010). Further, the correlation between the intercept and slope was found significant and positive in Models 1 and 2, but was no longer significant, once adult SES is included (Models 3 and 4). In other words, childhood SES does not influence the slope indirectly through its association with the intercept once adult SES is taken into account. In short, all significant mediation pathways between childhood SES and the slope involve adult SES.

To further illustrate this point, Table 4 presents the estimates from the equations predicting the CM index and adult SES from Models 2 and 4. This demonstrates the extent to which childhood SES predicts cardiometabolic risk, with/without adult SES included, as well as the effect of childhood SES on adult SES. In Model 2, higher childhood SES predicts lower

cardio-metabolic risk (-0.040) but that is no longer the case in Model 4 (0.020). A one standard deviation increase in childhood SES predicts a 0.547 standard deviation increase in adult SES.

[table 4 here]

DISCUSSION

The life course represents the flow of time, beginning from conception to the moment of death, and individuals are exposed to various risk factors along the way, some of which have irreversible and persistent effects on health (Ben-Shlomo and Kuh 2002). In terms of cognitive health, the risk of cardio-metabolic dysfunction is considered as a risk factor of accelerated cognitive decline and cognitive impairment/dementia. Childhood adversity, through pre-natal exposure to malnutrition and other environmental hazard and poor and traumatic post-natal experience is known to predispose the body to develop risk in various systems. At the same time, socioeconomic status in adulthood profoundly determines the level of cardio-metabolic risk. To better understand the relative importance of childhood SES in relation to adult SES in the risk of cardio-metabolic dysregulation and cognitive decline, we tested the three hypotheses. H1) Greater childhood SES slows the rate of cognitive decline. H2) The linkage between childhood SES and the rate of decline operates partially through increased cardio-metabolic risk. H3) Childhood SES directly impacts cognitive decline and indirectly through cardio-metabolic risk, independently of adult SES.

In support of the first hypothesis, we find a significant and inverse association between childhood SES and the extent of cognitive decline over a 6-year period. Further, we observed the modest mediation of that linkage through later life cardio-metabolic risk. This modest support for the second hypothesis is insufficient to exclude the possibility that greater socioeconomic attainment in adulthood, rather than advantageous childhood environment, is ultimately

responsible for the roles of childhood SES in cognitive decline. Indeed, the results also show that childhood SES does not directly predict cardio-metabolic function in later life, or the rate of cognitive decline, net of adult socioeconomic resources. The lion's share of the total effects of childhood SES can be attributed to two indirect paths that involve adult SES. That is, childhood SES is transmitted to adult SES, which then determines the rate of cognitive decline either directly, or indirectly through the cardio-metabolic dysregulation.

The results confirm that cognitive health disadvantages in childhood are remediable later in life as long as individuals are able to develop adequate cognitive reserve in the form of adult socioeconomic attainment. It is important to keep in mind however, that childhood SES remains as a key determinant of adult SES, as such, childhood socioeconomic deprivation remains a systematic obstacle to the maintenance of cognitive health in later life (Currie and Moretti 2003). Constrained opportunities for upward mobility affects many aspects of population health that perpetuate health inequalities today (Woolf 2009). The increasing heterogeneity in the life chances of children based on their parental/family characteristics has important implications for trends in population health (McLanahan 2004). Indeed, socioeconomic disparities in health and mortality have been expanding (Masters, Hummer and Powers 2012; Preston and Elo 1995). The evidence presented here sheds light on the life course process of cognitive decline that can be traced back to individual childhood environment, while calling attention to the pathway mechanisms of cognitive health risks that manifest in adulthood.

We urge the readers to consider several caveats when interpreting the results. The array of biomarkers included in the study is not comprehensive even for cardio-metabolic markers, and limited by the design of Health Retirement Study (Crimmins et al. 2013). We emphasize that the inferences from the findings presented in this study are strictly limited to the linkage between

