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Early life exposures and the occurrence and timing of heart disease among the Puerto Rican elderly population

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Abstract

Background. Season of birth has been shown to be a useful proxy of early growth and development among adults. It is an indicator that disentangles the effects of childhood conditions (health, SES) on adult health and sheds light on the adult health effects of poor nutrition and infectious diseases in utero.

Methods. We used a sample of 1438 Puerto Ricans 60-74 years of age born in Puerto Rico who lived in the countryside during most of childhood. Retrospective measures of early childhood (health status, SES); knee height, height and weight measurements and adult risk factors (adult SES, obesity, self-reported smoking, exercise, diabetes) were obtained through home interviews. We defined exposure period to poor nutrition and infectious and parasitic diseases to be the third-fourth quarter. Using Cox and log logistic hazard models we examined the degree to which overlap between late gestation (last trimester of pregnancy) and exposure period had important effects on the timing of onset of and the probability of ever experiencing adult heart disease while controlling for other risk factors.

Results. Risk of onset of heart disease was 65% higher among those born when the third trimester of gestation overlapped completely with exposure period compared with unexposed individuals but there were no differences in median time of onset by exposure for those reporting heart disease.

Conclusions. Effects of exposure to a high risk period operate through the probability of ever experiencing heart disease not through the timing of onset among those who do experience it.

Keywords: early growth, early childhood, adult health, coronary heart disease, event history

Introduction

Disentangling the effects of substandard nutrition in utero from the effects of other childhood conditions (health, SES) that could influence adult health status requires good measures of early growth and development. In theory at least, season of birth is such an indicator because it is unrelated to background factors such as socioeconomic status[1] but captures the seasonality of food supply. Being born during or right after a harvest, when nutritional supplies are more plentiful, is associated with longer life[1-5]. Increased exposure to seasonal infectious and parasitic diseases can also have a powerful impact on nutritional status for mother and fetus[6-8].

Exposure to poor nutrition in utero during mid to late gestation is believed to predispose individuals to later coronary heart disease and diabetes[9]. However, there is disagreement in the literature about the exact mechanisms involved and the signals from extant empirical evidence are quite mixed[10-13]. Postnatal conditions such as slow infant growth or rapid weight gain in childhood after a period of sub-optimal development are also associated with heart disease[14-16] and are believed to enhance effects of exposure to poor nutrition in utero[15]. Nevertheless, accumulated research suggests that the period of late gestation (third trimester of pregnancy) is particularly important in the development of later adult heart disease[1, 17, 18].

Our objective in this paper is quite modest: we attempt to show that, as originally postulated, there is an association between exposure to conditions that enhance chances of malnutrition/infection in utero and the timing of onset of adult heart disease. Although we are not able to elucidate the mediating mechanisms we are able to eliminate some competing hypotheses explaining the observed association.

The case of Puerto Rico provides an interesting case study. During the late 1920s-1930s most Puerto Rican families living in rural areas were poor, landless, did not own their own home, could not rely on self-subsistence since availability of garden plots was a rarity, did not own livestock, were scattered and isolated with no strong social ties and were unemployed or underemployed during extended periods of the year[19]. Wages were the single most important source of income to purchase food but they were highly seasonal, especially for those working in the sugar cane industry which dominated the agricultural sector beginning in the early nineteen hundreds (Figure 1). Periods of high employment coincided with the cutting season or harvest for sugar cane during the first half of the year (January-June) followed by a second period with high rates of unemployment when purchase power plummeted and existing savings or stocks were exhausted. The second half of the year also coincided with the hurricane season (August-October) which increased exposure to infectious and parasitic diseases such as malaria and dengue and the transmission of bacterial diseases such as dysentery, cholera, diarrhea[20].

We hypothesized that late gestation (third trimester) is particularly important for nutritional deficiencies and that the highest and lowest risk of exposure for rural Puerto Rican families in the late 1920s-early 1940s was prior to the beginning of the sugar cane harvest (October-December) and towards the end of the harvest (April-June) respectively. We now raise the conjecture that the **extent of exposure during late gestation** is associated with early onset of and the probability of ever experiencing heart disease. More concretely, the timing of onset of heart disease should be earlier for those born towards the end of the lean season and who were completely exposed during late gestation to the exposure period and later for those born during seasons of abundance [close to the end of the harvest season] where there was no exposure during late gestation. Risks of contracting heart disease should be higher for those born towards the end of the learn season and lower for those born during seasons of abundance. We use data from a new study on the Puerto Rican elderly population to test this conjecture.

