DO CHILDHOOD CIRCUMSTANCES PREDICT ADULT BIOMARKERS?

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Abstract

It is well known that childhood circumstances affect adult self-reported health, specific chronic diseases, disability, and mortality. In this paper we address the question: do childhood circumstances affect mid-life biologic risk factors for disease? We specifically consider as outcomes, levels of glycosylated hemoglobin (Hb_{A1c}) and high density cholesterol (HDL) as measured in the 2006 Health and Retirement Study. Our approach is grounded in a life-course perspective. We adjust for current demographic, health and socioeconomic variables. We find that father's education and being in poor health as child predict the risk of having unfavorable HDL levels above age 50 even after controlling for current SES characteristics. Mother's education is strongly associated with Hb_{A1c}: respondents with better educated mothers are less likely to have elevated levels of Hb_{A1c}, an association that remains statistically significant after accounting for current SES and health characteristics.

1. Introduction and Background

It is by now well known that childhood circumstances are strongly associated with and predict adult self-reported health (Moody-Ayers et al.2007), specific chronic diseases (Lawlor et al. 2004, 2005; Wadsworth et al. 2005), performance measures of function (Kuh et al. 2006), disability (Guralnik et al. 2006; Kuh 2007), and mortality (Kuh et al. 2002; Hayward and Gorman 2004). Yet, limited knowledge exists about the pathways through which childhood conditions affect risk factors and disease presentations later in life. Looking at markers of system-specific biological functioning may illuminate some pathways through which childhood conditions increase risk for late life diseases.

In this paper we address the question: do childhood circumstances affect mid-life biologic risk factors for disease? We specifically consider two outcomes, glycosylated hemoglobin ($Hb_{A!c}$)[3] and high density cholesterol (HDL), as measured in the 2006 Health and Retirement Study (HRS). Hb_{A1c} is a measure of the relative amount of hemoglobin to which glucose is bound and is now accepted as a first stage diagnostic tool for diabetes, as well as a monitoring tool.

Both biomarkers have been shown to predict independently cardiovascular disease risk and risk for diabetes as well as current diseases (Assmann et al. 1996; Curb et al. 2004; Sharett et al. 2001; Turner et al. 1998; Barter et al. 2007). Thus, Hb_{A1c} and HDL also provide information on

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[3] See Nathan et al. (2008) for issues in converting Hb_{A1c} to levels of circulating glucose.

pre-disease pathways that are causally proximate to a wide range of current or future health outcomes.

This paper will represent one of the first attempts to analyze the effect of childhood characteristics on biologic risk factors for disease using a newly released biomarker data from the Health and Retirement Study (HRS). Current preliminary results suggest that childhood conditions, specifically father's and mother's education, are strongly associated with HDL and HbA1c, biomarkers for cardiovascular disease and diabetes.

Our approach to investigating how childhood circumstances are associated with biologic risk factors for disease is grounded in a life-course perspective (Davey-Smith 2003). We add to the growing literature on the social and biologic pathways linking early life conditions and mid-and late-life health by looking at biological risk factors for disease as an outcome rather than at disease per se. The early life course research focused on the fetal origins hypothesis, in its original genesis formulated by Barker and colleagues (Barker 2000; Barker et al. 2002; and Hales and Barker 2001) linked early life circumstances, even *in utero*, to risks of late life health and chronic disease. Later formulations known as the 'thrifty phenotype concept' modified the original hypothesis characterized by its emphasis on the effects of an early, critical developmental period to incorporate notions of how exposures and behaviors later in life (e.g., diet, physical activity, and obesity) alter initial risks.

Davey-Smith and colleagues have described a more generalizable 'life cycle epidemiologic' framework that allows for shocks in multiple critical periods when susceptibility to health damage is thought to be high, including childhood as well as other periods (Davey-Smith 2003;Galobardes et al. 2004;Hart et al. 2003; Kuh and Ben-Shlomo 2004; Kuh et al. 2003). The effects of these exposures accumulate over time and across life-cycle stages and may exacerbate physiologic damage to a number of biologic systems by simply increasing the absolute number of exposures and their duration, initiating 'chains of risk' as suggested by Ben-Shlomo and Kuh (2002) and Brown et al. (2004) or by the cumulative intensity of assaults on a multisystem homeostasis.