childhood SES and the cardio-metabolic risk. In addition to childhood SES, the inclusion of early-life health conditions such as infection as well as childhood health status was considered, but they were subsequently dropped from the main analysis because none of the reported childhood conditions significantly predicted cognitive decline, independently of adulthood SES. Furthermore, we conducted a series of sensitivity analyses, including alternative models that include health behavior variables and tested the interaction between childhood SES and adult SES. We also ran the final model based on an alternative sample whose age ranges between 55 and 73, in order to alleviate the potential confounding of cohort effects. This age range reflects the first and third quartiles of the age distribution in the HRS biomarker sample. Also, we examined the estimates based on an alternative specifications of the cardio-metabolic risk index including forced expiratory volume, which is linked to the cardio-metabolic risk (Beijers et al. 2017). The results from those were presented in Appendix A. These alternative models did not alter the substantive conclusions. Towards a better understanding of cumulative damage resulting from childhood adversity and its manifestation as accelerated cognitive decline, the incorporation of stress hormones and other biomarkers that are indicative of cumulative damage over the life course is necessary. The future expansion of HRS biomarker data assessing the integrity of multiple systems in the body is expected to further this endeavor. Finally, there is the issue of mortality selection of the sample before biomarker data collection began in 2006. Even with the "refresher" samples of younger individuals added to HRS, the average age in the sample at the first observation in this study is nearly 71 years old. It ls likely that those who are at higher cognitive risk were more likely to have died prior to 2006, thus causing a downward bias in the estimated effects of childhood SES on cognitive decline.

Despite these caveats, the present study is one of the first to provide evidence on the linkage between childhood SES and the rate of cognitive decline while accounting for cardio-metabolic biomarkers and adult SES. Greater socioeconomic resources available in childhood, such as having well-educated parents who worked in cognitively stimulating jobs are linked to a slower rate of cognitive decline. Consistent with a pathways life course perspective, the findings suggest that the influences of childhood SES on cognitive reserve are attributed primarily to their profound roles in adult socioeconomic attainment. It is adult SES that ultimately determines both the preserved differentiation and differential preservation of cognitive decline that unfolds in later life. With growing public interests in the maintenance of cognitive health, the promotion of individual strategies to develop resilience tends to dominate public discourse on cognitive aging. However, the present study illustrates key structural mechanisms that underscore the limitations to individual-level interventions to mitigate cognitive decline. The results also highlight the importance of growing socioeconomic inequality to future population trends in cognitive health, and warns that high rates of childhood poverty and socioeconomic deprivation, coupled with reduced levels of upward social mobility (Chetty et al. 2017), are likely to pose significant challenges to public health efforts to promote successful cognitive aging.

NOTES

1. We conducted auxiliary analysis to assess the representativeness of the study sample against the HRS biomarker subsample. We found that the two samples do not differ in terms of education, income, and the occupational status of longest-held job, race or Hispanic ethnicity. However, the analytic sample was younger by nearly 5 years.

2. We followed this conventional practice to construct an index for cardio-metabolic risk over other methods such as factor analysis (Howard and Sparks 2016). Auxiliary analysis as well as prior literature show that the predictive power of such a biomarker index for cognitive decline is similar, regardless of how it was constructed (Gruenewald et al. 2006; Karlamangla et al. 2002).

3. While there is a considerable overlap in the array of biomarkers used to assess cardio-metabolic risk and so-called allostatic load (Gallo, Fortmann and Mattei 2014). For multiple reasons our measure most closely aligns with the former. First, allostatic load measures require

the inclusion of stress hormones (Gallo et al. 2014) which we do not include. The array of biomarkers used in this study is hence too limited to be considered as a comprehensive measure of cumulative damage in the body as a whole. Second, it's not possible to determine whether the level of the biomarkers observed here reflect recent, day-to-day fluctuation, acute responses, or decades of exposures across the life course, including childhood adversity. Finally, these biomarkers are most likely to capture cardio-metabolic risk, a particular biological pathway that we hypothesize links childhood SES and cognitive decline.