[Insert Figure 1 about here.]

Methods

The Puerto Rican Elderly: Health Conditions (PREHCO) project is a cross-sectional survey of the non-institutionalized population age 60 and over and their surviving spouses in Puerto Rico[21]. The sample is a multistage, stratified sample of the elderly population residing in Puerto Rico with oversampling of regions heavily populated by people of African descent and of individuals aged over 80. The project offers substantial information on health issues of elderly Puerto Ricans within the bounds of face-to-face interviews in a cross section of 4,293 target individuals. The overall response rate was 93.9% and preliminary analyses indicate that there are no significant differences between non-respondents and respondents.

We defined the exposure period to be July-December--the months of the off season in the Puerto Rican sugar cane industry characterized by high employment[19, 22] and the peak season for infectious diseases[20]. We used quarter of birth to define the **extent of exposure during late gestation** (third trimester) and distinguished the following cases: full exposure (fourth birth quarter); partial early exposure (third birth quarter), partial late exposure (first birth quarter); no exposure (second birth quarter).

Childhood health (overall health, rheumatic fever) was assessed by classifying childhood health status as poor or not and rheumatic fever affirmatively or not according to respondent's self-report. Knee height, measured during home interviews and tapping the presence of growth and developmental problem associated with nutritional status, was defined using gender-specific quartiles (low versus other) where low were individuals classified in the lowest quartile. Poor socioeconomic status was classified as either with or without formal education using self-reports of father's education. The occupation of the respondent's father was self-reported and classified as either agricultural or not according to the International Standard Classification of Occupations (www.ilo.org/public/english/bureau/stat/isco/index.htm).

Major adult risk factors for heart disease[23] were measured: 1) body mass index (BMI) was calculated from weight and height measurements as weight in kilos divided by height in meters squared and then classified obese or not if BMI was greater than or equal to a BMI of 30; 2) respondents who ever smoked were identified in response to survey questions about whether they had smoked more than 100 cigarettes in their lifetime. Similarly, individuals who exercised were identified according to responses about whether or not they had done strenuous exercise during the last 12 months on a regular basis; 3) diabetes was defined based on respondent's answers to questions about whether a doctor had ever diagnosed them with diabetes; 4) respondent's assessment of number of years of schooling was used to identify maximum primary education from higher attainment.

We used multiple imputation procedures[24-27] implemented in IVEware (http://www.isr.umich.edu/src/smp/ive/) to include all relevant cases and selected a sub-sample of 60-74 year old elderly born in Puerto Rico and who indicated that they had lived a prolonged period of time in the countryside prior to the age of 18.

Respondents experienced the event (heart disease) if they answered affirmatively to a question about whether a doctor had ever diagnosed them with heart disease. We defined time at onset of heart disease as the self-reported age identified by the respondent, including those with an age of onset of at least 40 years.[a] We rescaled the time of onset of heart disease to start at zero by subtracting age of diagnosis from age 40 for respondents with heart disease and current age from 40 for respondents without heart disease. We evaluated irregularities and heaping by examining a plot of the frequency distribution of the estimated age of onset.

We estimated Kaplan Meier (KM) survival, hazard, and cumulative hazard functions and employed the log rank test to test statistical differences between survival curves. Median age of onset for those who experience heart disease was computed using Kaplan Meier and was observed to be 60. We estimated the effects of extent of exposure on the timing of heart disease through a series of Cox regression models and parameterized the baseline hazard with a log logistic regression because the KM estimates for the hazards suggested strong non-monotonicity of duration to the event. Standard tests were carried out to assess the adequacy of model fit and assumptions[b] and we calculated predicted values for the hazard and cumulative hazard.

