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Research Article

The Relationship Between Fertility History and Incident Dementia in the U.S. Health and Retirement Study

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Abstract

Objectives: An emerging literature suggests that fertility history, which includes measures of parity and birth timing, may influence cognitive health in older ages, especially among women given their differential exposure to pregnancy and sex hormones. Yet, few studies have examined associations between measures of fertility history and incident dementia in population-based samples.

Method: We examined the associations between parity, younger age at first birth, and older age at last birth with incident dementia over a 16-year period in a prospective sample of 15,361 men and women aged 51–100 years at baseline drawn from the Health and Retirement Study. We used Cox regression and the Fine and Gray model to obtain cause-specific hazard ratios (csHRs) and subdistribution hazard ratios for incident dementia from gender-stratified models, with the latter method accounting for the semicompeting risk of death.

Results: During the follow-up period (median 13.0 years), the crude incidence rate for dementia was 16.6 and 19.9 per 1,000 person-years for men and women, respectively. In crude models estimating csHRs, higher parity (vs parity 2) and younger age at first birth were associated with increased risk of dementia for both genders. These associations did not persist after adjusting for sociodemographic characteristics, smoking status, and health conditions, with much of the attenuation in estimates occurring after adjustment for sociodemographic characteristics.

Discussion: In this population-based, multiethnic cohort, we observed limited evidence for an association between measures of fertility history and incident dementia among men and women after adjusting for potential confounders.

Keywords: Cognitive health, Gender, Parity, Postreproductive health

Dementia is a leading cause of death and disability in the United States (Alzheimer's Association, 2020; Stokes et al., 2020) and its impact on society is expected to increase in response to population aging (Hurd et al., 2015; Shah et al., 2016). Because dementia is strongly related to life course processes and is more prevalent among women (Mazure & Swendsen, 2016; Mielke, 2018; Whalley et al., 2006), several researchers have hypothesized that women's reproductive characteristics, such as parity and sex hormone exposure, could influence cognitive trajectories and dementia risk through understudied biological pathways (de Lange et al., 2020; Fox et al., 2018). Indeed, emerging evidence finds that reproductive events leave "residual signatures" on inflammatory markers, blood counts, and telomere length that could in turn influence the risk of chronic conditions in later life (Cramer & Vitonis, 2017; Pollack et al., 2018; C. P. Ryan et al., 2018). Because Alzheimer's disease—which comprises the fractional majority of dementia cases—is largely a systemic inflammatory disease (Britschgi & Wyss-Coray, 2007; Meraz-Ríos et al., 2013),

it is plausible that experiences of pregnancy, in particular, may modify immunologic and inflammatory trajectories over the life course, thereby altering the risk for dementia.

In recent years, several studies have attempted to elucidate the biological underpinnings that link reproductive and fertility histories with later-life cognitive health, with a focus on women. For example, one dominant explanation posits that women's endogenous estrogen exposure over the life course, often proxied by length of the reproductive period (i.e., time from menarche to menopause), can affect women's brain aging trajectories (J. Ryan et al., 2009). The empirical evidence for this appears mixed, with some studies showing a protective role of longer reproductive periods (Gilsanz et al., 2019; Karim et al., 2016) or no association (Prince et al., 2018), while others find opposite relationships (de Lange et al., 2020; Najar et al., 2020). Another explanation posits that immunological changes induced by pregnancy, such as the proliferation of regulatory T cells that protect against inflammation (Kieffer et al., 2017), are a likely mechanism. For example, in their small study of British women ($n = 95$), Fox and colleagues (2018) found that increased exposure to first trimesters of pregnancy—regardless of pregnancy outcome—appeared to be protective against dementia, which is consistent with an immunologic, rather than an estrogenic, explanation.

Other biological mechanisms might operate through indirect pathways. In previous studies, researchers have found associations between reproductive factors and cardiovascular outcomes (Hall et al., 2017; Oliver-Williams et al., 2019), diabetes (Nicholson et al., 2006; Yang et al., 2016), later-life depression (Grundy et al., 2020), and allostatic load (Grundy & Read, 2015), all of which have been linked with dementia in prior research (Livingston et al., 2020; Matos & Souza-Talarico, 2019). Multiple measures of fertility history, including parity, timing of childbearing, and birth intervals, are also associated with the development of overweight and obesity in later life (D. M. Brown et al., 2017; Davis et al., 2014; Zoet et al., 2019), as well as more rapid weight gain trajectories (Laroche et al., 2013; Umberson et al., 2011), which could also indirectly influence dementia risk. Additionally, women might have increased dementia risk as a result of pregnancy complications, such as preeclampsia, which have been linked with dementia (Basit et al., 2018).

Importantly, though, the association between reproductive factors and cognitive health in later life may not operate solely through biological processes. Studies that have examined relationships in both males and females often find similar patterns for both genders, suggesting that social and lifestyle pathways or selection mechanisms, rather than sex-specific biological mechanisms, better explain observed findings (Grundy & Kravdal, 2008; Hipp et al., 2020; Read & Grundy, 2017; Umberson et al., 2011). For example, younger ages at first birth may limit educational and economic opportunities that have been linked with increased cognitive reserve later in life (Sharp & Gatz, 2011). Moreover, because social factors such as socioeconomic position, education, marital status, and place of birth collectively shape both childbearing and health behaviors across the life course, a spurious association between fertility history and later-life outcomes could arise if sociodemographic confounding variables are not adjusted for.

