Racial disparities in biomarkers of health among the survivors of the 1918 Influenza Pandemic: A natural experiment exploring the role of early life events in health and longevity

Background

Between August 1918 and March 1919, pandemic influenza swept the globe killing five times as many people as World War I and reconfiguring conventional expectations about the social stratification of disease and mortality (Crosby 2003; Barry 2004). The pervasive and unexpected nature of the pandemic makes it a unique natural experiment for studying the influence of an external 'shock' to established patterns of human development, aging, and longevity. This is because studying the effects of early life exposure through the pandemic helps to minimize the problem that distinguishes experimental studies from observational studies—that is that people (in this case parents) select infants into and out of exposure to risk in a way that can bias the findings of early life exposures on later life outcomes. This study extends previous research on the relationship between early life events and later life aging by using biomarkers and social group patterns to study the mechanisms linking early and later life health and survival.

The use of the 1918 pandemic as a natural experiment to study the influence of early life exposures on later life outcomes follows from a well established literature on famine and other natural disasters (Susser and Lin 1992; Preston et al. 1998; Almond 2006; see also for review O'Connor 2003). This literature has described how exposures in early life have been associated with both positive and negative influences on the long-term health (Preston et al. 1998). The potential negative influence is theorized to operate through 'scarring' in which an early life exposure carries a lasting negative influence on health and development throughout an individual's life. The potential positive influence is most typically associated with health-selective mortality, or 'culling', whereby an exposure is associated with selective survival of the strongest. Another theoretical possibility that has not been considered in other literature, is that the observed positive effect of an early life exposure could also be attributed to a type of 'immunization-effect' in which the early life exposure reduces the likelihood of later life exposures.

To date, none of the previous studies on exposure to famine and other 'external shocks' in early life have employed biomarkers of infectious disease or inflammatory response to explore potential mechanisms through which these early life exposures influence later life health and aging. In addition, only one known study has used the 1918 Influenza Pandemic as a natural experiment to study health and cognitive development of U.S. adults in later life (Almond 2006). Consistent with previous work on famines, Almond has observed a negative influence of the early life exposure to the pandemic on later life health and cognition (e.g. self-rated health, educational attainment and income). Moreover, in the study by Almond, as in others on famines that preceded it, the issue of whether and how early life exposures affected different social groups was not been extensively examined. Again, the 1918 Influenza Pandemic provides a unique opportunity for considering this question because it did not follow the social patterning of morbidity and mortality in the periods that preceded or followed it.

Research Questions

In order to examine the mechanisms linking early life exposures to later life health and aging, this study takes advantage of unique patterns of exposure to and mortality resulting from the 1918 Influenza Pandemic (by age, race, and gender) at the time of the pandemic. I compare the patterns of acquired immune response for cohorts that were and were not exposed to the pandemic at different ages. Using these comparisons, I can develop a better understanding of the various pathways that early life events shape health and longevity. By using cohort comparisons, I am not only interested in studying the survivors of the epidemic, but also their children. I will address a special subset of children who were exposed to potentially "scarring" (Preston et al 1998) influence of infectious exposures and nutritional deficits. My specific research questions about the relationship between the 1918 Influenza Pandemic and biomarkers of acquired immunity follow:

1. Are cohorts who were exposed to the pandemic at different ages (e.g. in utero, infancy and early life, adolescence, adulthood) more or less likely to have greater acquired immunity and inflammatory response than cohorts not exposed to the pandemic at all?

2. Are the cohort differences in acquired immunity and inflammatory the same for blacks and whites, and how do any differences relate to the social epidemiology of exposure to the pandemic?

Findings on the above specific questions will help to illuminate the overarching research question, e.g. what do these potentially cohort-specific, race and gender differences in patterns of the biomarkers suggest about the mechanism through which early life exposures operate on later life health and longevity – is it culling, scarring, or both?

Methods

Data

Data for cohorts of adults who were unexposed and exposed to the pandemic at different ages will be compiled from the National Health and Nutrition Examination Survey 1988-1994 (NHANES III). This is the largest population-representative survey of adults for which data is available on a range of biomarkers relevant to this study, with sufficient sample size of minority men and women and that includes older adults who would have been exposed to the 1918 Pandemic.

Markers of acquired immunity include seropositivity for *Helicobacter pylori (H-pylori)*, cytomegalovirus, Epstein–Barr virus, *Varicella zoster*, and the rheumatoid-factor antibody. Markers of inflammation are selected from those used in the MacArthur Study on Successful Aging and include C-reactive protein, interleukin-6, and fibrinogen.

Trends in the biomarkers are assessed for cohorts, who by nature of their date of birth, are considered to have been exposed to the pandemic at a specific age. For example using data is available for all of the following cohorts: 80-89 year-olds who were adolescents (age 4-15) in 1918; 70-79 year-olds who were children (age 0-9) in 1918; and 60-69 year-olds who were born immediately following 1918. There are approximately 4500 men and women ages 70 and older who would have been exposed to the 1918 Pandemic and there are approximately 5000 respondents ages 50-70 who were born after the pandemic. Preliminary findings shown below use data from the public release sample of the NHANES III (from the Centers for Disease Control, CDC). This data does not allow researchers to precisely identify

the date of birth (day and month but not year is available, and age is only reported for the date of the survey which may occur at anytime during a six-year window from 1988-1994). Currently, I am accessing the restricted use dataset from the NCHS. These findings will be reported in the final paper.