Results

General Characteristics of the Sample

Statistically significant differences in the prevalence of heart disease were strongly associated with extent of exposure during late gestation (Table 1). Those who experienced full exposure during late gestation [fourth quarter] showed the highest prevalence of heart disease (.23) as compared with those with partial exposure (.18, .15) and with unexposed individuals [second quarter] (.11). Differences were significant at p=.006 (chi-square 12.37, 3 df). Examination of the distribution of self-reported age at diagnosis revealed no systematic biases generated by heaping or other types of distortions that are common with recall of timing of events (results not shown).

[Insert Table 1 about here.]

Kaplan Meier Estimates

A log rank test confirmed strong significant differences between the survival curves of time to diagnosis of heart disease by extent of exposure (p=0.0306, chi-square=8.91 with 3 degrees of freedom). There was a much lower number of events (diagnosis of heart disease) among unexposed persons than among those with complete exposure: the observed number of events among those exposed was 86 whereas the expected number was 68.18. Among the unexposed the observed number of events was 55 versus the expected 72.29. There was no difference between observed and expected in the other categories of exposure. The estimates of the smoothed hazard and cumulative hazard functions by quarter of birth suggest larger differences due to extent of exposure after age of 60 (Figure 2). Hazards in the group with full exposure during late gestation (fourth quarter) were approximately twice as high as among those within the unexposed category (second quarter) at later ages. The baseline hazard function showed a monotonic increase with age, peaking at around age 65-67 and then decreasing.

[Insert Figure 2 about here.]

Multivariate Models: Simple Cox Models

Age- and sex-adjusted relative hazards for full exposure during late gestation and for childhood health and rheumatic fever using Cox regressions were 1.71 (95% CI 1.22-2.41), 1.38 (95% CI 1.06-1.79) and 2.69 (95% CI 1.57-4.58) respectively. Very similar relative hazards were obtained in a model including all covariates (Table 2). The risk of reporting heart disease was 65% higher among those born with full exposure (fourth quarter) compared with unexposed individuals (second quarter). As expected, and confirming other findings in the literature[28], early experience with rheumatic heart fever had the most powerful effects, more than doubling the risk of heart disease. The model was deemed appropriate.[c]

[Insert Table 2 about here.]

Multivariate Models: Log Logistic Models

Age- and sex-adjusted log logistic regression TR (time ratio) for full exposure during late gestation, childhood health and rheumatic fever were .78 (95% CI .67-.92), .86 (95% CI .76-.98) and .61 (95% CI .46-.81) respectively and these effects were largely unchanged when these variables were combined into one age- and sex-adjusted model (TR .79, 95% CI .68-.93; TR .86, 95% CI .76-.98; TR .62, 95% CI .46-.83). Similar results were obtained when a model with all covariates was estimated (Table 2). Being born with full exposure (fourth quarter), poor childhood health, rheumatic fever, obesity and diabetes "sped" the time of onset of heart disease with the strongest effect observed for rheumatic fever. The (expected) median time for onset of heart disease for those born with full exposure (fourth quarter) was about .80 times that of the median time to diagnosis for unexposed persons (second quarter). Tests for the adequacy of this model suggest that it successfully captures empirical patterns.[d]

[Insert Table 3]

Given that both the Cox and log-logistic models produced similar fit with the data, it is not surprising that predicted hazards and cumulative hazards from each are very similar although the log logistic model tended to produce greater hazards at older ages (Figures 3 & 4). At older ages the hazard doubled for full exposure (fourth quarter) in contrast with unexposed persons (second quarter). Hazards of partial exposure appeared closer to that of full exposure.

[Insert Figures 2-4]

Interpretation

The above tests reveal that the lifetime (after age 60) of risks of contracting heart disease are significantly different among those whose late pregnancy coincided with a high risk period than among those whose gestational experience was outside the risk period. Two mechanisms or a combination thereof can produce these results: different gestational exposure can affect the 1) timing of onset of the disease and 2) probability of ever experiencing the event. To discriminate between these two mechanisms we carried out auxiliary tests. The first is to compare the median time to the onset of the disease among those who actually experienced the event in the high and low exposure groups. The second is to compare the proportion who ever develop the disease across the same exposure groups. There was no difference in the timing of onset of heart disease but there were important differences in the proportion ever experiencing heart disease (Table 3): the highest difference was between full exposure (.34) and unexposed individuals (.23) with partial exposures in between (.27).

[Insert Table 3 about here.]

