The Effect of In-Utero Conditions on Long Term Health: Evidence from the 1918 Spanish Flu Pandemic

Craig Garthwaite
Department of Economics
University of Maryland
College Park, MD 20742
Vmail: 202-746-0990
Email: cgarthwaite@gmail.com

May 2008

Abstract

The fetal origins hypothesis posits that in-utero stress increases the incidence of chronic conditions later in life. Utilizing 21 years of National Health Interview Survey data, this study estimates the health effect of in-utero exposure to the 1918 Spanish Flu pandemic. Exploiting the fact that people were exposed to the flu at different points during fetal development, the model tests precise predictions from the medical literature about when exposure to in utero insults should damage organs later in life. The pattern of results demonstrates the necessity of using a short duration event as a source of variation in fetal conditions and helps explain previously mixed evidence regarding the fetal origins hypothesis.

JEL Classification Numbers: I1; I12; I18

I am indebted to Bill Evans for advice and feedback throughout the entire process. I am also grateful to Kerwin Charles, Jonah Gelbach, Melissa Kearney, Mark Duggan, Timothy Moore, and an anonymous reviewer for helpful comments on previous drafts. All errors remain my own.

Introduction

The differing incidence of chronic health conditions by individuals with similar backgrounds, lifestyles, and blood chemistry has caused medical professionals and health economists to look beyond these factors for other sources of these health problems. Spurred by a compelling correlation between birth weight and later life health, this search has increasingly focused on fetal conditions. This literature is often referred to as the "fetal origins hypothesis" or the "Barker hypothesis." According to these theories, in-utero malnutrition or other complications cause the fetus to shift blood and nutrients from vital organs to the brain.[1] This diversion is an attempt to protect the fetus and improve the chances for survival, but leaves certain organs preprogrammed for failure in later life—often after 50 years or more.

Controlled experiments using animal subjects provide the most complete evidence to date of the fetal origins hypothesis.[2] The evidence for humans is decidedly less conclusive. The bulk of studies to date are primarily cross-sectional in nature with most showing adults born with low birth weights having higher rates of particular diseases and mortality. These studies, however, suffer from the problem that low birth weights might signal other unmeasured characteristics that predict higher adult mortality. Absent random assignment, the best hope for testing the fetal origins hypothesis is through quasi-experimental variation in fetal conditions. For example, economists have separately used famines and the 1918 flu pandemic as an exogenous source of fetal stress. Previous research using famines, however, has found only mixed evidence in support of the fetal origins hypothesis. As shown in Almond and Mazmunder (2005) and discussed in detail below, the short term and intense nature of the flu pandemic creates a better design for estimating the long term health impacts of fetal stress.

Often called the Spanish flu, the 1918 global flu pandemic killed between 50 and 100 million people in the course of a year. In the United States, the flu struck hardest during the last quarter of 1918. Its effects largely dissipated by the first months of 1919. Over this time period, the flu killed 675,000 people—more than AIDS has ever killed in the United States (Barry, 2004). Despite its virulence, 25

[1] For an excellent discussion of the fetal origins hypothesis, see Barker (2001)
[2] Nathanielsz (2006) provides a comprehensive overview of these animal studies.

million Americans contracted the flu and survived. Women of childbearing age and pregnant women suffered some of the worst effects from the pandemic with approximately one third becoming infected (Almond, 2006). While there was geographic variation in the spread of the flu, within each region, the virus struck without concern for race, income, or other socio-economic factors.

The large number of pregnant survivors combined with the random nature of the outbreak provides a clear design for testing the fetal origins hypothesis using the 1918 pandemic. Almond (2006) exploited this fact to examine differences in education levels and disability rates for individuals exposed to the flu pandemic in-utero. Almond and Mazmunder (2005) examined specific medical conditions using roughly 25,000 observations of adults from the 1915 to 1923 birth cohorts from the Survey of Income Program Participation (SIPP). The authors find evidence of an impact on a variety of health outcomes such as stroke, diabetes incidence, self reported health status, and trouble hearing, talking, walking, and lifting, from in-utero exposure to the flu pandemic.

This study uses the larger National Health Interview Survey (NHIS) dataset to expand upon these earlier results. Specifically, this analysis uses 21 years of repeated cross-sections of the National Health Interview Survey (NHIS) to examine the impact of the 1918 flu pandemic on the incidence of coronary heart disease, diabetes, and kidney disorders. The analysis sample used in this work is approximately 384,000 observations or roughly 15 times the size of the sample used in Almond and Mazmunder.

An advance of this work over previous efforts is an attempt to test precise predictions from animal studies and the medical literature about when exposure to in utero insults should damage organs later in life. Nathanielsz (2006) states “critical time windows exist during development when organs are vulnerable to challenges such as decreased oxygenation, nutrient supply, and altered hormone exposure. The period of vulnerability varies from organ to organ” (p. 74). Medical knowledge of the progress of fetal organ development leads to relatively precise predictions of the effect of differential timing in fetal insults. As will be discussed in more detail below, the heart primarily develops early in gestation and thus individuals affected by the flu in the early-to-middle months of pregnancy have a higher probability of heart disease later in life. Similarly, the nutrition delivery system is developed early in pregnancy

suggesting that individuals affected during the first months of pregnancy would be more likely to develop metabolic disorders later in life. At the other extreme, the kidneys primarily develop during the last months of pregnancy. Individuals affected during these last months should be more likely to develop kidney disorders later in life. This study finds statistically and qualitatively significant increases in chronic conditions during the time periods predicted by the medical literature.

This time connection provides quasi-experimental evidence of the mechanism underlying the fetal origins hypothesis in humans and confirms that the timing of fetal stress is critically important in predicting which organs are weakened. Furthermore, these strong and consistent results show that an identification strategy involving the 1918 flu (or another short duration event) is necessary to isolate in-utero stress to particular months of development. As a result, the estimates in the analysis stand in contrast to the previously mixed results from other identification strategies.

.

Medical Basis of the Fetal Origins Hypothesis

The most complete evidence to date supporting the fetal origins hypothesis comes from experiments with animals where researchers alter uterine conditions by either depriving the mother of nutrients or stopping nutritional transfer to the fetus through uterine blood flow restriction (Ozanne et al., 1996; Blondeau et al., 1999; Simmons et al., 2001). These restrictions have been imposed both throughout the entire gestation and during particular periods of in-utero development. They have also been paired with differing post-natal nutrition levels in order to determine if a discrepancy between conditions in these time periods is important (Ozanne and Hales, 1996). In total, these studies have shown that periods of fetal stress in rats, sheep, and other animals cause a weakening of the vital organs that manifests itself in poor later life health.

Among humans, in the medical literature, poor in-utero conditions have been linked to a variety of ailments ranging from coronary heart disease to cancer. These studies, however, rarely utilize exogenous variation in fetal conditions creating a concern of an omitted variable bias. Three of the more

frequently cited outcomes in the medical literature link fetal conditions to coronary heart disease, diabetes, and kidney disorders (Barker, 2001).

Barker (1992) first noted the striking relationship between low birth weights and heart disease rates using a unique data set of births from Hertfordshire, England. Subsequently, Barker (2003) documented this same relationship among men in Helsinki. Similar findings have been documented in North America, India, and Europe (Leon et. al, 1998; Frankel et al., 1996; Rich-Edwards et al., 1997; and Eriksson, 2001). The biological mechanism thought to be the source of this link is the diversion of blood and nutrients to the brain and away from other vital organs. This diversion represents an evolutionary response designed to protect the brain and increase the likelihood that the fetus will survive until and immediately after birth. This process is also an attempt to condition the fetus for a lifetime of deprivation following birth. Evidence of this phenomenon has been documented in animal experiments (Barker and Hanson, 2004). For example, the development of the heart muscle is believed to be affected by fetal stress. Unlike other organs, the heart does not begin as a miniature version of its fully developed shape. Instead, it grows throughout the first half of pregnancy from a mass of cells into its final complex form (Thornburg, 2001). As a result, complications or insufficient nutrition during the early-to-mid period of embryonic development is critical for future heart health. Hoet and Hanson (2001) stated, "it appears that the timing of the insult in gestation is all-important, with insults occurring earlier having greater effects on cardiovascular development in the offspring" (p. 78). Medical theory predicts an increased incidence of coronary heart disease concentrated among, but not limited to, individuals born in the first and second quarters of 1919. These individuals were exposed to the pandemic during their first and second trimesters—the critical time period in terms of fetal development for future cardiac health.

A second group of conditions believed to arise from poor in-utero nutrition are metabolic disorders such as insulin resistance and non-insulin dependent diabetes mellitus (NIDDM) or Type II diabetes. Hales et al. (1997) states, "archival records of early life anthropometry have shown that reduced birth weight, weight at 1 year, and thinness at birth are strongly associated with an increased susceptibility to NIDDM and IGT (impaired glucose tolerance) in adult life and to insulin resistance" (p. 191). Hales et

al. (1991) found that men who have the lowest birth weights were seven times more likely to have diabetes and/or insulin resistance than those who were heaviest at birth. Often described as the "thrifty phenotype hypothesis," this process is believed to be an attempt to condition the fetus for future periods of poor nutrition. Upon receiving adequate nutrition later in life, the individual is thought to be more likely to develop metabolic disorders (Hales and Barker, 1992). The importance of the difference between in-utero and after birth nutrition is demonstrated by the relative lack of metabolic disorders in African countries—where poor nutrition in-utero is followed by equally poor infant and lifetime conditions (Stocker, et al., 2005).[3] This observation has also been supported by animal experiments where rats who were deprived of nutrients in-utero and then given generous diets after birth suffered worse health outcomes than similar rats who had a restricted calorie diet during life, though both had poor health outcomes overall (Ozanne and Hales, 1999, 2004).