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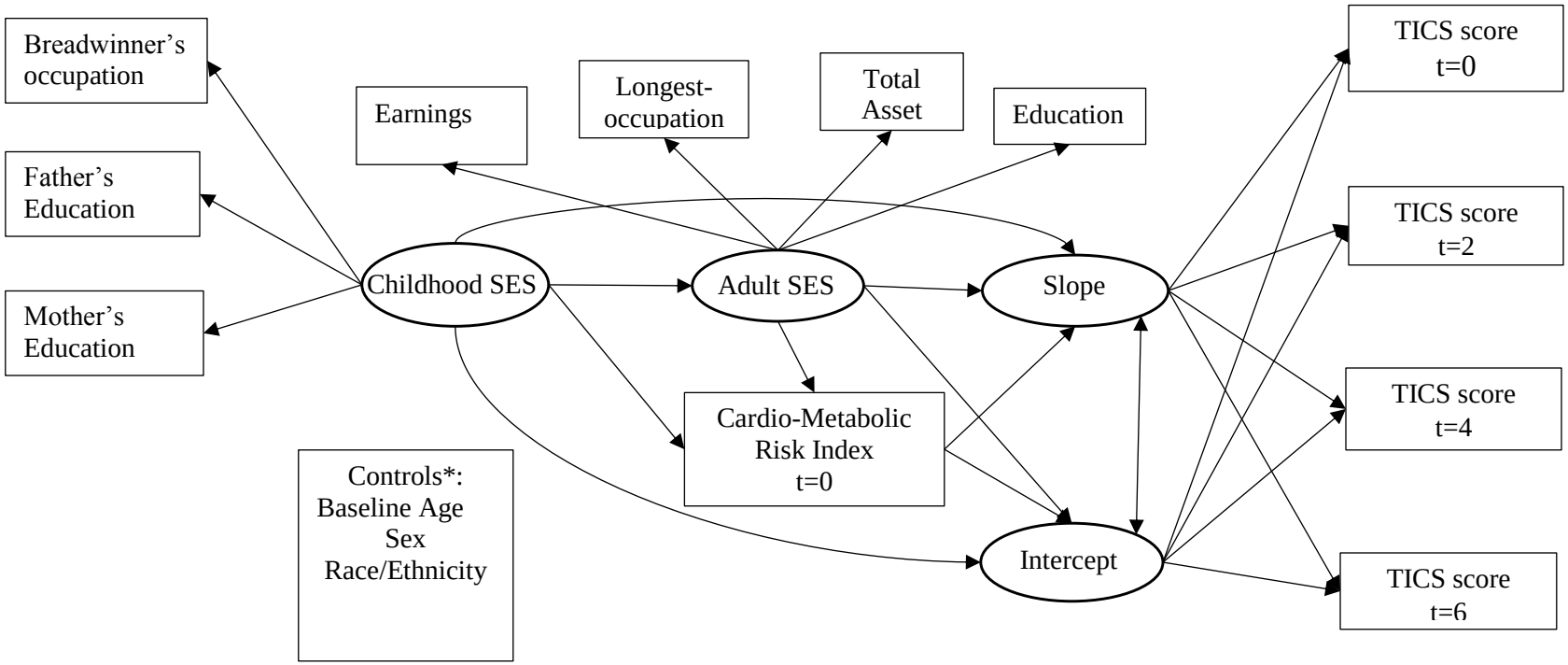

Figure 1. Latent Growth Curve Model fitted to the TICS score observed at four time points, with Parental SES, Adult SES, and Cardio-metabolic Risk Index as covariates.

Notes:* Parental SES, SES, Biomarkers, Slope and Intercept are regressed on controls.