Discussion

The results presented above suggest that, consistent with our expectations, the lifetime (after 60) risks of experiencing heart disease are significantly higher among those with high exposure to poor nutrition and infectious diseases during late gestation (as proxied by an indicator of season of birth) among 60-74 year Puerto Ricans. Full exposure (being born at the end of the lean season) produced risks of onset of heart disease that are 65% as high as among unexposed individuals (born at the end of the harvest season). As shown above, this is a result mainly of differences in the cumulated risk of experiencing heart disease and not on the timing of onset among those who experience it. Childhood health, rheumatic fever, obesity and diabetes also showed important effects on the risk and timing of the onset of heart disease. An important finding is that the effects of (self–reported) childhood health and rheumatic fever are not attenuated when the extent of exposure during late gestation is included in the model. This suggests that seasonality of birth is capturing something other than effects that could be associated with general health status during childhood and experience of a heart-related microbial infection.

The results we obtain are consistent with other studies which have shown associations between seasonality of birth and adult health status[1-5]. However, our empirical evidence is inconsistent with evidence from famine studies highlighting early gestation[11-12]. This may reflect that the physiological mechanisms related to timing in non-famine conditions may be different than those operating with timing during conditions of famine[10]. It is also possible that in Puerto Rico the peak season for infectious diseases coincides almost perfectly with the lean season and that we are not able to clearly separate out the effects of nutritional deficiencies from those that result from maternal contraction of infection or parasitic illnesses.

There are a number of key issues that remain unresolved. The first is the degree to which season of birth adequately reflects conditions experienced in utero or is a better indicator of those experienced immediately after birth. The differential effects on adult health of the timing of exposure during mid and late gestation, on the one hand and during early infancy, on the other are largely unknown. In the case of Puerto Rico those born towards the end of the lean season would have been fully exposed during late gestation to the lean period but then are exposed during their early infancy (the first 6-8 months) to less harsh conditions during the harvest time. The results we obtained, however, suggests that the negative effects of exposure during late gestation completely overwhelms beneficial effects derived from spending early infancy during times of relative slack.

A second issue is the degree to which the use of national level data is appropriate to test a hypothesis that is clearly sensitive to community heterogeneity. This difficulty is of less importance in small and highly homogeneous countries such as Puerto Rico, where national and regional seasonality and economic indicators are highly consistent with each other, but it is a stumbling block otherwise.

Thirdly, there are limitations of measurement in population surveys which make it impossible to obtain precise estimates of effects. Seasonality of birth is problematic partly because it is not exact and may not coincide with the critical time for everyone and partly because focusing exclusively on the third trimester may miss the mark. It is also possible that self-reported time of first diagnosis for heart disease contains systematic biases, other than those generated by random noise or heaping, that are not visible to the naked eye. Self reported chronic conditions although underreported[29, 30] have been shown to identify quite well underlying conditions[31] and thus, underreporting of heart disease would lead to an understatement of effects and not to an exaggeration. The finding that seasonality of birth does not attenuate the effects of childhood health poses a puzzle. It could well be that early life exposures (as assessed by season of birth) have direct effects on adult heart disease that are not mediated by early childhood health status as measured here. However, this interpretation is inconsistent with a body of literature documenting the influence of early childhood health on adult health[28, 32-35,23]. A more likely explanation is that self reported childhood status is not a good measure of the health status conditions that matter as mediators between exposure in utero and adult disease. Although we know that self-reported childhood health has good reliability[36-37], it is not clear which dimensions of health are being captured nor the extent to which adult health status self-perception influences self-rating of childhood health. Nevertheless, our results are consistent with those obtained in studies where health outcomes and birth seasonality was much more precisely measured[1-5]. Thus, seasonality of birth under certain strict conditions may be a useful proxy to examine associations between early and late adult health.

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Conflict of interest: None declared.

Notes

[a]This exclusion left out only a small number of respondents—21—and made no difference in the analysis.

[b] Standard tests included: a) Cox Snell residuals to test for the overall fitness of the models and least square regression models to describe the slope and y-intercept of plots of Cox Snell residuals and Nelson-Aalen estimator hazard estimates; b) graphical examination (plot the log-log of survival against the ln of time) to test the proportional hazards assumption of the Cox model; c) graphical examination (ln of the cumulative hazard from the Nelson-Aalen estimator, and the ln of the exponential of the cumulative hazard minus one and the ln of time[38] to test appropriateness of the log logistic model.