Studies examining the effect of under nutrition on later life metabolic disorders have found that it is specifically *early* exposure to poor nutrition that fundamentally changes the nutrition delivery system of the fetus (Harding and Gluckman, 2001). These changes are believed to be the source of later life metabolic disorders. Based on this fact, individuals born during the second quarter of 1919, and therefore exposed to the flu pandemic early in gestation, should have a higher probability of reporting the presence of diabetes.

In-utero malnutrition and other complications are also believed to decrease the size and, as a result, the later life functioning of kidneys. Restricted diet animal studies have shown reduced neonatal kidney weights. This small kidney size is believed to be irreversible by adequate post-natal nutrition (Thornburg, 2001). In humans, cross-sectional analysis has demonstrated a correlation between the number of nephrons (the basic structural units of the kidney) and birth weight. Brenner and Mackenzie (1997) state "low birth weight in humans resulting from intrauterine growth retardation may be associated with deficits in nephron numbers of up to 20%, even in full-term pregnancies" (p. 124). In turn, low

[3] The importance between this difference in nutrition and not solely in-utero nutrition could have important implications for optimal program design. Focusing government nutrition programs on the post-natal time period without adequate in-utero nutrition could, perversely, increase long term health problems.

nephron numbers are associated with renal disease later in life (Brenner and Chertow, 1993,1994). Without measuring the number of nephrons, Lackland et al. (2001) found a correlation between end stage renal disease (ESRD) and low-birthweight. Similarly, Martyn et al. (1996) found connections between later life renal functions and fetal growth.

Knowledge of fetal development provides predictions regarding the timing of fetal stress and later life renal disease. The kidneys experience dramatic growth during the last months of pregnancy (Martyn and Greenwald, 2001). Studies show that "60% of the normal complement of nephrons are laid down during the last trimester" (Lackland et al., 2001: 66). Therefore, the imposition of fetal stress during the last months of pregnancy should result in kidney disorders in later life. This would suggest a higher probability of kidney problems in later life for individuals born during the last quarter of 1918.

Exogenous Variation in Fetal Conditions

Efforts to document the fetal origins hypothesis in humans are plagued by an inability to separate the cause of fetal stress from other factors that generate poor long-term health outcomes. This presence of omitted variables bias casts doubt on the accuracy of many previous estimates. Even when a source of exogenous variation in fetal conditions can be identified, the lack of high quality data on both fetal conditions and long-term health outcomes is often a substantial problem. This lack of data limits many estimates to outcomes at relatively young ages. For example, Banerjee et al. (2007) examines the long term health effects of the phylloxera outbreak in France on long-term health outcomes. This outbreak destroyed wine crops throughout the countryside depressing economic conditions for many families. The authors are able to show that men born in wine producing regions were shorter upon entrance into the army twenty years later. Due to the lack of long-term health data, however, the authors are unable to test the hypothesis that certain organs (such as the heart or metabolic system) are preprogrammed for failure in later life.

One frequently utilized source of exogenous variation in fetal conditions is famines. Authors have used the Dutch famine during World War II (Roseboom et al., 2000; Roseboom et al., 2001; Ravelli

et al., 1997), the Chinese Famine (Meng and Qian, 2006), and the Siege of Leningrad (Stanner and Yudkin, 2001) to investigate the long run health effects of fetal stress. The results of these studies have provided mixed evidence regarding the importance of fetal origins. Roseboom et al. (2000) found differences in heart health and Ravelli et al. (1997) found increased glucose resistance in later life for babies born during the Dutch famine. This effect was more pronounced for individuals who later became obese. Meng and Qian (2006) found that individuals born during the Chinese famine were shorter in later life, but found no evidence of increased coronary heart disease or other traditional outcomes of the fetal origins hypothesis. Similarly, Stanner and Yudkin (2001) found no connection between later life metabolic health and poor fetal conditions for individuals born during the Siege of Leningrad.

Almond (2006) used the 1918 Spanish flu pandemic as a source of fetal stress. Standard influenza strains affect primarily the young, the old, and those with compromised immune systems. This effect can be seen by the "U" shaped dotted line in Figure 1 representing female deaths during the 1917 flu season. The 1918 flu, however, affected individuals in a decidedly different manner. Barry (2004) stated, "in 1918, the immune system of young adults mounted massive responses to the virus. That immune response filled the lungs with fluid and debris, making it impossible for the exchange of oxygen to take place. The immune response killed [the young and healthy]" (p. 250). This excessive immune response caused many of the deaths from the 1918 flu to occur among young and relatively healthy individuals. This effect can be seen by the "W" shaped curve in Figure 1.

Pregnant women were particularly hurt by the pandemic. Barry (2004) stated, "in thirteen studies of hospitalized pregnant women during the 1918 pandemic, the death rate ranged from 23 percent to 71 percent. Of those who survived, 26 percent lost the child" (p. 241). While the death rate was high for pregnant women, many survived and carried the child to term. As a result, a large number of individuals born during the last quarter of 1918 and the first two quarters of 1919 suffered from increased fetal stress. It is reasonable to assume that this stress was unrelated to any other observed or unobserved characteristics of the mother.

Almond (2006) used this variation to examine the effect of fetal stress on economic outcomes such as educational attainment, wages, and disability rates. Azambuja (2004) estimated a connection between the 1918 flu pandemic and later life heart disease. The author, however, focused on individuals that were adolescents and young adults, rather than those who were in-utero, during the peak of the flu pandemic. Almond and Mazmunder (2005) used ten panels of the SIPP database from 1984-1996. In total, their sample includes approximately 25,000 individuals born between 1915 and 1923. The authors estimated a linear probability model to determine the affect of being in-utero during the peak of the flu pandemic on a variety of health outcomes. They found statistically significant effects at the quarter of birth level for trouble hearing, trouble speaking , trouble lifting, trouble walking, diabetes, and stroke. A larger group of health conditions including heart conditions and kidney problems are significant in at least one month of birth. These results were significant at that 0.10 level. This analysis expands upon their work using a dataset with a larger sample size. This larger dataset allows for more precise estimation of the effect of the flu and explicitly connects the development of chronic conditions to particular time periods of fetal stress. This connection aids in the understanding of the dynamics of the fetal origins hypothesis.

An advantage of the flu pandemic over famines as an exogenous source of fetal stress is the short-term yet intense nature of the outbreak. As can be seen in Figure 2, 1918 represented a sixteen fold increase in flu deaths. This is followed by a dramatic decline in the following year. This is a shorter and more intense "treatment" period than the Chinese famine or the Siege of Leningrad, which carried on for several years. Babies born during these longer events experienced both poor in-utero conditions and nutritional deprivation during infancy. Disentangling these effects is difficult and limits the ability of famines to stand as a test of the fetal origins hypothesis as opposed to a test of the long term effects of child health conditions. In contrast, the more discrete nature of the pandemic flu improves the chance of isolating the long term impacts of this event from secular changes occurring at the same time.

Data

The data for this analysis is gathered from the 1982-2002 NHIS, the principal source of health statistics and information for the non-institutionalized population in the United States. While the survey has been in existence since 1957, information on the month and year of birth of respondents has only been collected since 1982.[4] During the time period in this sample, the NHIS was substantially redesigned. In both designs of the survey (before and after 1996) individuals were asked about their health in regards to coronary heart disease, poor health, diabetes, and kidney disorders.[5] Data for kidney disorders, however, are not comparable across the two survey designs and therefore only respondents from 1982-1996 are used with respect to kidney disorders. An advantage of the NHIS is that it contains detailed questions about disease prevalence. A disadvantage, however, is that all health data are self-reported leaving open the possibility of measurement error.[6] This is particularly true for self-reported health status, which is measured on a five point scale throughout the NHIS. For the purposes of this analysis, individuals are classified as being in poor health status if they report being in fair or poor health—the bottom two categories of the five point scale.

After pooling cross sections of the NHIS from 1982 to 2002, the observations are grouped into quarter of birth cohorts. Individuals born during the last quarter of 1918 and the first two quarters of 1919 were affected by the flu in-utero. Based on this fact, individuals in this dataset affected by the flu are between 62 and 84 years of age. The overall sample for this analysis is limited to individuals of similar age to the cohort affected by the flu. Respondents younger than 55 or older than 90 years of age are

[4] The lack of data prior to 1982 limits this analysis because individuals affected by the flu epidemic have already turned 62. This could make it difficult to detect an effect from the flu because many of those individuals affected could have already passed away by this age. This issue of mortality for those exposed to the flu is discussed later in the analysis.

[5] Prior to 1996 individuals are asked to identify the presence of chronic conditions. For the purposes of this analysis, individual identifying themselves with ischemic heart disease, hearth rhythm disorders, congenital heart disease, or other diseases of the heart (excluding hypertension) are classified as having coronary heart disease. Following 1996, individuals are asked individual questions about chronic conditions and those saying they have coronary heart disease are classified as such. Individuals are asked in both survey designs about the presence of diabetes. Prior to 1996, individuals are classified as having kidney disorders if they report have kidney infections or "other kidney trouble." There is no comparable question in the post-1996 redesign.

[6] To the extent that this measurement error is random it is not a concern. However, it could be that there is some systematic measurement error (individuals with low socioeconomic status or education levels may be less aware of their medical history), which would be a concern. Baker et al. (2001) discusses the problems related to self-reported health measures in general.

eliminated from the sample, which leaves slightly fewer than 384,000 observations ranging in year of birth from 1891 to 1947. Table 1 provides descriptive statistics for this sample compared to similarly aged individuals in the 1980-2000 United States Census five percent micro samples. In total, individuals in the NHIS are more likely to be female, Black, Hispanic, and a high school graduate. They are slightly less likely to be a married.