t represents the number of years elapsed since the baseline

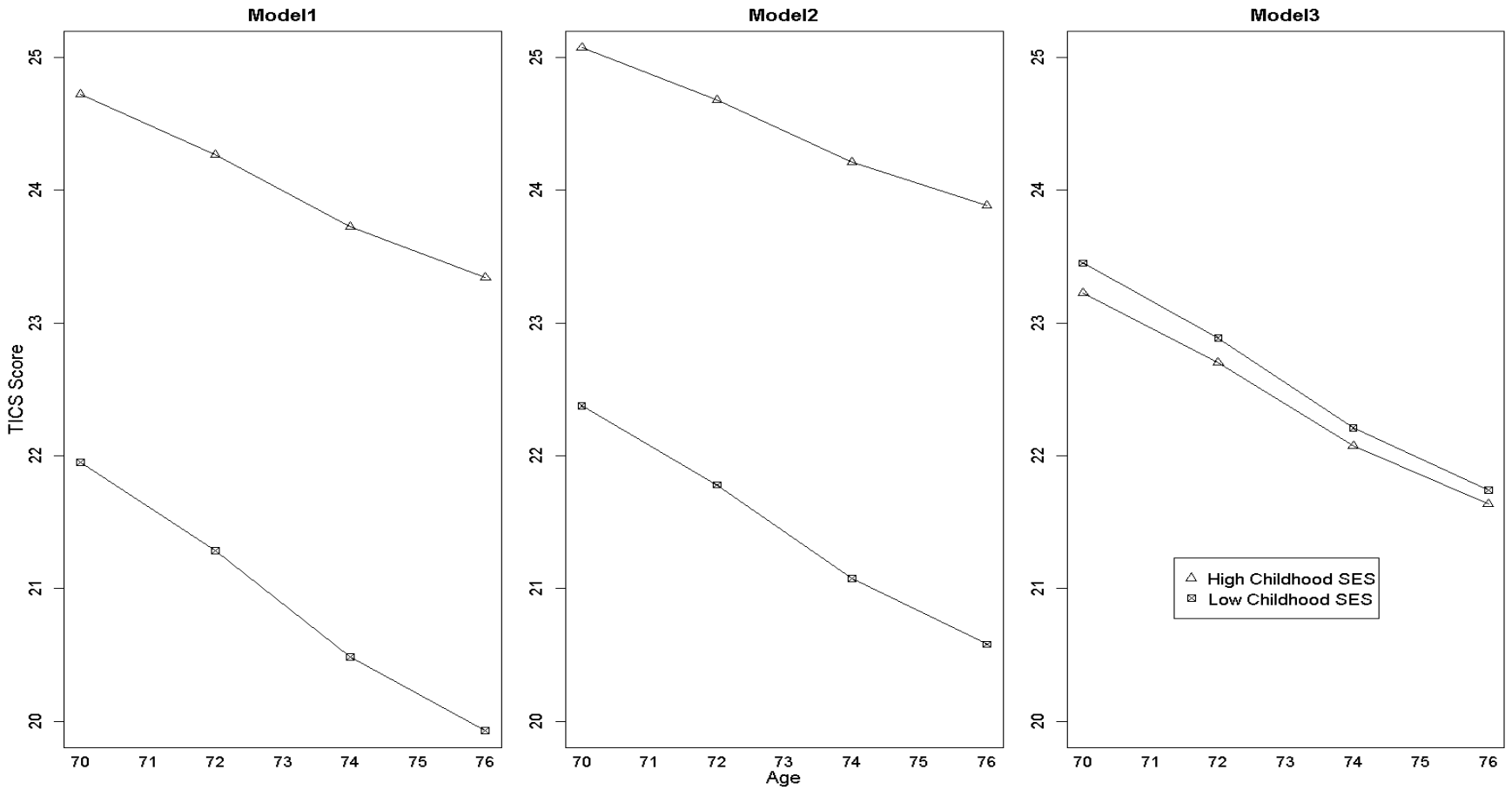

Figure 2. Aging trajectories of TICS Scores for those with high/low childhood SES. Model 1 includes childhood SES and controls. Model 2 holds

biomarkers constant. Model 3 holds adulthood SES constant. These age-specific predicted values are based on the sum of the intercept, which was adjusted at the baseline age of 70, and the slope value estimated for each of the three subsequent observations with two-year intervals.

Table 1. Descriptive of The Sample by Demographics and Cardio-Metabolic Biomarkers

Variable	Mean/Prop	SD	Min	Max	Quartile Threshold*
Baseline Age	70.723	10.306	50.000	100.321	
Non-Hispanic White	0.700				
Hispanics	0.113				
Non-Hispanic Black	0.162				
Others	0.025				
Male	0.438				
H1bAc (%)	5.888	1.002	3.01	17.26	6.14
CRP (ug/mL)	4.181	8.285	0.02	219.12	4.51
Cystatin C (mg/L)	1.115	0.568	0.07	10.17	1.20
Low Density Cholesterol (mg/dL)	144.636	39.412	33.02	378.62	171.273
High Density Cholesterol (mg/dL)	53.961	15.840	12.11	130.04	42.74
Systolic Blood Pressure	134.699	22.162	68	240	149
Diastolic Blood Pressure	80.332	12.781	23	146	91
Pulse	69.856	11.337	25	133	78
Waist Circumference (inch)	39.854	5.876	23	74.25	43.5
Cardio-Metabolic Risk Index	1.851	1.366	0	7	

Notes: N = 9449

*Quartile threshold was determined by taking the 75% quartile value for all biomarkers expect High Density Choresterol, whose threshold refers to the 25% quartile.