[c]A linear regression of the Cox Snell residuals on the Nelson-Aalen estimator hazard estimates produced an R-square of .98 with a slope close to one (1.04) and a y-intercept close to zero (-.01). A plot of the log-log of survival against the natural log of time and adjusted for covariates produced parallel lines across extent of exposure (quarter of birth) and thus the proportionality assumption of the Cox model was also deemed to be just right (results not shown).

[d]A linear regression of the Cox Snell residuals on the Nelson-Aalen estimator hazard estimates produced an R-squared of .98 with a slope close to one (1.18) and with a y-intercept close to zero (-.03). The fit is very similar to that obtained with a simpler Cox model An additional test using the Nelson Aalen estimate of the cumulated hazard again suggest (results not shown) strong concordance between the model and the empirical data.

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Table 1: Selected characteristics of sample

	Extent of Exposure During Late Gestation				
		Partial	Partial		
	Full	**Late**	**Early**	**None**	**All**
Demographic					
Female (%)	54	51	47	50	50
Age (yrs)	66(4)	66(4)	66(4)	66(4)	66(4)
Childhood					
Poor health (%)	27	19	28	22	24
Rheumatic fever (%)	2	2	2	2	2
Father no education (%)	46	44	39	48	44
Knee height (cm)	46(5)	46(5)	47(5)	46(5)	46(5)
Father worked in Agriculture	63	68	58	71	65
Adult Risk					
Obese (%)	25	31	27	28	28
Diabetes (%)	34	32	31	29	31
Ever smoked (%)	37	32	37	32	35
Exercises (%)	46	38	48	45	44
Primary (%)	62	68	57	64	63

Heart Disease (%)	23	18	15	11	17
Total Number	360	340	344	394	1438

Source: PREHCO imputed and weighted (n=1438); all 60-74 years old born in Puerto Rico and who lived in the countryside before the age of 18 and who indicated that the onset of heart disease was at least at age 40. Exposure period is July-December. Extent of exposure is based on third trimester of pregnancy: Full exposure (fourth quarter); partial exposure (first quarter or third quarter) and no exposure (second quarter). Mean age and knee height are followed by standard deviation in parentheses.

Table 2: Effects of early life conditions and adult risk factors on the onset of heart disease

	Cox		Log Logistic	
	Hazard	95% C.I.	Time Ratio	95% C.I.
Demographic				
Female	0.99	0.76-1.29	1.00	0.88-1.13
Age 60-64	1.62	1.13-2.31	0.85	0.74-0.99
Age 65-69	1.39	1.02-1.90	0.89	0.78-1.02
Age 70-74	1.00		1.00	
Extent of Exposure				
No (ref group)	1.00		1.00	
Partial early	1.32	0.91-1.90	0.87	0.74-1.03
Partial late	1.33	0.93-1.92	0.88	0.74-1.04
Full	1.65	1.18-2.33	0.79	0.68-.93
Childhood Conditions				
Health	1.36	1.04-1.78	0.87	0.77-.99
Father education	1.28	0.98-1.67	0.90	0.80-1.02
Knee height	0.89	0.67-1.19	1.06	0.93-1.21
Rheumatic fever	2.45	1.42-4.22	0.62	0.46-0.84
Father agriculture	0.94	0.72-1.23	1.03	0.91-1.16
Adult Risk				