Estimation Strategy

Many individuals born during the last quarter of 1918 and the first two quarters of 1919 experienced higher levels of fetal stress. If the fetal origins hypothesis is correct, these individuals should have increased rates of chronic health conditions in later life compared to individuals born in surrounding time periods.

While the identification strategy in this analysis is similar to that used in Almond (2006), there are several differences in the NHIS data that necessitate altering his basic specification. Almond utilized the 5 percent Public Use Micro Samples (PUMS) of the United States Census. This is a single cross section and therefore all individuals exposed to the flu in-utero are the same age and were interviewed during the same time period. In the NHIS data used in this analysis, there are multiple cross sections containing information on individuals interviewed as many as twenty years apart. As is discussed in more detail below, this model must carefully control for age and birth cohort effects.

All dependent variables are defined as the presence of chronic conditions and are thus binary. In the presence of a binary dependent variable, the linear probability model can produce inaccurate estimates, especially when incidence rates are low (as they are in this instance).[7] To avoid this problem I estimated a logit model of the following form:

[7] For a more detailed discussion of the failure of the linear probability model in this situation see Woolridge (2002), Chapter 15 and Johnston and Dinardo (1997), Chapter 13.

$$\Pr(Y_i = 1) = F(\alpha + \gamma X_i + \phi AGE_i + \beta_1 QOB_i + \beta_2 QOB_i * AGE_i + \beta_3 REGION_i + \beta_4 MOB_i + \beta_5 FLU_i), \quad \textbf{(1)}$$

where Y_i is equal to 1 if an individual reports having coronary heart disease, diabetes, a kidney disorder or poor health status respectively, and 0 otherwise; X_i is a vector of demographic control variables accounting for race, sex, and martial status; *AGE* is a cubic age term; QOB is the quarter of birth cohort (e.g., first quarter of 1917, second quarter of 1917, etc.); *REGION* controls for region of residence fixed effects; *MOB* controls for month of birth fixed effects. The explanatory variable of interest is FLU—a dummy variable indicating whether the individual was affected by the flu pandemic in utero.[8] F is the logistic function. In this analysis I allow for an arbitrary variance-covariance matrix accounting for within group correlation in the errors based on the year of birth/survey year cohort.[9]

It is important to also allow the coefficients on the cubic age term to also vary based on birth cohort. Consider the case of 55 year old respondents to the NHIS. Respondents of this age to the 1982 NHIS were born in 1927 while those in the 2002 NHIS were born in 1947. There are a multitude of factors affecting health that differ between these two birth cohorts even for individuals of the same age. This specification allows for cohort-specific age effects based on an interaction term between the quarter of birth cohort and age in quarters. This effect is also included as a cubic polynomial.

---

[8] Throughout this analyis, in-utero flu exposure will be defined at many levels of specificity.

[9] Kloeck (1981) provides a measure of the bias in standard errors in the presence of within group correlation in the errors. In the case where all regressors are fixed within group and all groups have the same size, *m*, the true variance-covariance matrix is $\sigma^2 (X'X)^{-1}[1+(m-1)\rho]$—where ρ is the amount of within group correlation. Even in the case of groups of differing sizes, $[1 + (m-1)\rho]$ serves as an approximate measure of the bias caused by within group correlation (Bertrand 1990). This bias is a function of both the size of the groups and the amount of correlation within the groups.

In most cases, researchers are concerned with positive within group correlation leading to a downward bias in the OLS standard errors. This dataset of repeated cross sections and negative health outcomes, however, contains a high level of negative within group correlation. At least a portion of this negative correlation is a mechanical result of the construction of the dataset. Groups with a high rate of chronic conditions in early survey years should experience higher mortality rates and as a result will appear healthier in later survey years. The mechanical negative correlation is magnified in this case by large group sizes—the average size of a year of birth cohort in the data is approximately 9,500. Groups of this size mean that even a small amount of negative correlation will lead to a large bias in the estimated standard errors.

In order to avoid this mechanical negative correlation but still account for correlation within year of birth cohorts, I allow for correlation between year of birth and year of survey cohorts. This results in 736 "clusters."

One concern for this analysis is that the relative rates of heart disease between men and women are strikingly different. Figure 3 contains incidence rates of heart disease in the sample by sex and age. The chart shows that men have higher rates of heart disease and perhaps more importantly for this analysis, their rate of heart disease at younger ages increases faster. Since the data available for this analysis does not contain individuals exposed to the flu younger than 62 years of age, it may be difficult to detect an effect for males, many of whom may have died before they enter the sample. Due to this fact, it will be important to estimate the effects for men and women separately. Significant effect for men and not women during certain time periods could provide suggestive evidence of this downward bias. The rates of other conditions do not drastically differ by sex in the age range analyzed in this paper and therefore results by sex are not reported.[10] The mean rate of kidney disorders in the sample is 0.59 percent for men and 0.69 for women. For diabetes, the rates are 4.76 percent for men and 4.62 percent for women.

There are several important identifying assumptions that are necessary for this model to accurately estimate the long term effect of in-utero exposure to the flu. The first is that the long-term incidence of these conditions is trending smoothly over time except for the in-utero exposure to the 1918 flu pandemic. Second, I assume that the long term health effects of the flu pandemic are felt solely by those exposed to the pandemic in-utero. A specific concern here is that individuals born in time periods in close proximity to the flu pandemic, but not exposed to the flu in-utero, should be no more likely to develop these chronic conditions later in life. I am unaware of explanations in the literature detailing a medical connection between being exposed to the flu during the early years of life and the specific conditions of coronary heart disease, diabetes, or kidney disorders. It is possible, however, that there are non-medical responses to the flu that could result in long-term health consequences. For example, some school-age individuals contracted influenza and survived. Their sickness may have caused them to acquire less total education in their lifetime. There is a documented connection between education levels and mortality (Lleras-Muney, 2005; Elo and Preston, 1996; Kitagawa and Hauser, 1973; Grossman and

[10] These results do not provide qualitatively different outcomes.

Kaestner, 1997). As a result, the flu could affect birth cohorts other than those in-utero during the pandemic by decreasing lifetime education. It is not clear, however, if this effect would result in specific medical conditions considered in this study or simply in increased mortality. Furthermore, the potential loss of education from the flu would likely be very small, limiting its ability to drastically affect long term health. In order to test a potential long term health effect from exposure to the flu pandemic at a young age, I will estimate a specification of equation (1) including a dummy variable indicating being between the ages of one and five during the flu pandemic.

The final assumption is that subsequent flu seasons did not substantially affect the in-utero conditions of immediately surrounding birth cohorts. Figure 2 shows the sharp increase in deaths in 1919 compared to surrounding years. In addition, as discussed previously, the 1918 flu affected the young and healthy to a greater degree than more standard flu variants. To the test this assumption, I will examine the effect of being born in birth cohorts immediately surrounding those affected by the pandemic.

Health Outcome Results

Table 2 reports logit estimates of equation (1). The first row contains results for a model identifying exposure to the 1918 pandemic as being born in the fourth quarter of 1918, the first quarter of 1919, or the second quarter of 1919. This is a relatively broad measure of flu exposure that cannot precisely define the timing of the increased fetal stress. This makes it difficult to detect the effects of specific chronic conditions. Column (1) contains the results for equation (1) with coronary heart disease as the dependent variable for both sexes. Column (6) contains reports for individuals reporting poor health status. These are the only results that are statistically significant at any level using this broad measure of the flu. The medical literature on the importance of the timing of in-utero stress combined with the lack of a response from a broad measure of in-utero flu exposure points to the importance of having a short-term and intense identification of times of fetal stress. As can be seen below, defining flu exposure using a more precise time period is a superior means of estimating disease specific conditions.

Defining in-utero flu exposure based on quarter of birth returns more precise estimates of the effect of fetal stress on developing certain chronic conditions. Rows (2)-(4) contain estimates for coefficients on dummy variables identifying individuals born in the fourth quarter of 1918, the first quarter of 1919, or the second quarter of 1919. The estimates in parentheses are standard errors and those in brackets are odds ratios, which due to the relatively low incidence of the dependent variable can be interpreted as an approximate risk ratio.

As can be see in columns (1)-(3) in-utero exposure to the 1918 pandemic increases the probability of developing coronary heart disease in later life. For the entire sample, being born in the first quarter of 1919 is associated with an approximately 11.8 percent increase in the probability of developing coronary heart disease. This result is statistically significant at the 10 percent level. For men, being born in the first quarter of 1919 increases the probability of developing coronary heart disease by 19.3 percent. This result is statistically significant at the 5 percent level. For women there is an increased probability of 14.7 percent for those born during the second quarter of 1919. This result is also statistically significant at the 0.05 level. A specification of equation (1) containing dummy variables identifying individuals born in the second and third quarters of 1918 and the third and fourth quarters of 1919 contained no positive statistically significant results for these cohorts.[11] A specification of equation (1) containing a dummy variable for being aged one to five during the 1918 pandemic. For both sexes the estimated coefficient (standard error) on this dummy variable was -0.01 (0.02), for men the result was 0.007 (0.03), and for women the result was -0.03 (0.03). These results suggest that exposure to the flu pandemic during the early years of life, as opposed to in-utero exposure, does not result in a higher probability of developing coronary heart disease.