Currie (2008) has recently published an analysis linking childhood circumstances to disease risks and the accumulation of human capital, that is, education and labor market outcomes. This is an important foundation for the current analysis because human capital is a potentially important intervening variable linking childhood adversity to delayed health outcomes. In the same vein, O'Rand and Hamil-Luker (2005) trace early life disadvantage to adult pathways and show differentially trajectories of heart attack risk that mediate the effects of early disadvantage.

Most prior analyses make three key assumptions: *i)*, there is a direct pathway linking childhood circumstances and adult health outcomes, in other words, only the direct effect is noteworthy; *ii)*, biomarkers are not pathognomonic with a disease entity; and, *iii*), the trajectory linking early life circumstances and biomarkers contains no information on the trajectory from risk factor to disease presentation. The confounding of biomarker and disease is difficult to unravel because both key biomarkers and chronic diseases accumulate with age (Crimmins et al. 2005). In the following analysis we model adult biomarkers as a stochastic process involving childhood and mid-life. In sum, life cycle approach provides a flexible framework for addressing the question

of whether childhood antecedents are associated not only with disease outcomes, but also with biological risk factors in later health.

2. Data and Methods

We use data from the Health and Retirement Study (HRS), a nationally representative longitudinal survey of Americans over the age of 50. The study tracks health, assets and liabilities, and patterns of wellbeing of individuals aged 51 and over at the time of their baseline interview. Starting in 1992, a 90-minute core questionnaire has been administered every two years to age-eligible respondents and their spouse/partners. The initial or "original" HRS cohort was age 51-61 when first interviewed in 1992 (along with their spouses of any age). Subsequently, two new cohorts at ages 51-56 "aged-in" in 1998 and 2004. In addition, the cohorts born <1923, the "AHEAD" cohort extended the age range of the study in 1993 and the so-called CODA cohort joined the study in 1998. With these cohorts, the HRS panel was also a representative cross-section of the population aged 51 and older in 1998 and 2004. In 2006, HRS initiated so-called Enhanced Face-to-Face Interviews that include in addition to the core interview a set of physical performance measures, biomarker collection, and a Leave-Behind-Questionnaire on psychosocial topics (see for example Weir 2008). A random 50% sample of all eligible persons identified to participate in this interview. In couple households, both members of the household were selected. Respondents who completed the in-person questionnaire, and who were non-institutionalized were eligible for the physical measures and collection of the biomarkers components.

The focus of the present analysis is on the association of childhood circumstances with two biomarkers—*HDL* and Hb_{A1c}. The measures for both biomarkers (as well as total cholesterol, C-reactive protein and cystatin-C collected in HRS) are based on blood spots collected with kits from Biosafe Laboratories, Chicago, Il. The laboratory is certified to provide values of sufficient accuracy for clinical use.[4]

HDL cholesterol, also known as the 'good' cholesterol, carries the excess cholesterol from the body's tissues back to the liver for processing. Low HDL levels ((below 50 mg/dL) are associated with an increased risk of coronary artery disease even in people whose total cholesterol and LDL cholesterol levels are normal. Research based on the Framingham Heart Study has shown that low HDL is a more potent risk factor for heart disease than low density lipoprotein (LDL) cholesterol (Gordon et al. 1977). HDL levels greater than 50 mg/dL are desirable for individuals. In the present analysis we dichotomize the respondents' HDL measures into two groups, individuals with HDL above (the non-risk group) or below 50mg/dL (the risk group).

The second biomarker considered in the present analysis, Hb_{A1c}, is a percent of glucose attachment to red blood cells. It is a measure of the 3-month average of circulating of glucose and is primarily tested to monitor the degree of control over of glucose metabolism in diabetics.

[4] For more information on how the blood spots were collected see *http://hrsonline.isr.umich.edu/meta/sho_meta.php?hfyle=descrip*

For a diabetic, persistent elevations of Hb_{A1c} increase the risks for a number of complications, such as coronary disease, heart attack, stroke, and other vascular problems. Although the Hb_{A1c} has been recommended primarily for assessing metabolic control of diabetics, its value as a screening tool has recently been considered. Earlier this year Saudek et al. (2008) reported the results of a consensus conference on the utility of Hb_{A1c} for screening large populations with acceptable levels of sensitivity and specificity. For a clinical diagnosis, however, follow-tests, such as glucose tolerance test are also recommended. Following the recommendations of the International Diabetes Federation and American College of Endocrinology, we use a Hb_{A1c} level of 6.5% as a cut-off point to classify respondents into a risk group (Hb_{A1c}>=6.5%) and non-risk group (Hb_{A1c}<6.5%). Since individuals with diabetes have higher levels of Hb_{A1c}, we eliminate these cases from our analysis for Hb_{A1c}.[5]