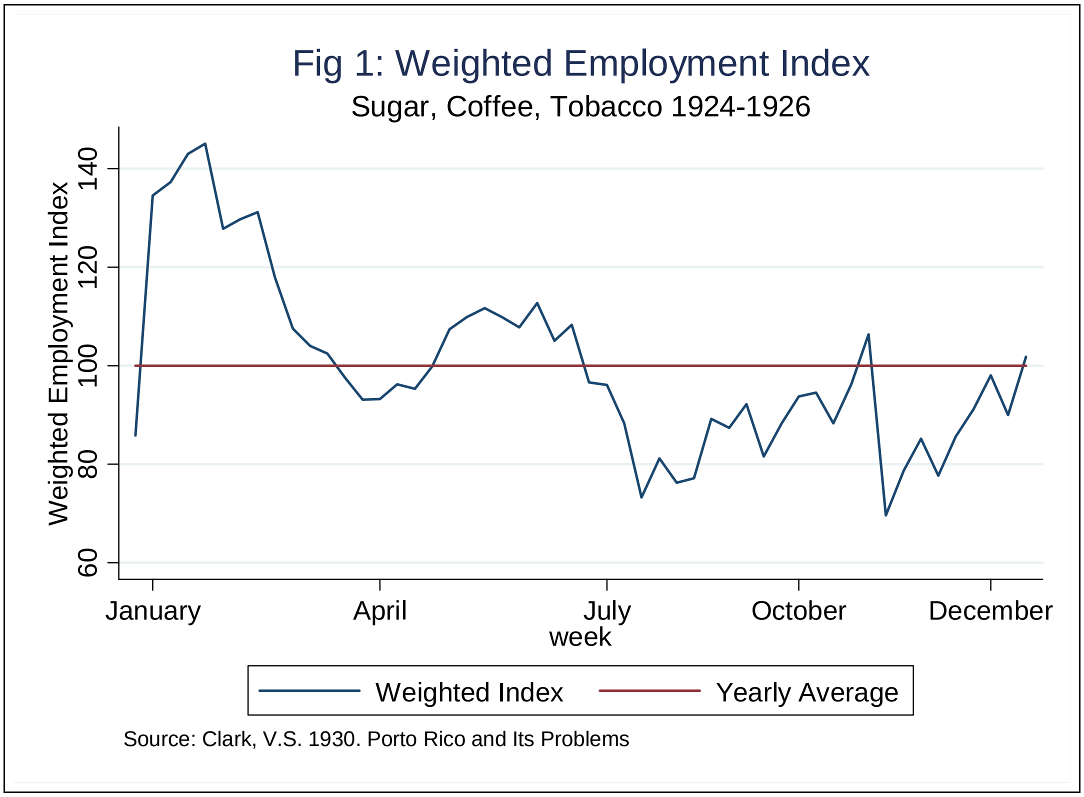
Obesity	1.65	1.28-2.13	0.79	0.70-0.89
Diabetes	1.56	1.21-2.00	0.82	0.73-0.92
Smoking	1.14	0.87-1.49	0.94	0.83-1.06
Exercise	0.85	0.65-1.10	1.09	0.97-1.23
Education attained	1.00	0.76-1.32	1.00	0.89-1.14
Gamma			0.41	0.37-0.46
Log likelihood	-1796		-715	
N observations	1438		1438	

Source: PREHCO imputed, 60-74 years old (n=1438) who were born in Puerto Rico and lived in the countryside before the age of 18 years Exposure period is July-December. Extent of exposure is based on third trimester of pregnancy: Full exposure (fourth quarter); partial exposure (first quarter or third quarter) and no exposure (second quarter).

Table 3: Median age at onset of heart disease and ever experienced heart disease across extent of exposure during late gestation

	Extent of Exposure During Late Gestation				
	Full	**Partial Late**	**Partial Early**	**None**	**All**
Median age at onset of heart disease	60	60	59	59	60
Ever experienced heart disease (%)	34	27	27	23	28

Source: PREHCO imputed and weighted (n=1438); all 60-74 years old born in Puerto Rico and who lived in the countryside before the age of 18 and who indicated that the onset of heart disease was at least at age 40. Exposure period is July-December. Extent of exposure is based on third trimester of pregnancy: Full exposure (fourth quarter); partial exposure (first quarter or third quarter) and no exposure (second quarter).



Note: Graph depicts a composite employment index weighting the number of days worked in the three most important agricultural areas (sugar cane, coffee and tobacco) by the number of laborers reported in these industries in the 1920. Agricultural employment followed a cyclical pattern similar to that of the sugar cane industry where employment was highest during the first 6 months of the year and lowest during the later part of the year (Clark, 1930).