Assuming a normal gestation length, individuals born in the first quarter of 1919 were exposed to the flu during anywhere from the fifth to ninth months in-utero. Fetal stress during this period has a detrimental effect on later life coronary health. For women, this effect occurs during the second quarter

[11] There is a statistically significant, but negative result, for men born during the third quarter of 1918.

of 1919. These results are consistent with the medical predictions that fetal stress in the mid-to-early stages of pregnancy has a negative effect on cardiac health.

Table (3) contains results for equation (1) where flu exposure is defined at the month of birth level. For both sexes, a statistically significant result is found for individuals born in December, 1918. For men, there are statistically significant results for December, 1918 and January, 1919. For women, there are statistically significant results for December, 1918, May, 1919 and June 1919. As will be discussed later, the stark difference between men and women born during June, 1919 may provide evidence of attrition in the sample creating a downward bias to the results.

Column (4) contains the results for equation (1) with diabetes as the outcome of interest. In-utero exposure to the 1918 pandemic increases the probability of reporting diabetes in later life. Specifically, being born in the second quarter of 1919 increases the probability of developing diabetes by 23 percent. This result is significant at the 0.05 level. No statistically significant effect is found for individuals born in surrounding birth cohorts or for individuals affected by the flu during the earliest years of life. A specification of equation (1) containing a dummy variable indicating individuals between the ages of 1 and 5 during the flu pandemic returns a statistically insignificant estimated coefficient (standard error) of -0.02 (0.03). The month results in Table (3) show a positive and statistically significant result for individuals born during April and May, 1919.

Individuals experiencing fetal stress very early in pregnancy have a higher probability of reporting diabetes. The timing of this effect could be troubling for public health policymakers as it is more difficult for nutrition and other public health programs aimed at new mothers to effect in-utero conditions during the earliest months of pregnancy. This may suggest a need for general public health programs aimed at women of child-bearing age regardless of their current pregnancy status.

Column (5) contains estimates for equation (1) with kidney disorders as the dependent variable. In-utero exposure to the flu pandemic increases the probability of reporting a kidney disorder later in life. Individuals born during the fourth quarter of 1918 face a statistically significant 51 percent increase in the probability of having a kidney disorder. No statistically significant effect is found for individuals born in

surrounding birth cohorts. Individuals between the ages of one and five during the pandemic also appear to not have a higher probability of developing kidney disorders later in life. The estimate coefficient (standard error) on a dummy variable indicating being between these ages during the pandemic is -0.08 (0.08). The results in Table (3) show a statistically significant result for individuals born during October and November, 1918. These results suggest that increased fetal stress during the last months of a pregnancy affects later life kidney health. This is consistent with the biological fact that the majority of kidney development occurs during the last trimester.

The results for equation (1) with self-reported poor health status as the dependent variable are contained in column (6). As would be expected based on the results for the chronic conditions listed above, fetal stress caused by the flu pandemic increases the probability of reporting poor health status. Individuals born during the first and second quarters of 1919 are more likely to report being in poor health. This should not be surprising based on the previous results regarding heart conditions and diabetes. The overall incidence of poor health status in the sample is much greater than any of the specific chronic conditions discussed above. This is likely a result of the advanced age of the sample. Reporting poor health status is more likely for older individuals. In the sample of NHIS respondents from 1982-2002 of all ages, only 15 percent of individuals younger than age 40 report being in poor health compared to 39 of individuals age 60 or higher. Due to this high incidence of poor health, it is not appropriate to interpret the odds ratio as a risk ratio.

Attrition in the Sample

An overriding concern for this analysis is that mortality can cause a downward bias in the estimated effect of a treatment expected to cause a negative health outcome. This bias results from many individuals with chronic conditions dying before they were surveyed in later life—raising the average health of the remaining cohort. This "survivor bias" causes adults surveyed by the NHIS in later life to appear healthier on average as a result of their in-utero flu-exposure.

As a test for the presence of this survivor bias, I re-estimated equation (1) with coronary heart disease as the outcome of interest using three sub-samples of differing ages. If attrition were affecting the results, the estimated coefficients should decrease across these samples, with the lower probabilities resulting from mortality increasing the average health of older groups. Figure 4 displays the estimated logit coefficients and 95 percent confidence intervals for males born during the first quarter of 1919. There is a clear downward trend in the logit estimates across the three samples. I conducted similar analyses for kidney disease and diabetes but because of high standard errors generated by low incidence rates (or smaller samples in the case of men), there was no clear pattern in the data.[12]

A sensible interpretation of this pattern of decreasing estimates for older individuals is attrition among the cohorts exposed to the flu. Older individuals have a decreased probability of reporting chronic health conditions because each year individuals with these chronic conditions perish. Culling these unhealthy individuals from the group increases the average health of the remaining cohort. As a result of the advanced age of this sample, many of the results above should be viewed as lower bound estimates of the health effects of fetal stress related to the flu pandemic.

Further support for the presence of attrition in the sample can be found in the divergent results by sex with respect to coronary heart disease for individuals born during June, 1919. The result for men is large and negative with a p-value slightly above 0.10. For women, the result is positive and statistically significant at the 0.05 level. The counterintuitive result of men being "healthier" if exposed to the flu pandemic during the early months of pregnancy, combined with the negative health outcome for women with similarly timed births, could be a result of attrition. This attrition would be caused by the higher rate of death by cardiovascular disease for men causing the sample of men to be culled of sick individuals and therefore be, on average, healthier.

Effect on Education

[12] The sample size issue for men results from the fact that the percentage of women at each age increases throughout the sample. This is to be expected due to the longer life expectancy for women.

A primary finding of Almond (2006) was a decrease in both years of total education and the likelihood of graduating high school for individuals born in 1919. Figures 5a and 5b show the average highest grade completed and the percentage graduating high school in the sample by year of birth. Similar to the graphical evidence in Almond, it appears that there may be some effect for those born during 1919. Before and after this year there is a clear upward trend in education outcomes. Examining educational attainment by quarter of birth, the potential effect of the flu is less clear due to a number of other factors correlated with quarter of birth that affect education levels.[13]

Similar to equation (1), pooling data across many cross sections of the NHIS can potentially mix age and cohort effects across samples. To control for variation across cohorts and age in the NHIS, I estimated that following OLS model:

$$EDUCATION_i = \alpha + \beta_1 X_i + \beta_2 AGE_i + \beta_3 QOB_i + \beta_4 QOB_i * AGE_i + \beta_5 REGION_i + \beta_6 MOB_i + \beta_7 FLU_i + \varepsilon_i \quad \textbf{(2)}$$

Where *EDUCATION* is a variable for highest grade level completed. The other coefficients are the same as equation (1). I also estimated a logit model with a dependent variable equal to 1 if an individual was a high school graduate.

Table 3 reports the estimates from equation (2). Columns (1) – (3) contain the OLS estimates for all NHIS respondents, men, and women with the highest grade completed as the dependent variable. Row (1) contains results for flu exposure defined as being born in either the fourth quarter of 1918 or the first or second quarters of 1919. There are no statistically significant results on highest grade completed for flu exposure defined in this manner. Row (4) contains results for the effect on highest grade completed for individuals born during the second quarter of 1919. There is a statistically significant decrease of -0.137 for these individuals. This result is similar in magnitude to those reported in Almond (2006).

[13] To some extent this fact should be expected since previous work has demonstrated a strong quarter of birth effect on education (Angrist and Krueger, 1991). This increases the signal-to-noise ratio making it more difficult to visually detect an effect from the flu pandemic based on quarter of birth.

Columns (4) – (6) contains logit estimates for equation (3) where the dependent variable is a binary variable indicating the individual being a high school graduate. There are statistically significant decreases in the probability of graduating from high school for all respondents and for women who were affected by the flu during some period of gestation. For example, the odds-ratio for women born during either the fourth quarter of 1918 or the first or second quarter of 1919 is 0.936. The underlying rate of graduating from high school for women in this sample between the ages of 62 and 84 is 60 percent—making it inappropriate to interpret the odds-ratio as a relative risk ratio.

These results provide a weaker case for the effect of the flu on education than those in Almond (2006). This is likely a result of the NHIS being a less appropriate dataset for estimating the effect of the flu pandemic on educational outcomes. Compared to the PUMS sample used by Almond, the NHIS sample in this case is much smaller and the respondents are in general older. Due to these factors, it should be unsurprising that the estimates related to education are less precise.

Conclusion

The results of this analysis suggest that in-utero exposure to the 1918 flu pandemic had long lasting negative health consequences. Depending on the period of fetal development during which exposure occurred, individuals have a higher probability of developing coronary heart disease, diabetes, kidney disorders, or being in poor health. There is limited evidence from this analysis that exposure to the flu in-utero also affects education levels.

The strong relationship between in-utero stress during certain periods of fetal development and specific conditions in later life shows that the duration of the event used for quasi-experimental variation in fetal conditions is critical to analyses involving specific diseases. When flu exposure was defined over several quarters of birth, it is not possible to pinpoint stress to particular periods of fetal development. As a result, many of the individuals who received the "treatment" of fetal stress should not be expected to develop particular conditions. For example, the nutrition delivery system of the fetus is almost fully developed by the last trimester. Individuals experiencing fetal stress during this time period should not be

expected to have a higher probability of developing diabetes in later life. Grouping all individuals into one large category (including both "treated" and "untreated" individuals with respect to certain conditions) limits the ability of the analysis to detect any effect from fetal stress on particular diseases. Unsurprisingly, when flu exposure was defined at its broadest level and diabetes is the dependent outcome of interest there was no statistically significant effect. When flu exposure is defined using particular quarters of birth, however, there is an approximately 23 percent increase in the probability of developing diabetes for individuals exposed to the flu during the first months of pregnancy.