We assume that the health status of individual evolves over the life cycle as a function of age, years of education, race and other socioeconomic characteristics that are acquired at different life-cycle stages. We use standard logistic models, in which the dependent variable—HDL or Hb_{A1c}—indicates whether a respondent is in a risk group, that is having unfavorable biomarker's values at the time blood spots were collected. We build our models on a life-cycle sequence: we first estimate how the probability of being in a risk group, as indicated by HDL and Hb_{A1c}, is affected by early life traits, such as family socioeconomic status, spending childhood in harsh economic conditions, and parental education. We then estimate models in which we adjust for current demographic and socioeconomic variables (notably age, sex and race). Last we estimate joint models of the effect of childhood and current demographic and socioeconomic characteristics on biological risk factors.

3. Preliminary results

Table 1 shows descriptive statistics for the samples used in our analysis. The number of cases in the two samples used for the analysis of HDL and Hb_{A1c} differs slightly since we do not include respondents diagnosed with diabetes in the analysis of Hb_{A1c} and there are some respondents with missing values on one of the analyzed biomarkers. Table 1 shows that women have higher levels of 'good' cholesterol than men. Blacks/African Americans have slightly higher levels of HDL than Whites and respondents of other race. The higher the BMI the lower is the measured level of HDL, that is the lower is the measured level of 'good' cholesterol in the blood. The level of 'good' cholesterol also increases with schooling: respondents with high education have a mean of HDL=58.32, while the mean of HDL for respondents with less than high school education equals to 54.65.

In contrast to HDL, where higher levels are more desirable, having lower levels of Hb_{A1c} below 6.5% are targeted. Table 1 shows that men have slightly lower levels of Hb_{A1c} compared to women. The Hb_{A1c} level of Whites is also lower than the levels measured for Blacks/African Americans and other races. Hb_{A1c} increases with BMI: the mean of Hb_{A1c} for obese respondents is 5.9 in contrast to the mean of respondents with normal BMI that is 5.71. Similar to HDL,

[5] Including respondents with diabetes in the analysis would result in ambiguous results: if a respondent is diabetic, but medicated, and the condition is well-controlled, the observation would be classified as "normal" level of Hb_{A1c}; if the control of diabetes is poor, Hb_{A1c} would be of high/very high level to the extent of an outlier and the coefficients would biased.

individuals with higher education have better Hb_{A1c} levels. For instance, the mean of Hb_{A1c} for those with education above high school is 5.57, and individuals with education below high school have a mean of Hb_{A1c}=5.68.

Table 2 shows the odds ratios for the probability of having low HDL levels (HDL< 50mg/dL) and thus being in a risk group at ages 50 and over derived from logistic models. Model 1 shows the association of demographic variables such as age, age squared, gender, and race with HDL. We find statistically significant associations between gender and race with HDL levels. In particular, females have about 70% lower odds to have low levels of HDL than men and thus be in a risk group. This association remains stable in all other models that control for current socioeconomic, childhood and health characteristics. Being of other race than Black/African or White is associated with 45% higher odds of having low HDL levels than the reference group Whites. This magnitude of this association declines and looses its statistical significance in the remaining 4 models.

Having spent childhood in excellent socioeconomic (SES) status reduces the odds of having low levels of HDL above age 50 compared to individuals who report average SES during childhood. In contrast, respondents who spent their childhood in poor SES, have 18% higher odds to have unfavorable HDL levels. The magnitude of these associations is reduced and the statistical significance is lost in Models 3 and 5 that control for additional childhood and current characteristics. In particular, in Models 3 and 5 we also include a variable that indicates whether the respondent experienced a harsh childhood. This is a composite variable that takes the value of 1 if a respondent has experienced at least one of the following conditions: family moved because of financial difficulty, family received financial help in from his/her extended family, father was unemployed during respondent's childhood or never worked, and mother worked during childhood. The correlation of the harsh-childhood variable with SES during childhood is 0.4. We think that this variable capture different and broader aspects of the respondent's childhood environment than the more conventional SES measure. The variable is statistically significant only in Model 3, but the magnitude of the association with the dependent variable suggests that respondents who had difficult childhoods have about 15% higher risk of having low HDL. Models 3 and 4 show that if a respondent was in poor health as a child, they have about 40 percent higher odds of having unfavorable HDL levels above age 50. This association remains statistically significant when controlling for current health status (as captured by BMI).