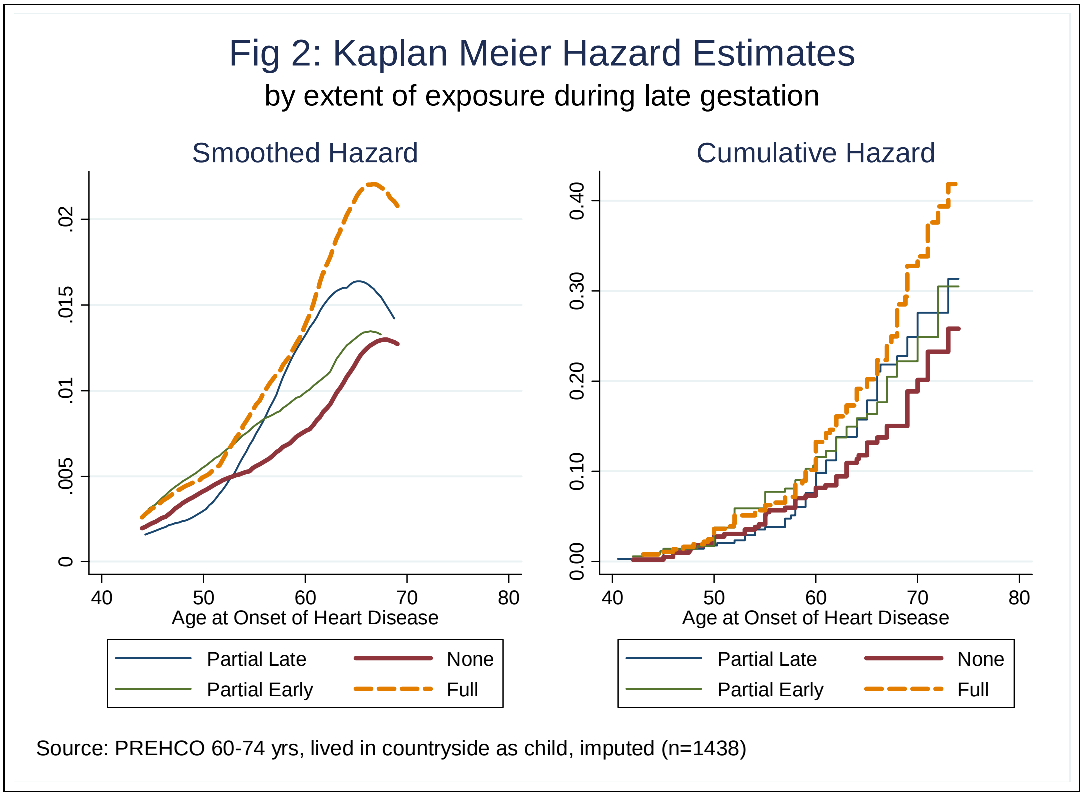


Fig 2: Kaplan Meier Hazard Estimates
by extent of exposure during late gestation
Smoothed Hazard
Cumulative Hazard
0
.005
.01
.015
.02
0.00
0.10
0.20
0.30
0.40
40
50
60
70
80
Age at Onset of Heart Disease
Partial Late
None
Partial Early
Full
Source: PREHCO 60-74 yrs, lived in countryside as child, imputed (n=1438)