The short duration of the 1918 pandemic allows researchers to attribute flu exposure to these particular time periods of development. Identification strategies using long-lasting events such as the Chinese famine or the Siege of Leningrad, on the other hand, are hampered by their inability to determine particular time periods of fetal stress. The long duration of these events is at least one reason that previous attempts to document disease specific outcomes of the fetal origins hypothesis have been more mixed than these results.

While the long term health impact of the flu pandemic is interesting, the insight gained by this analysis can be beneficial in understanding a number of important questions regarding the effects of poor in-utero conditions from other sources. Generalizing the results of this analysis to all cases of fetal stress raises a question of external validity. There is biological evidence, however, that the effect of in-utero flu exposure is similar to other complications. Irving et al. (2000) found that in-utero exposure to influenza resulted in a higher rate of complications in pregnancy. This provides a connection between the fetal origins hypothesis and the 1918 pandemic. Taken together, the animal studies, cross sectional analysis of humans, and the results of this analysis suggest that maternal health during pregnancy is an important contributor to the long-term health of their offspring.

The long term health effects of fetal stress and malnutrition can generate significant societal costs. The management of chronic conditions makes up an increasing share of expenditures in the

Medicare program.[14] In particular, heart disease and diabetes are primary cost drivers. For example, 42 percent of the top quartile of Medicare patients in terms of spending have coronary heart disease. Additionally, 32 percent of these high cost patients suffer from diabetes (Congressional Budget Office, 2005). A RAND study states, "chronic illnesses such as heart disease, cancer, and diabetes are expensive to treat. As a consequence, the relatively small proportion of Medicare beneficiaries with such diseases account for a disproportionate share of Medicare spending — perhaps as much as three-quarters of the total" (RAND, 2005).[15] To the degree that in-utero stress increases the incidence of these conditions it also generates higher Medicare spending.

Beyond simply the impact on medical spending, the presence of chronic conditions leads to a lower quality of life, work effort, and productivity. Almond (2006) found that in-utero exposure to the flu led to a 20 percent increase in disability and a 5-9 percent decrease in wages. These results are similar to previous estimates of the effect of chronic conditions and health status on labor supply. Bartel and Taubman (1979) found statistically and economically significant decreases in labor force participation and earnings for individuals with a variety of chronic conditions including heart disease. Mitchell (1990) states, "[p]oor health is associated with reduced hours of work, lower wage rates, early retirement and disability transfer programs" (p. 928). These lower work levels and earnings add another dimension to the social cost of chronic conditions and the importance of fully understanding their origins.

While these health benefits must be discounted due to their accrual so long after birth, it is clear that they represent a valuable and previously ignored benefit of improved fetal conditions. Several federal, state, and private programs attempt to improve access to prenatal care—particularly for underserved populations. For example, Medicaid now provides prenatal care services. In addition, the Women, Infants, and Children (WIC) program is explicitly intended to improve nutrition for pregnant women. There is often debate about the net efficacy of these per-natal programs. Evaluations of their

[14] Due to their age, early all individuals affected by the flu that are considered in this study qualify for Medicare benefits.

[15] While the higher likelihood of an early death for individuals with these chronic conditions does limit their effect on total Medicare costs, RAND still estimates that coronary heart disease and diabetes increase lifetime Medicare spending by anywhere from $14,000 to $17,000.

benefit, however, fail to consider the potential long term health benefits (Evans and Lien, 2005; Wayne et al., 1998; Currie and Gruber, 1996; Devaney et al., 1992). Instead, these programs are traditionally judged based on immediate infant health concerns such as birthweight, 28 day readmission rates, and infant mortality. The results for this study show that long term health benefits should also be a factor in these evaluations. This will provide a more accurate assessment for long term health policy development.

References

Almond, Douglas "Is the 1918 Influenza Pandemic Over? Long-Term Effects of In Utero Influenza Exposure in the Post-1940 U.S. Population," *Journal of Political Economy*, August 2006.

Almond, Douglas and Bhashkar Mazumder, "The 1918 Influenza Pandemic and Subsequent Health Outcomes: An Analysis of SIPP Data," *American Economic Review,* May 2005.

Angrist, J.D., and A.B. Krueger, "Does Compulsory Schooling Affect Schooling and Earnings?"*Quarterly Journal of Economics*, 106, 1991.

Azambuja, Maria, "Spanish Flu and Early 20th Century Expansion of a Coronary Heart Disease-Prone Subpopulation," *Texas Heart Institute Journal,* 2004.

Baker, Michael, Mark Stabile, and Catherine Deri, "What do Self-Reported, Objective, Measure of Health Measure," NBER Working Paper No. 8419, August 2001

Banerjee, Abhijit, Esther Duflo, Giller Postel-Vinay, and Timothy M. Watts, "Long Run Health Impacts of Income Shocks: Wine and Phylloxera in 19th Century France," NBER Working Paper No. 12895, Feb. 2007.

Barker, DJP, "Fetal Origins of Coronary Heart Disease," *British Medical Journal*, 1995.

Barker, DJP (ed), *Fetal Origins of Cardiovascular and Lung Disease,* New York: Marcel Dekker, Inc, 2001.

Barker DJP, "Coronary Heart Disease: A Disorder of Growth," *Hormone Research,* 2003.

Barker, DJP and MA Hanson, "Altered regional blood flow in the fetus: the origins of cardiovascular disease?," *Acta Paeditr,* Sep, 2004.

Barker, DJP, "The Developmental Origins of Insulin Resistance," *Hormone Research,* 2005.

Barry, John. *The Great Influenza: The Epic Story of the Deadliest Plague in History,* Viking Press, 2004.

Bartel, Ann and Paul Taubman, "Health and Labor Market Success: The Role of Various Diseases," *The Review of Economics and Statistics,* Feb 1979.

Blondeau, B., A. Garofano, P Czernichow, B. Breat, "Age-dependent inability of the endocrine pancreas to adapt to pregnancy: A long-term consequence of perinatal malnutrition in the rat," *Endocrinology,* Sept 1999.

Brenner BM and CM Chertow, "Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury," *American Journal of Kidney Diseases,* 1994.

Brenner BM and Chertow CM, "Congenital iligonephropathy: an inborn cause of adult hypertension and progressive renal injury?" *Current Opinions in Nephrology and Hypertension*, Sep 1993.

Brenner BM, and HS Mackenzie, "Nephron mass a risk factor for progression of renal disease," *Kidney International,* 1997.

Case, Anne, Darren Lubotsky, and Christina Paxson. "Socioeconomic Status and Health in Childhood: The Origins of the Gradient," *American Economic Review,* December 2002.

Congressional Budget Office, "High Cost Medicare Beneficiaries," May 2005.

Currie, Janet and Jonathan Gruber, "Saving Babies: The Efficacy and Cost of Recent Changes in the Medicaid Eligibility of Pregnant Women," *Journal of Political Economy,* Dec 1996.

Devaney, Barbara, Linda Bilheimer, and Jennifer Schore, "Medicaid Costs and Birth Outcomes: The Effects of Prenatal WIC Participation and the Use of Prenatal Care." *Journal of Policy Analysis and Management,* Autumn 1992.

Elo, I.T., and S.H. Preston, "Education Differentials in Mortality: United States, 1979-85," *Social Science and Medicine,* Jan 1996.

Eriksson, JG, T Forsen, J Tuomilehto, C Osmond, DJP Barker, "Early Growth and coronary heart disease in later life: longitudinal study," *British Medical Journal,* 2001.

Evans, William N. and Diana S. Lien, "The Benefits of Prenatal Care: Evidence from the PAT Bus Strike," *Journal of Econometrics,* Mar-Apr 2005.

Frankel S, P Elwood, P Sweetnam, J Yarnell, G Davey Smith, "Birthweight, body-mass index in middle age, and incident coronary heart disease," *Lancet*, 1996.

Grossman, M. and Kaester, R, "The Effects of Education on Health," in J.R. Berhman and N. Stacey (eds.) *The Social Benefits of Education,* University of Michigan press: Ann Arbor, 1997.

Hales CN, DJP Barker, PM Clark, LJ Cox, C Fall, C Osmond, and PD Winter, "Fetal and infant growth and impaired glucose tolerance at age 64," *British Medical Journal,* 1991.

Hales CN and DJ Barker, "Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis," Diabetologia, 1992.

Hales, C.N., M. Desai, and S.E. Ozanne, "The Thrifty Phenotype Hypothesis; How Does it Look After 5 Years," *Diabetic Medicine,* vol. 14: 1997

Harding, Jane E. and Peter D. Gluckman, "Growth, Metabolic, and Endocrine Adaptations to Fetal Undernutrition," in David J. P. Barker ed. *Fetal Origins of Cardiovascular and Lung Disease,* New York: Marcel Dekker, Inc, 2001.

Hoet, Joseph J. and Mark A. Hanson, "Intrauterine Nutrition," in David J. P. Barker ed. *Fetal Origins of Cardiovascular and Lung Disease,* New York: Marcel Dekker, Inc, 2001.

Irving, WL, DK James, T Stephenson, P Laing, C Jameson, JS Oxford, P Chakraverty, DW Brown, AC Boon, MC Zambon, "Influenza Virus Infection in the Second and Third Trimesters of Pregnancy: A Clinical And Serodemiological Study," BJOG: An International Journal of Obstetrics and Gynecology, Oct 2000.