The association of parental education with HDL levels at ages 50 and over is shown in Models 2, 3 and 5. We find that only father's education is statistically significant: a one year increase in father's education is associated with 5% lower risk of having low levels of HDL above age 50. The magnitude and significance level of this association remains stable when we control for additional childhood and current health and socioeconomic characteristics.

Models 4 and 5 reveal that better educated respondents have lower odds to have bad levels of HDL above age 5. One year increase in respondent's education is associated with 4% decrease in the odds of having an unfavorable HDL. . Being overweight or obese is also strongly associated with HDL: individuals with BMI above 30 have 2.5 times higher risk of having an unfavorable HDL than respondents with normal BMI. For overweight individuals the odds are lower (41% higher risk).

Table 3 shows the odds ratios for having unfavorable Hb_{A1c} levels (Hb_{A1c}>=6.5%) at age 50 and over derived from 5 logistic models. The picture for the association of childhood and current demographic and socioeconomic characteristics with Hb_{A1c} is intriguing. Among all variables included in this analysis only being Black/African American, health during childhood and maternal education are statistically significant. Black/African Americans have about two times higher odds to have elevated Hb_{A1c} levels (Hb_{A1c}>=6.5%) than Whites, with the odds ranging from 2.3 in Model 1 to 1.92 in Model 5 that controls for childhood and current socio-demographic characteristics. The results suggest that respondents of other races have also higher odds for having unfavorable Hb_{A1c} levels (Hb_{A1c}>=6.5%) than the reference group, but these differences are not statistically significant.

Models 3 and 5 include health status during childhood. In both models, respondents who rated their childhood health as being good have about 60 percent higher risk of having elevated Hb_{A1c} levels than the reference group of respondents who rated their health status during childhood as excellent. Although the difference is not statistically significant, the magnitude of the coefficients suggests that respondents who rated their childhood health as poor have more than 70 percent higher odds to measure levels of Hb_{A1c}>=6.5% compared to the reference category.

The most intriguing result shown in Table 3 is the association of mother's education with Hb_{A1c}. The magnitude and significance level of this association is remarkably stable in all models that control for past and current demographic, social and health characteristics. Respondents with better educated mothers have lower odds to have elevated Hb_{A1c} levels: one year increase in mother's education is associated with about 11 percent lower odds for Hb_{A1c} levels above the cut-off point of 6.5%.

4. Further analysis

The present analyses are preliminary. The results suggest that there is a significant association between childhood characteristics and biomarkers for disease risks. In particular, the results obtained for Hb_{A1c} are consistent with previous research by Kohler and Soldo (2007): the authors have shown that maternal education is a significant predictor for type-2 diabetes above age 50. In the present analysis, we find a similar pattern. Maternal education is significantly associated with Hb_{A1c} levels above age 50. This biomarker is also a strong predictor of diabetes. In summary, the current results suggest that childhood circumstances, in particular maternal education, predict not only disease outcomes, but also biologic risk factors for disease. The interpretation of this result is not straightforward and the pathway through which mother's education affects the risk for having high levels of HbA1c in late life is not clear. The observed association supports the hypothesis that it may stem from conditions of poor pre- or post-natal nutritional environment that is more typical for mothers with low levels of education.

We are aware that the current models omit some important variables such as various current health outcomes. Moreover, the current models do not sufficiently control for current SES. For example, we currently do not include current wealth of the individuals. In our future work we plan to expand the analyses and account for these shortcomings.

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Table 1. Mean and standard deviation (in paranthesis) of HDL and HbA1c.

	HDL	Hba1c
Men (n_1=1528; n_2=1552)	51.26	5.59
	(11.75)	(0.50)
Women (n_1=2135; n_2=2207)	61.64	5.62
	(14.60)	(0.45)
White (n_1=3207; n_2=3342)	57.24	5.59
	(14.44)	(0.47)
Black (n_1=316; n_2=296)	58.41	5.75
	(14.13)	(0.53)
Other race (n_1=140; n_2=)	56.58	5.68
	(14.73	(0.44)
18.5<=BMI<25 (n_1=263; n_2=353)	63.52	5.71
	(15.30)	(0.84)
25<=BMI<30 (n_1=1059; n_2=1403)	60.04	5.70
	(15.37)	(0.75)
BMI>=30 (n_1=2341; n_2=2965)	55.38	5.90
	(13.45)	(0.87)
Below high school education (n_1=573; n_2=538)	54.65	5.68
	(12.92)	(0.46)
High school education (n_1=1260; n_2=1275)	57.06	5.62
	(14.23)	(0.50)
Above high school education (n_1=1830; n_2=1946)	58.32	5.57
	(14.89)	(0.46)