Analytical Approach

Linear regression models (parametric and non-parametric) are employed to test the statistical significance of the differences in acquired immunity and inflammatory response between the cohorts at different points in the cohorts' lives using the different waves of the NHANES (III-V). Models with interactions between cohort and race, cohort and gender, and cohort and both race and gender will be used to test Question 1 and Question 2. All analyses will adjust for the complex survey sampling schemes used in the NHANES surveys.

Preliminary Findings

In these preliminary findings, I report the findings for H-pylori among white and black adults using the public-use NHANES III data. I begin with H-pylori because it may have the largest potential relationship with early life exposures. It is more likely that a later life exposure to H-pylori may be influenced by earlier life exposure to the 1918 Pandemic than for example the rheumatoid-factor or C-protein levels. The final report will include findings for H-pylori using the restricted data, as well as other biomarkers.

The probability of positive H-pylori (HPP-CagA) is estimated using logistic regression models for the odds of seropositivity to H-pylori as a function of cohort of birth (parameterized with age-splines to best fit the data), sex, race, and interactions between all three. I also predict the probability of positive H-pylori using non-parametric smoothing functions applied to the raw data. The findings from both are both depicted in Figure 1.

[Figure 1 about here]

From Figure 1, one first observes an overall fairly smooth age or cohort trend whereby there are lower infection rates in more recent birth cohorts (or younger ages). For example among white men, serpositivity declines from a rate of about 40% among the oldest surviving adults born about 15 years

prior to the 1918 Pandemic (e.g. they were 12-17 years old at the time of the pandemic) to a rate of about 25% among the youngest adults born about 55 years after the pandemic (e.g. they were -52 to -57 years old in 1918). Similarly, among blacks, about there is about 80% seropositivity among the oldest respondents in the NHANES III (i.e. surviving blacks who were about 15 years old at the time of the pandemic) and there is nearly 40% seropositivity among the youngest respondents (i.e. surviving blacks who were born about 55 years after the pandemic). However, especially among Whites, there is an up-tick in the prevalence of seropositivity among adults who were about 5 years old, and there may also be a decrease in the prevalence for blacks who were born between the period about 5 years before and five years after the pandemic.

These differences are even more clearly observed via the ratio of the seropositivity +HPP (Cag-A) prevalence using the non-parametric, polynomial smoothing function. In the surviving population born about 12 years prior to the pandemic, blacks have about twice the prevalence as whites (relative ratio 2.10), and in the surviving population born about 12 years after the pandemic blacks also have about twice the prevalence as whites (relative ratio 1.98). However, in the surviving population born at the time of the pandemic, this disparity is reduced by nearly one-quarter (relative ratio 1.62).

As a result, *Figure 1 shows clear evidence of an age-specific period effect (or cohort effect) in the prevalence of H-pylori among survivors of the 1918 Pandemic who would have been exposed in utero, birth, or early life that is different for whites and blacks.* Among whites, seropositivity increases survivors exposed in early life. Among blacks seropositivity remains the same or possibly even declines for this group of survivors.

Discussion

I first underscore that the finding that there is a disjuncture in the seroprevalence of H-pylori that is consistent with the 1918 Pandemic infant and child survivors is remarkable given that the data from the public-use file are very imprecise about exact birth date. Recall that birthdates for respondents may range around a six-year window. In addition, it is striking that this 'sloppy data' from the public-use dataset (which will be refined using the restricted data), also show a race-specific difference in the disjuncture in

seroprevalence for these infant and child survivors of the 1918 Pandemic, that suggests a race-specific mechanism. Whites appear to have been more susceptible to H-pylori if they were from the birth and child cohorts from 1918, while blacks seem to have been less susceptible if they were from this birth cohorts.

The higher susceptibility among whites is consistent with a "scarring" hypothesis described earlier. It is also consistent with Almond's previous findings that men and women from the 1918 Pandemic had lower health and socioeconomic outcomes in later life. The lower susceptibility among blacks is a new finding in the literature on early life exposures. Though a new finding to the study of social disparities in aging, health and survival, it is consistent with methodological research on the "paradoxes" that can occur in health and mortality in later life for sub-populations that have been essentially "culled" on the basis of health-selective mortality (Vaupel and Yashin 1985). Another possible explanation for the "lower" rates among blacks may be related to the finding that blacks had lower than expected mortality during the 1918 Pandemic. One explanation for this is that blacks may have been exposed to earlier, less virulent waves of the influenza that offered them a form of acquired immunity in 1918 (Crosby 2003) . These findings thereby open an exciting possibility for further research on whether exposure to early life infectious exposures may in some cases actually offer a "protective" effect for later infectious exposure. Moreover, the findings have the potential to further illuminate a rapidly expanding literature on the influence of early life exposures in later life health and survival (Barker et al 1989; Elo and Preston 1992; Preston et al 1998; Hayward and Gorman 2004; for review see Doblhammer 2004) , as well as the potential role of cohort trends in future dynamics in mortality (Wilmoth 1990; Finch and Crimmins 2004 and related commentary; Guillot 2003; Crimmins and Finch 2006).