Table 2. Descriptives and Factor Loadings of CFA models for Parental SES, SES, and TICS score

	Mean	Unstandardized		Standardized		R-Squared	Observed N
Childhood SES							
Mother's Education	9.378	1.000		0.805		0.649	8494
	(0.039)			(0.018)			
Father's Education	9.117	1.063	***	0.792	***	0.627	7976
	(0.043)	(0.019)		(0.015)			
Father's Occupation	-0.524	0.096	***	0.521	***	0.272	6189
	(0.006)	(0.004)		(0.013)			
Adult SES							
Logged Income	10.340	1.000		0.487		0.238	9449
	(0.011)			(0.012)			
Logged total asset	11.097	0.137	***	0.431	***	0.186	9449
	(0.022)	(0.004)		(0.011)			
Years of education	12.373	0.335	***	0.871	***	0.758	9449
	(0.023)	(0.010)		(0.008)			
Longest-held Occupation	-0.220	0.188	***	0.561	***	0.272	5920
	(0.009)	(0.006)		(0.011)			
Latent Growth Curve Model fitted to the TICS score							
	Mean	Slope Coefficients				R-Squared	Observed N
		Unstandardized		Standardized			
Baseline (t =0)	21.717	0.000		0.000		0.751	9449
	(0.050)						
2nd observation (t =2)	21.255	0.331	***	0.136	***	0.713	6392
	(0.067)	(0.021)		(0.014)			
3rd observation (t =4)	20.754	0.725	***	0.290	***	0.798	4812
	(0.076)	(0.030)		(0.022)			
4th observation (t =6)	20.710	1.000		0372	***	0.793	3240
	(0.121)			(0.031)			
RMSEA				0.017			
CFI/TFL				0.996/0.987			

Notes: N = 9449 *** P <0.001 ; ** P <0.01 ; * P< 0.05. Standard Errors are in ().

Table 3. Structural coefficients (β) predicting the intercept/slope of the latent growth model fitted to observed TICS score

	Model 1		Model 2		Model 3		Model 4	
Intercept	β	SE	β	SE	β	SE	β	SE
Baseline Age	-0.132***	0.005	-0.131***	0.005	-0.132***	0.005	-0.132***	0.005
Male	-0.683***	0.089	-0.627***	0.089	-0.925***	0.086	-0.915***	0.084
Hispanics[a]	-2.265***	0.190	-2.281***	0.189	-0.528***	0.191	-0.525***	0.197
Blacks [a]	-3.388***	0.139	-3.319***	0.140	-2.555***	0.139	-2.539***	0.132
Others[a]	-2.221***	0.320	-2.218***	0.317	-2.602***	0.288	-2.602***	0.284
Childhood SES	0.407***	0.022	0.386***	0.029	-0.059	0.033	-0.052	0.032
Adult SES					1.002***	0.047	1.001***	0.047
CM Index[b]			-0.197***	0.029			-0.024	0.029
Constant	23.339***	0.068	23.726***	0.087	23.340***	0.068	23.612***	0.091
R-Squared	0.306		0.309		0.480		0.496	
Slope	β	SE	β	SE	β	SE	β	SE
Baseline Age	-0.178***	0.013	-0.186***	0.011	-0.180***	0.013	-0.188***	0.015
Male	0.002	0.132	0.030	0.129	-0.055	0.132	-0.029	0.139
Hispanics[a]	0.636	0.273	0.678*	0.284	0.932***	0.279	0.972***	0.292
Blacks [a]	0.089	0.229	0.146	0.266	0.221	0.231	0.269	0.241
Others[a]	0.877	0.527	0.887	0.506	0.905	0.522	0.934	0.545
Childhood SES	0.097***	0.032	0.086***	0.031	0.027	0.045	0.034	0.047
Adult SES					0.114**	0.040	0.100*	0.040
CM Index[b]			-0.132***	0.046			-0.114**	0.042
Constant	-1.701***	0.119	-1.493***	0.153	-1.652***	0.120	-1.343***	0.152
R-Squared	0.467		0.473		0.495		0.497	
$R_{\text{Intercept with Slope}}$	0.190**		0.179*		0.137		0.136	
CFI/TFL	0.978/0.967		0.979/0.965		0.996/0.995		0.986/0.979	

Notes: [a]Non-Hispanic Whites as the reference. [b]Cardio-Metabolic Risk Index
*** P <0.001 ; ** P <0.01 ; * P< 0.05. Standard Errors are in ().