Notes: n1denotes number of cases used in the analyses of HDL.

n2 denotes number of cases used in the analyses of $Hb_{a1c.}$

Table 2. Odds ratios for the probability of having low (bad) HDL level below 50 mg/dL at ages 50 and over derived from logistic regression models

	Model 1	Model 2	Model 3	Model 4	Model 5
Age	1.078	1.070	1.071	1.039	1.039
	(0.051)	(0.050)	(0.050)	(0.050)	(0.050)
Age squared	1.000	1.000	1.000	1.000	1.000
	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Female	0.301**	0.294**	0.294**	0.275**	0.274**
	(0.022)	(0.022)	(0.022)	(0.022)	(0.022)
Black/African American	0.969	0.896	0.873	0.859	0.804
	(0.131)	(0.122)	(0.120)	(0.119)	(0.112)
Other race	1.455*	1.292	1.281	1.337	1.267
	(0.276)	(0.252)	(0.250)	(0.257)	(0.249)
Separated/divorced				1.213	1.219+
				(0.145)	(0.146)
Widowed				1.071	1.071
				(0.123)	(0.124)
Never married				0.973	0.987
				(0.246)	(0.249)
Overweight (25<=BMI<=29.9)				1.439*	1.413+
				(0.259)	(0.255)
Obese (BMI>= 30)				2.578**	2.518**
				(0.443)	(0.434)
Years of own education				0.943**	0.960**
				(0.012)	(0.014)
Excellent SES during childhood	0.773+		0.884		0.883
	(0.118)		(0.138)		(0.140)
Poor SES in childhood	1.183*		1.000		0.990
	(0.099)		(0.094)		(0.095)
Experienced harsh childhood			1.169+		1.159
			(0.106)		(0.107)
Was in good health during childhood			1.063		1.029
			(0.111)		(0.109)
Was in poor health during childhood			1.414*		1.393*
			(0.223)		(0.222)
Father's education in years		0.947**	0.952**		0.965**
		(0.012)	(0.013)		(0.013)
Mother's education in years		0.999	1.000		1.011
			(0.015)		(0.015)

Notes: Standard errors in paranthesis. P-values: +p<0.10; *<0.05; **p<0.01.

Table 3. Odds ratios for the probability of having high (bad) HbA1c level above 6.5% at ages 5 derived from logistic regression models

	Model 1	Model 2	Model 3	Model 4	Model 5
Age	1.064	1.042	1.049	1.072	1.065
	(0.117)	(0.115)	(0.116)	(0.120)	(0.120)
Age squared	1.000	1.000	1.000	1.000	1.000
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
Female	1.050	1.038	1.028	0.956	0.948
	(0.200)	(0.198)	(0.196)	(0.192)	(0.191)
Black/African American	2.290**	2.055**	2.011*	2.085**	1.924*
	(0.613)	(0.560)	(0.553)	(0.571)	(0.538)
Other race	2.151^{+}	1.642	1.571	2.018	1.564
	(0.944)	(0.738)	(0.710)	(0.893)	(0.710)
Separated/divorced				0.987	0.996
				(0.309)	(0.313)
Widowed				1.270	1.261
				(0.326)	(0.325)
Never married				1.139	1.237
				(0.688)	(0.751)
Overweight (25<=BMI<=29.9)				0.753	0.757
				(0.286)	(0.288)
Obese (BMI>= 30)				1.324	1.327
				(0.459)	(0.461)
Years of own education				0.952	0.999
				(0.030)	(0.036)
Excellent SES during childhood	0.755		0.857		0.854
	(0.325)		(0.374)		(0.373)
Poor SES in childhood	1.152		1.031		1.035
	(0.235)		(0.243)		(0.245)
Experienced harsh childhood			0.896		0.886
			(0.209)		(0.207)
Was in good health during childhood			1.605*		1.580*
			(0.367)		(0.365)
Was in poor health during childhood			1.712		1.742
			(0.576)		(0.590)
Father's education in years		1.023	1.027		1.032
		(0.035)	(0.036)		(0.036)
Mother's education in years		0.890**	0.896**		0.897**
		(0.033)	(0.033)		(0.034)

Notes: Standard errors in paranthesis. P-values: $^{+}$p<0.10; *<0.05; **p<0.01.