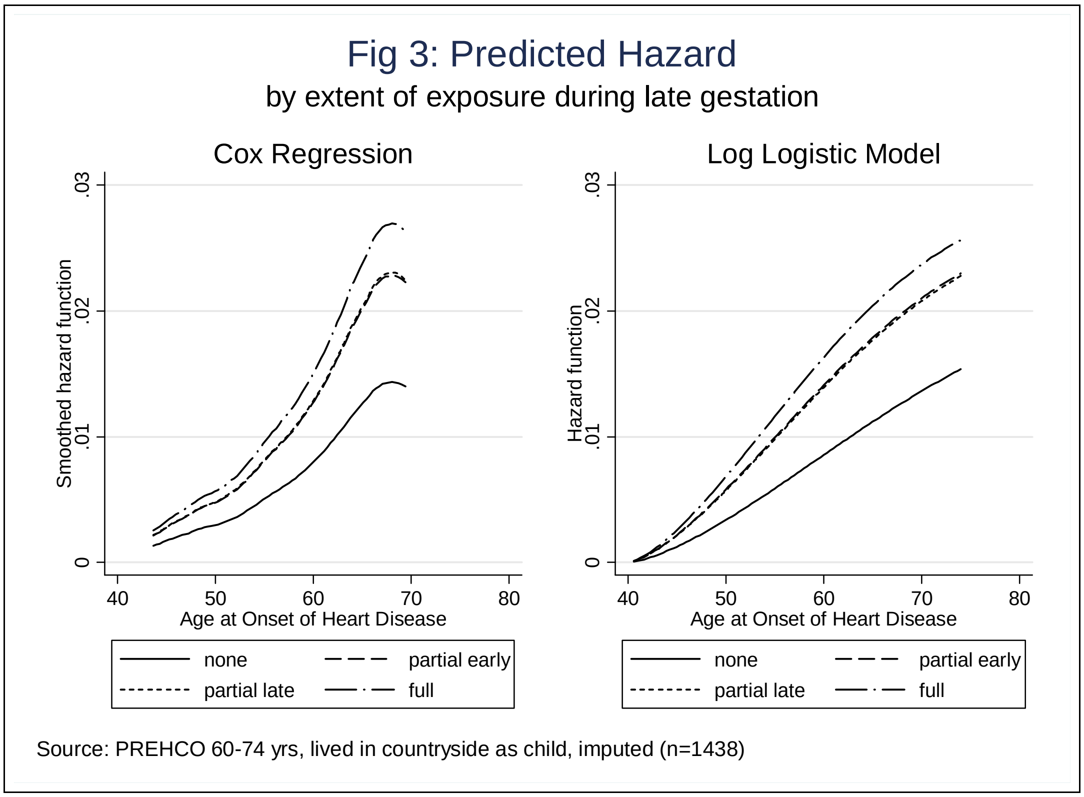
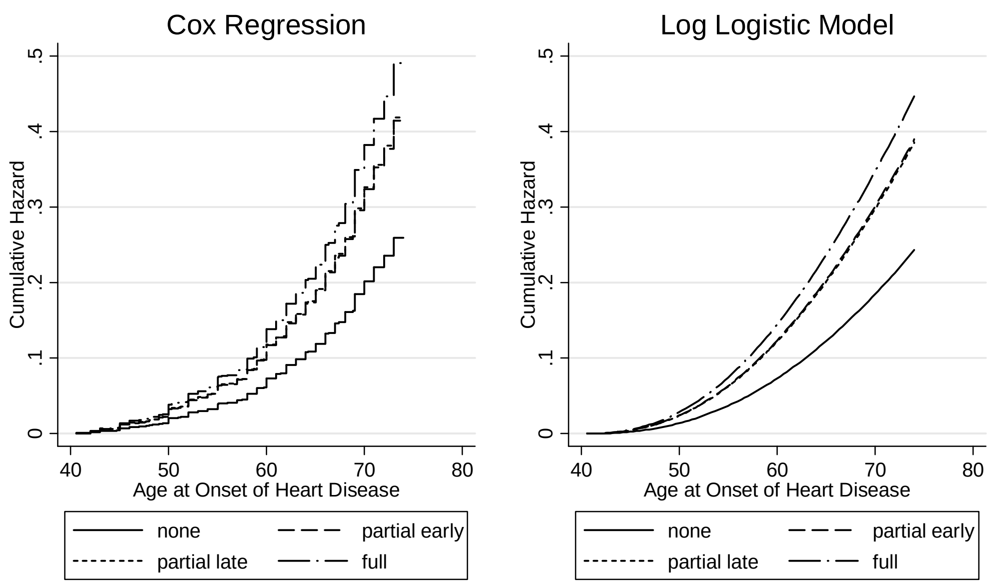


Fig 3: Predicted Hazard
by extent of exposure during late gestation
Cox Regression
Log Logistic Model
Smoothed hazard function
Hazard function
0
.01
.02
.03
40
50
60
70
80
Age at Onset of Heart Disease
none
partial early
partial late
full
Source: PREHCO 60-74 yrs, lived in countryside as child, imputed (n=1438)

Fig 4: Cumulative Predicted Hazard

by extent of exposure during late gestation



Source: PREHCO 60-74 yrs, lived in countryside as child, imputed (n=1438)

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