Kitagawa, Evelyn, and Philip Hauser, *Differential Mortality in the United States: A Study in Socioeconomic Epidemiology*, Harvard University Press: Cambridge, Massachusetts, 1973

Kloeck, Teun, "OLS Estimation in a Model Where a Microvariable is Explained by Aggregates and Contemporaneous Disturbances," *Econometrica*, January 1981

Leon D., HO Lithell, D Vagero, I Koupilova, R Mohsen, L Berglund, UB Lithell, P McKeigue, "Reduced fetal growth rate and increased risk of deth from ischaemic heart disease: Cohort study of 15000 Swedish men and women born 1915-1929," *British Medical Journal*, 1998.

Lleras-Muney, Adriana, "The Relationship Between Education and Adult Mortality in the United States," *Review of Economic Studies*, January 2005.

Martyn CN, and Stephen Greenwald, "Mechanism for In Utero Programming of Blood Pressure," in David J. P. Barker ed. *Fetal Origins of Cardiovascular and Lung Disease*, New York: Marcel Dekker, Inc, 2001.

Martyn CN, AF Lever, JJ Morton, "Plasma concentrations of inactive renin in adult life are related to indicators of fetal growth," *Journal of Hypertension*, 1996.

Meng, Xin and Nancy Qian, "The Long Run Health and Economic Consequences of Famine on Survivors: Evidence from China's Great Famine," Working Paper, Nov. 28, 2006.

Mitchell, Jean M., "The Effect of Chronic Disease on Work Behavior over the Life Cycle," *Southern Economic Journal*, Apr 1990.

Moulton, Brent, "An Illustration of a Pitfall in Estimating the Effects of Aggregate Variables on Micro Units," *Review of Economics and Statistics*, 1990.

Nathanielsz, Peter W., "Animal Models That Elucidate Basic Principles of the Developmental Origins of Adult Diseases," *ILAR Journal*, January 2006.

Ozanne, SE, GD Smith, J Tikerpae, CN Hales, "Altered Regulation of Hepatic Glucose Output in the Male Offspring of Protein-Malnourished Rat Dams," *The American Journal of Physiology*, Apr 1996

Ozanne, Susan E. and C. Nicholas Hales, "The long-term consequences of intra-uterine protein malnutrition for glucose metabolism," *Proceedings of the Nutrition Society*, 1999.

Ozanne, Susan E. and C. Nicholas Hales, "Lifespan catch-up growth and obesity in male mice," *Nature*, Jan 2004.

RAND Health, "Future Health and Medical Care Spending of the Elderly: Implications for Medicare," 2005.

Ravelli, ACJ, JHP Van der Meulen, RPJ Michels, C Osmond, DJP Barker, CN Hales, OP Bleker, "Glucose tolerance in adults after prenatal exposure to famine," *Lancet*, 1997.

Rich-Ewards JW, MJ Stampfer, JE Manson, B Rosner, SE Hankinson, GA Colditz, WC Willett, CH Kennekens, "Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976," *British Medical Journal*, 1997.

Roseboom, TJ, JHP van der Meulen, C Osmond, DJP Barker, ACJ Ravelli, JM Schroeder-Tanka, GA van Montfran, RPJ Michels, and OP Bleker, "Coronary Heart Disease After Prenatal Exposure to the Dutch Famine, 1944-45," *Heart*, 2000.

Roseboom, Tessa J., Jan H.P. van der Meulen, Anita C.J. Ravelli, Clive Osmond, David J.P. Barker, Otto P. Bleker, "Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview," *Molecular and Cellular Endocrinology*, 2001.

Simmons, RA, LJ Templeton, SJ Gertz, "Intrauterine Growth Retardation Lead to the Development of Type 2 Diabetes in a Rat," *Diabetes*, Oct 2001.

Snyder, Stephen E., "Another Sort of Intergenerational Transfer? Influenza and the Fetal Origins Hypothesis," mimeo, Lehigh University, 2004.

Stanner, Sara A. and John S. Yudkin, "Fetal Programming and the Leningrad Siege Study," *Twin Research*, Oct 2001.

Stocker, Claire J., Jonathan R.S. Arch, and Michael A. Cawthorne, "Fetal origins of insulin resistance and obesity," *Proceedings of the Nutrition Society*, 2005.

Thornburg, Kent L., "Physiological Development of the Cardiovascular System In Utero," in David J. P. Barker ed. *Fetal Origins of Cardiovascular and Lung Disease*, New York: Marcel Dekker, Inc, 2001.

Wayne A. Ray, Joseph Gigante, Edward F. Mitchel, Jr, Gerald B. Hickson, "Perinatal Outcomes Following Implementation of TennCare," *Journal of the American Medical Association*, 1998.

Table 1
Descriptive Statistics
Adults aged 55 to 90, 1982 to 2002 NHIS and 1980 to 2000 Census

	NHIS	1980-2000 PUMS
% Female	56.93	56.3
% Black	11.07	8.1
% Hispanic	6.15	4.3
% High School Graduate	63.1	62.8
% College Graduate	15.84	13.6
% Married	60.1	62.8

Source: Public Use Micro Samples and NHIS

Table 2
Logit Estimates of Health Outcomes, Adults aged 55 to 90, 1982 to 2002 NHIS

Parameter estimates (standard errors) [Odds ratios]

		Heart Disease			Diabetes	Kidney Disease	Poor Health
		(1)	(2)	(3)	(4)	(5)	(6)
	Quarter of Birth	Total n= 383.785 mean dep. var. = 0.1074	Men n=165,308 mean dep. var. = 0.1243	Women n=218,477 mean dep. var. = 0.0946	Total n= 383,785 mean dep. var. = 0.0671	Total n=383,785 mean dep. var. = 0.0058	Total n=383,785 mean dep. var. = 0.2649
1	Flu Season[1]	0.065* (0.038) [1.067]	0.064 (0.053) [1.066]	0.065 (0.048) [1.067]	0.045 (0.061) [1.046]	0.153 (0.129) [1.165]	0.079*** (0.022) [1.082]
2	Fourth Quarter , 1918	0.054 (0.046) [1.055]	0.093 (0.078) [1.097]	0.011 (0.065) [1.011]	-0.06 (0.076) [0.942]	0.41** (0.196) [1.51]	0.066 (0.043) [1.061]
3	First Quarter , 1919	0.112* (0.066) [1.118]	0.177** (0.087) [1.193]	0.051 (0.076) [1.052]	-0.027 (0.098) [0.973]	-0.11 (0.24) [0.896]	0.078** (0.028) [1.081]
4	Second Quarter , 1919	0.028 (0.061) [1.028]	-0.083 (0.091) [0.92]	0.137** (0.068) [1.147]	0.21** (0.1) [1.23]	0.139 (0.252) [1.15]	0.091** (0.035) [1.095]

Other covariates include controls for age, quarter of birth trend, race, ethnicity, marital status, month of birth, and region. Standard errors are clustered on year of birth/year of survey cohorts to allow for within group correlation.

[1] Flu season is defined as being born in the fourth quarter of 1918, the first quarter of 1919, or the second quarter of 1919.

* Significant at .10 level

** Significant at .05 level

*** Significant at .001 level

Table 3
Logit Estimates of Health Outcomes, Adults aged 55 to 90, 1982 to 2002 NHIS

Parameter estimates (standard errors) [Odds ratios]

		Heart Disease			Diabetes	Kidney Disease	Poor Health
		(1)	(2)	(3)	(4)	(5)	(6)
		Total	Men	Women	Total	Total	Total
		n= 383.785	n=165,308	n=218,477	n= 383,785	n=383,785	n=383,785
	Quarter of	mean dep. var. =	mean dep. var. =	mean dep. var. =	mean dep. var. =	mean dep. var. =	mean dep. var. =
	Birth	0.1074	0.1243	0.0946	0.0671	0.0058	0.2649
		-0.104	0.009	-0.217**	-0.041	0.525*	-0.167
	October,	(-.74)	(0.124)	(0.107)	(0.111)	(0.311)	(0.069)
(1)	1918	[0.9]	[1.009]	[0.8]	[0.96]	[1.69]	[0.846]
		-0.009	0.027	-0.05	-0.097	0.631**	-0.031
	November,	(0.09)	(0.163)	(0.127)	(0.143)	(0.258)	(0.078)
(2)	1918	[0.991]	[1.027]	[0.951]	[0.91)	[1.88]	[0.97]
		0.249**	0.224**	0.261*	-0.044	-0.116	0.235***
	December,	(0.1)	(0.11)	(0.142)	(0.104)	(0.449)	(0.073)
(3)	1918	[1.28]	[1.25]	[1.3]	[0.96]	[0.89]	[1.26]
		0.143	0.284**	-0.143	-0.101	0.467	0.142**
	January,	(0.1)	(0.109)	(0.133)	(0.166)	(0.29)	(0.068)
(4)	1919	[1.15]	[1.33]	[0.867]	[0.9]	[1.6]	[1.15]
		0.074	0.114	0.052	0.145	-0.634	0.012*
	February,	(0.11)	(0.11)	(0.151)	(0.14)	(0.524)	(0.069)
(5)	1919	[1.077]	[1.12]	[1.053]	[1.16]	[0.53]	[1.012]
		0.116	0.123	0.11	-0.122	-0.485	-0.014
	March,	(0.112)	(0.141)	(0.128)	(0.139)	(0.433)	(0.056)
(6)	1919	[1.13]	[1.13]	[1.12]	[0.89]	[0.616]	[0.986]
		-0.286	-0.04	-0.018	0.259*	0.333	0.127**
	April,	(0.114)	(0.129)	(0.162)	(0.133)	(0.345)	(0.056)
(7)	1919	[0.751]	[1.041]	[0.982]	[1.3]	[1.4]	[1.14]
		0.083	0.006	0.165*	0.219**	0.167	0.094
	May,	(0.9)	(0.141)	(0.095)	(0.098)	(0.39)	(0.08)
(8)	1919	[1.087]	[1.006]	[1.18]	[1.24]	[1.18]	[1.099]
		0.029	-0.249	0.252**	0.145	-0.111	0.05
	June,	(0.01)	(0.155)	(0.125)	(0.159)	(0.486)	(0.079)
(9)	1919	[1.03]	[0.78]	[1.29]	[1.16]	[0.895]	[1.05]

Other covariates include controls for age, quarter of birth trend, race, ethnicity, marital status, month of birth, and region. Standard errors are clustered on year of birth/year of survey cohorts to allow for within group correlation.