Table 4. Structural coefficients (β) predicting the Cardio-Metabolic Risk index in Models 2 and 4

	Model 2		Model 4	
Cardio-Metabolic Risk Index	β	SE	β	SE
Baseline Age	0.012***	0.002	0.012***	0.002
Male	0.282*	0.032	0.310***	0.032
Hispanics[a]	0.037***	0.065	-0.168	0.067
Blacks [a]	0.506***	0.048	0.405***	0.050
Others[a]	-0.056***	0.106	-0.011	0.103
Childhood SES	-0.040***	0.007	0.020	0.011
Adult SES			-0.115***	0.013
R-Squared	0.034		0.053	
Adult SES	β	SE	β	SE
Baseline Age			0.000	0.003
Male			0.241***	0.059
Hispanics[a]			-1.690***	0.133
Blacks [a]			-0.818***	0.094
Others[a]			0.428***	0.197
Childhood SES			0.547***	0.016
R-Squared			0.532	

Notes: [a]Non-Hispanic Whites as the reference

*** P <0.001 ; ** P <0.01 ; * P< 0.05. . Standard Errors are in ().

Appendix A. Structural coefficients (β) predicting the intercept/slope of the TICS score trajectory, with alternative model specifications

	Model 3 + Behavioral		Model 4 + Child X Adult SES		Model 4 (Alternative CM Index[b])		Model 4 (Truncated[c])	
Intercept	β	SE	β	SE	β	SE		SE
Baseline Age	-0.120***	0.005	-0.134***	0.005	-0.130***	0.005	-0.041***	0.010
Male	-0.990***	0.084	-0.938***	0.087	-0.923***	0.084	-0.863***	0.110
Hispanics[a]	-0.658***	0.180	-0.472*	0.209	-0.507***	0.191	-0.563*	0.229
Blacks [a]	-2.511***	0.130	-2.535***	0.139	-2.478***	0.138	-2.473***	0.156
Others[a]	-2.377***	0.268	-2.577***	0.288	-2.592***	0.287	-2.751***	0.351
Childhood SES	-0.068	0.032	-0.062	0.032	-0.063	0.033	-0.063	0.043
Adult SES	1.032***	0.045	1.015***	0.048	1.008***	0.049	0.952***	0.052
Child X Adult SES			-0.001	0.005				
Exercise	0.172***	0.030						
BMI	0.038***	0.007						
Ever Smoked	0.046***	0.086						
Currently Smoke	-0.215*	0.134						
CM Index			-0.006	0.030	-0.096***	0.029	-0.051	0.047
Constant	23.006***	0.242	23.356***	0.090	23.562***	0.094	23.947***	0.121
R-Squared	0.513		0.504		0.500		0.523	
Slope	β	SE	β	SE	β	SE		SE
Baseline Age	-0.172***	0.011	-0.161***	0.011	-0.159***	0.015	-0.170***	0.037
Male	-0.102	0.132	-0.023	0.129	-0.108	0.138	-0.061	0.173
Hispanics[a]	0.764*	0.277	0.803***	0.273	0.834***	0.292	0.898***	0.331
Blacks [a]	0.177	0.219	0.277	0.225	0.318	0.241	-0.048	0.273
Others[a]	0.476	0.457	0.884	0.486	0.857	0.544	0.828	0.651
Childhood SES	0.032	0.044	0.027	0.044	0.035	0.045	-0.001	0.056
Adult SES	0.085	0.052	0.105*	0.054	0.093*	0.042	0.098*	0.045
Child X Adult SES			0.003	0.008				
Exercise	-0.100***	0.047						
BMI	0.003	0.012						
Ever Smoked	0.029	0.132						
Currently Smoke	-0.461	0.222						
CM Index			-0.099**	0.032	-0.137***	0.045	-0.171***	0.052
Constant	-1.366***	0.402	-1.363***	0.136	-1.375***	0.160	-1.442***	0.176
R-Squared	0.469		0.473		0.488		0.495	
$R_{\text{Intercept with Slope}}$	0.167*		0.175*		0.126		0.134	

Notes: [a]Non-Hispanic Whites as the reference. *** P <0.001 ; ** P <0.01 ; * P< 0.05. Standard Errors are in ().

[b] Using a CM index that includes Forced Expiratory Volume, with the threshold of 250 liters or below.

[c] N = 4845. Based on the alternative sample that imposes a narrower age range between 55 and 73