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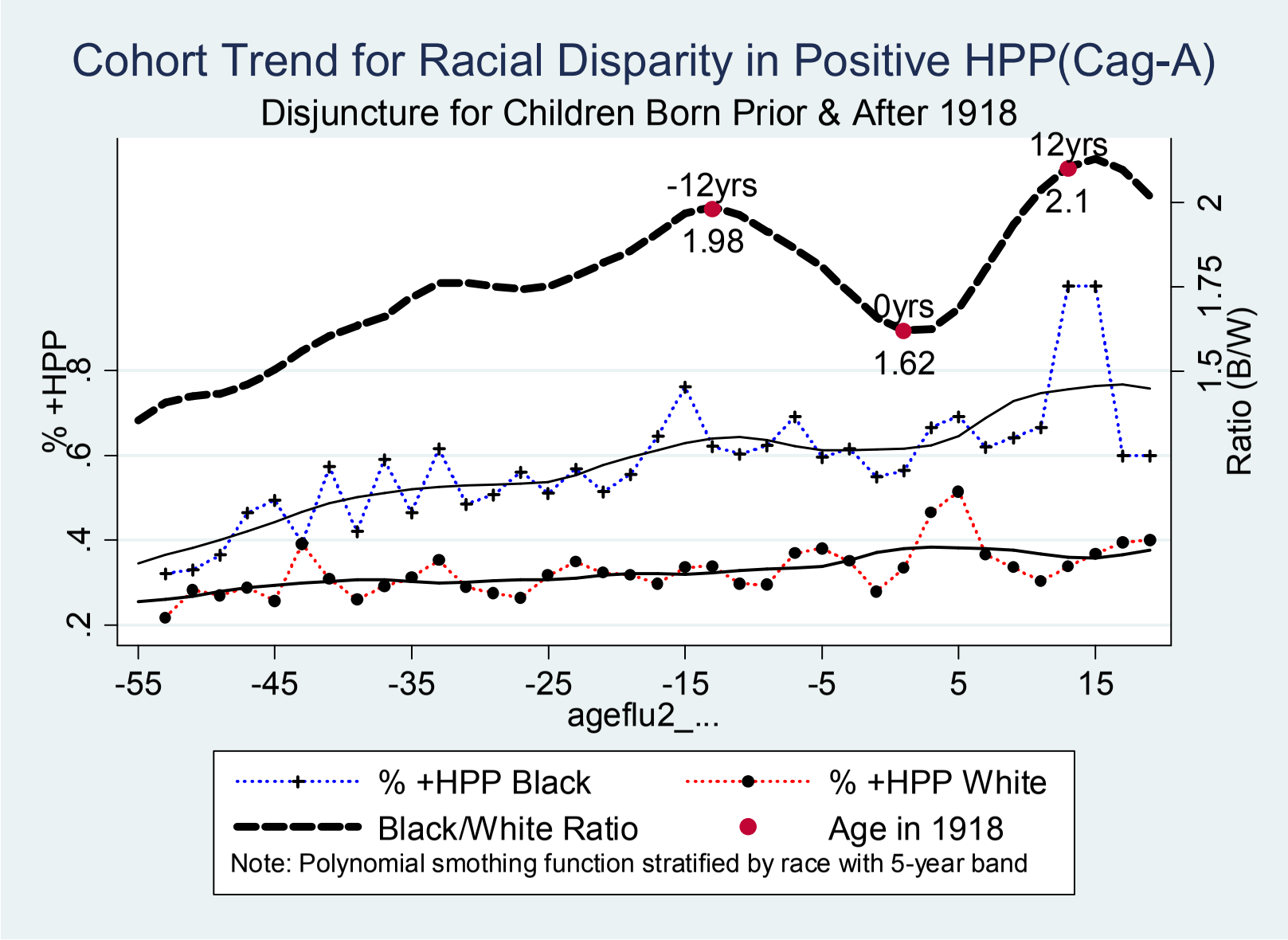
Figure 1.


Cohort Trend for Racial Disparity in Positive HPP(Cag-A)
Disjuncture for Children Born Prior & After 1918
12yrs
2.1
-12yrs
1.98
0yrs
1.62
% +HPP
.2
.4
.6
.8
Ratio (B/W)
1.5
1.75
2
-55
-45
-35
-25
-15
-5
5
15
ageflu2_...
% +HPP Black
% +HPP White
Black/White Ratio
Age in 1918
Note: Polynomial smothing function stratified by race with 5-year band