* Significant at .10 level

** Significant at .05 level

*** Significant at .001 level

Table 4
Estimates for Educational Attainment, Adults aged 55 to 90, 1982 to 2002 NHIS

Parameter estimates (standard errors) [Odds ratios]

		(1)	(2)	(3)	(4)	(5)	(6)
		Highest Grade Completed OLS Coefficient Total n=383,785 Mean Dep. Var = 11.82	Highest Grade Completed OLS Coefficient Men Only n= 165,308 Mean Dep. Var = 11.56	Highest Grade Completed OLS Coefficient Women Only n= 218,477 Mean dep. Var. = 11.67	High School Graduate Logit Coefficient Men Only n=383.785 Mean dep. Var=0.6301	High School Graduate Logit Coefficient Men Only n=165,308 Mean dep. Var = 0.6286	High School Graduate Logit Coefficient Women Only n=218,477 Mean dep. var. = 0.6312
					-0.045**	-0.019	-0.066**
	Flu	-0.076	-0.074	-0.071	(0.02)	(0.035)	(0.025)
(1)	Season[1]	(0.05)	(0.07)	(0.071)	[0.956]	[0.981]	[0.936]
	Fourth	-0.01	0.014	-0.025	-0.034	0.000	-0.059
	Quarter,	(0.08)	(0.11)	(0.1)	(0.036)	(0.06)	(0.05)
(2)	1918				[0.967]	[1.00]	[0.943]
	First	-0.081	-0.088	-0.063	-0.042	-0.012	-0.064
	Quarter,	(0.097)	(0.013)	(0.117)	(0.043)	(0.067)	(0.042)
(3)	1919				[0.96]	[0.988]	[0.938]
	Second	-0.137*	-0.146	-0.128	-0.06	-0.043	-0.076
	Quarter,	(0.072)	(0.103)	(0.115)	(0.039)	(0.058)	(0.046)
(4)	1919				[0.942]	[0.958]	[0.927]

Other covariates include controls for age, quarter of birth trend, race, ethnicity, marital status, month of birth, and region. Standard errors are clustered on year of birth/year of survey cohorts to allow for within group correlation. Odds ratios are in brackets.

[1] Flu season is defined as being born in the fourth quarter of 1918, the first quarter of 1919, or the second quarter of 1919.

* Significant at .10 level

** Significant at .05 level

*** Significant at .001 level

.

Figure 1 – Deaths from Influenza by Age

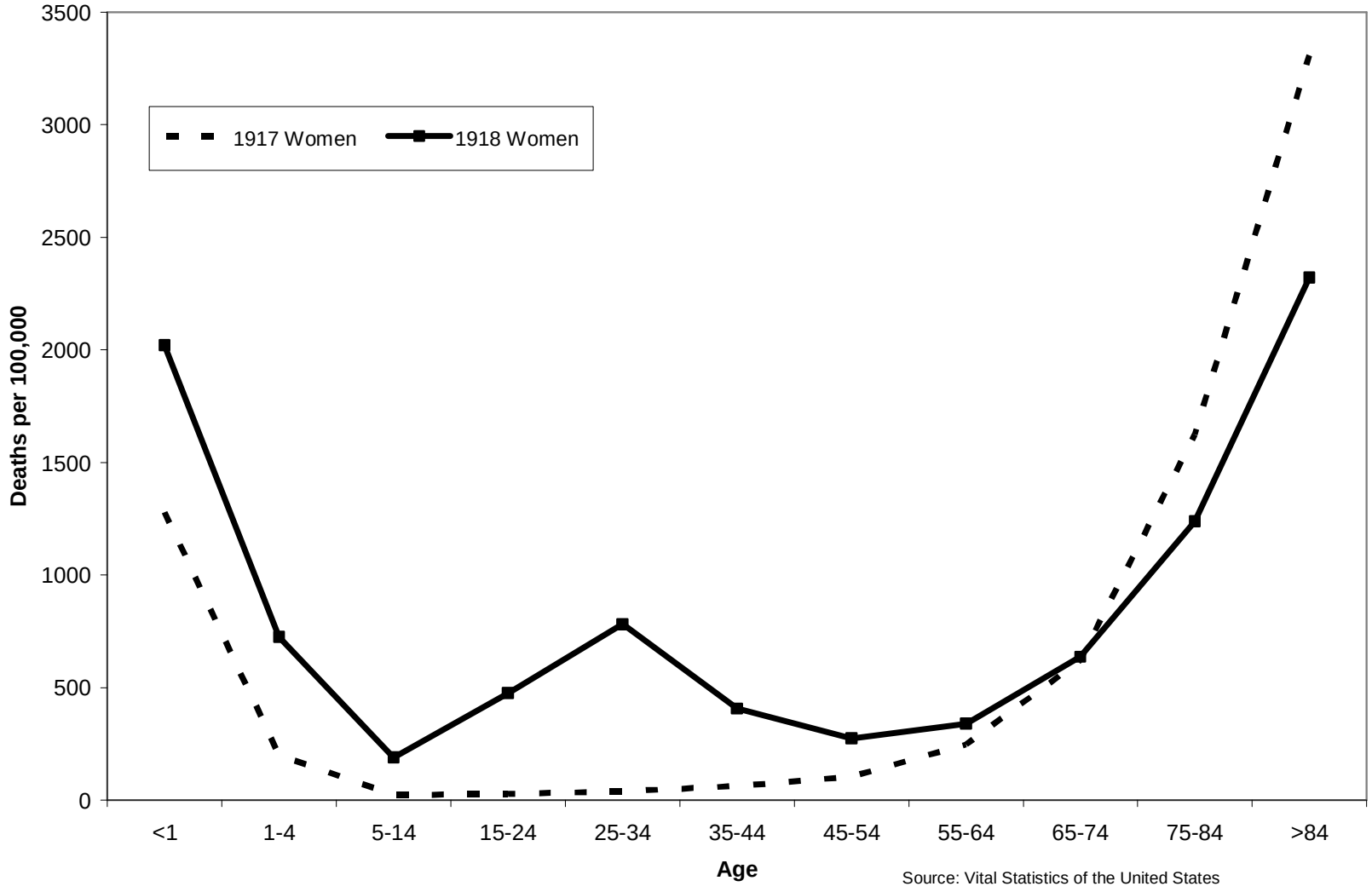

Figure 2 – Influenza Deaths by Year

Figure 3: Coronary Heart Disease Rates, by Age
Adults, Aged 55 to 90, 1982 to 2002 NHIS

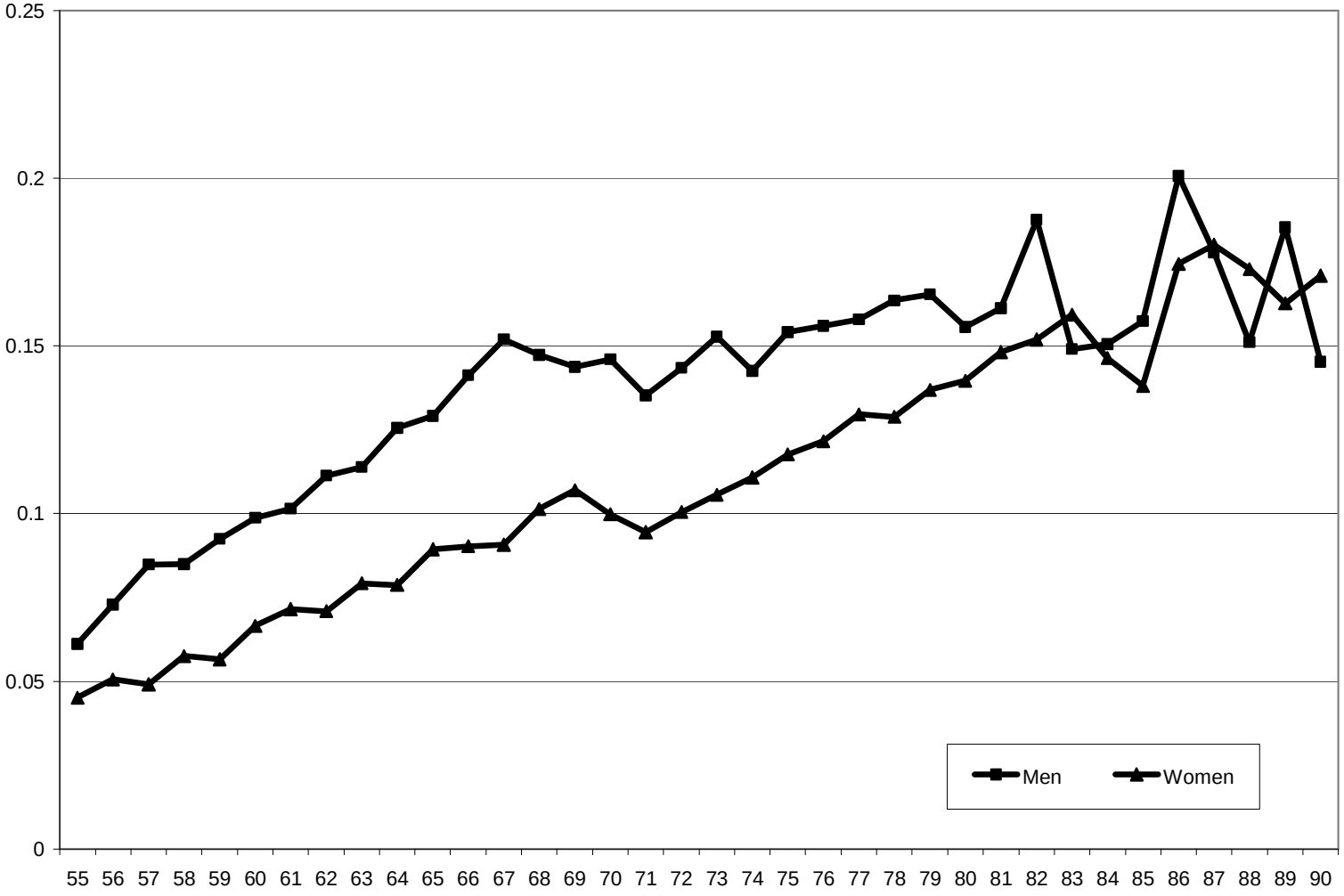

Figure 4 – Estimated Effect of In-Utero Flu Exposure on Coronary Heart Disease by Age, Men Born During the 1st Quarter 1919, 1982 to 2002 NHIS

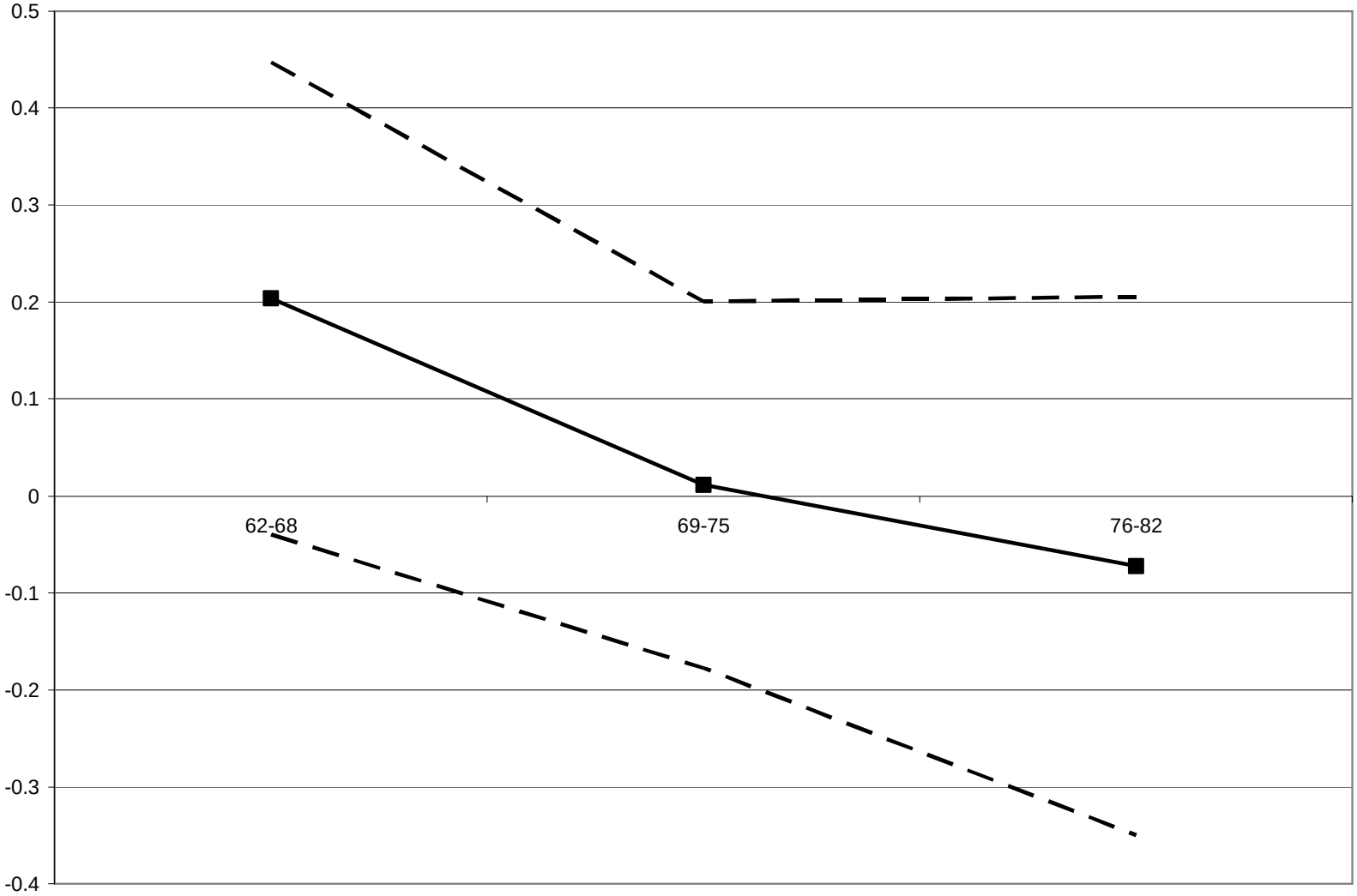

Figure 5a – Highest Grade Completed by Year of Birth
Adults, Aged 55-90, 1982-2002 NHIS

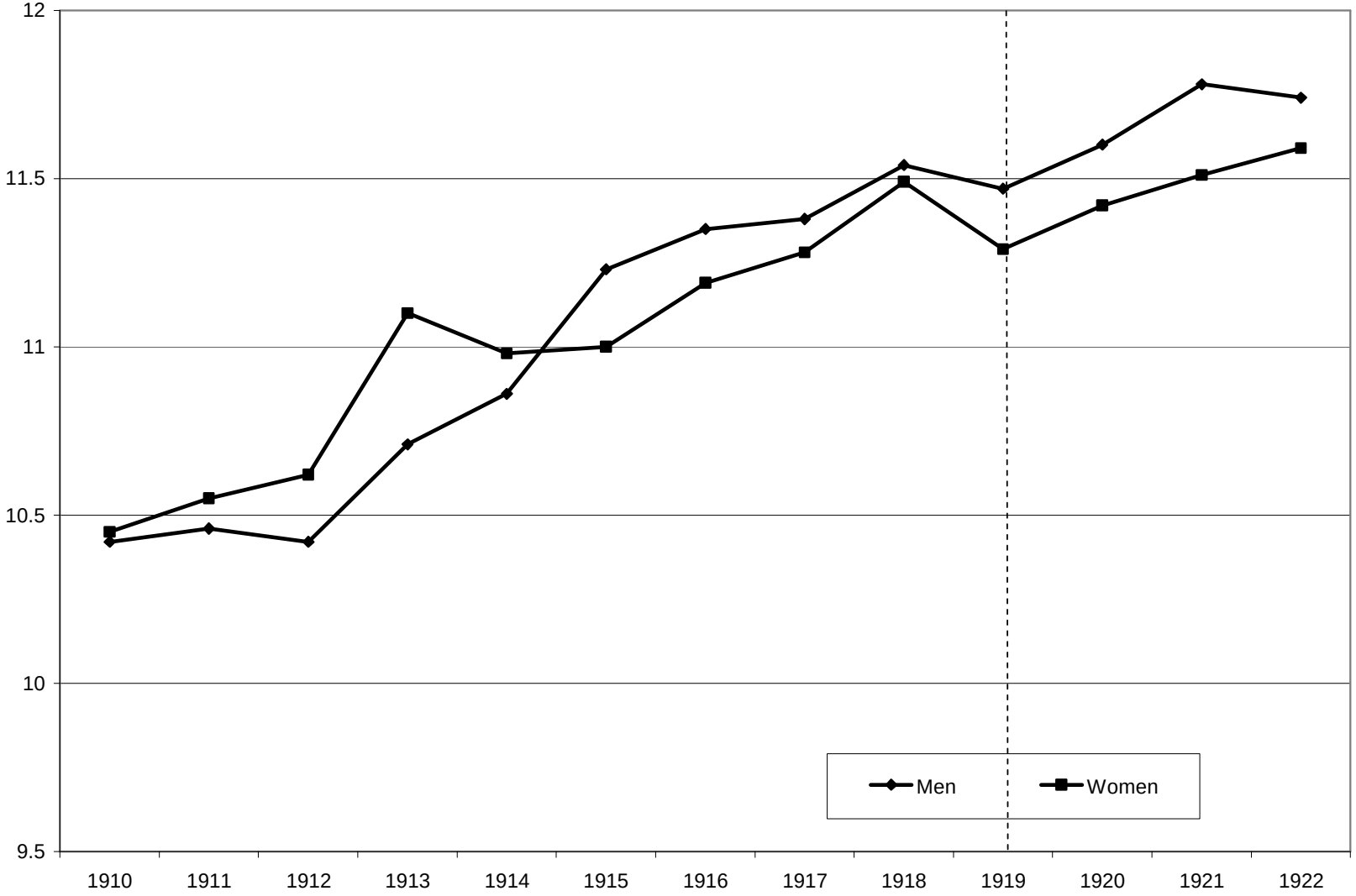

Figure 5b – Percent Graduating High School by Year of Birth
Adults, Aged 55-90, 1982-2002 NHIS