Parenthood could also influence cognitive health through socially mediated channels, such as caregiving, social support, and social interaction (Seeman et al., 2001; Walsh et al., 2019). Social support from children may buffer against loneliness and stress in later life, thereby potentially lowering the risk of dementia (Kelly et al., 2017; Sundström et al., 2020). The act of raising children may also provide cognitive benefits, as prosocial, helping behaviors are hypothesized to influence to a chain of biochemical processes that reduce stress and inflammation (S. L. Brown & Brown, 2015). Grandparent caregiving may also be beneficial for cognitive health. A study of noncustodial grandparents from the U.S. Health and Retirement Study (HRS) found that more hours spent providing care to grandchildren was associated with less decline in cognitive scores (Sneed & Schulz, 2019).

While the mechanisms reviewed thus far suggest that fertility history is an important life course determinant of cognitive health, existing literature is far from conclusive and yields mixed findings. This may be due, in part, to the use of different study populations, designs, and measures, as well as conflicting directionality of proposed mechanisms. Moreover, the relationship between fertility history and later-life cognitive health might vary by geographic context. In a pooled study of 11 population-based cohorts from Europe, Asia, and Latin America, Bae and colleagues (2020) found an overall association between parity and women's risk of dementia, but this relationship was not uniform across regions. Studies have also differed in their extent to adjusting for confounding variables and the role of selection, which could also account for differences (Read & Grundy, 2017; Read et al., 2011). Other limitations of previous research include the use of models that do not account for the competing risk of death, which is especially critical to longitudinal studies of older adults. Lastly, the proliferation of recent studies that have found associations between fertility history and dementia risk focused almost exclusively on women. The omission of men, however, limits inferences about the mechanistic underpinnings of reproductive events on later-life cognitive health.

We add to this growing body of research by examining the relationship between two dimensions of fertility history—parity and timing of childbearing—with incident dementia in a large, multiethnic, population-based study in the United States. We include both men and women in the sample to distinguish between biological and social processes that have been proposed in the literature. As noted above, biological pathways associated with pregnancy-induced immunological changes and/or endogenous estrogen exposure during reproductive years would be

unique to females. Further, we assess whether associations between fertility history and dementia risk are robust after adjustment for potential confounding variables, including sociodemographic, lifestyle, and health factors. Lastly, our analyses include a methodological approach that accounts for the semicompeting risk of death, which may enable more accurate estimates of the association between fertility history and incident dementia.

Method

Data

The HRS is a nationally representative and longitudinal survey of U.S. adults over the age of 50 and their spouses of any age (Sonnega et al., 2014). Since 1992, HRS investigators have assessed a wide range of social, economic, and health characteristics among respondents approximately every 2 years with response rates for follow-up interviews greater than 85% at every survey wave (Sonnega et al., 2014). Respondents who are unable or unwilling to participate may be surveyed by a proxy respondent (typically a spouse or adult child) who completes the survey on their behalf. The HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and has been approved by the Health Sciences and Behavioral Sciences institutional review board at the University of Michigan (Sonnega et al., 2014).

We used data from nine waves (2000–2016) of the HRS. We selected the year 2000 survey wave as the baseline year because it marks the first year in which consistent cognitive information was ascertained for both community-dwelling and nursing home residents in the HRS. Among 19,578 individuals who responded to the year 2000 survey wave, we restricted our analytic sample to adults aged 51 years and older at baseline (n = 18,874) with valid sampling weights (n = 18,617) who were dementia-free (n = 17,096). Respondents who self-reported their race as "Other Race" (n = 578) or for whom race or Hispanic origin was missing (n = 4) were excluded due to low sample sizes. We further excluded respondents with incomplete exposure data (n = 902) as well as those with only one available survey wave (n = 251), resulting in an analytic sample of 15,361 respondents.

Outcome

All-cause dementia among self-respondents was ascertained at every wave using a 27-point cognitive scale that included immediate and delayed 10-noun free recall tests (range: 0–10 points each), a serial seven subtraction test (range: 0–5 points), and a backward count from 20 test (range: 0–2 points) (Crimmins et al., 2011; M. B. Ofstedal et al., 2005). On the basis of their continuous score, we discretized cognitive status into two categories—with and without dementia—using cutpoints which were clinically verified in the Aging, Demographics, and Memory Study (ADAMS). The ADAMS is a supplemental study of the HRS that involved in-home neuropsychological and clinical assessment combined with expert clinician adjudication to obtain a gold-standard diagnosis of cognitive status (Crimmins et al., 2011; Langa et al., 2005). Respondents with scores from 12 to 27 were classified as nonimpaired; 7–11 with cognitive impairment and no dementia (CIND); and 0–6 with dementia. In this paper, we pooled nonimpaired and CIND respondents as our reference category.

Dementia among respondents surveyed by proxy was detected using an 11-point version of the validated Informant Questionnaire on Cognitive Decline in the Elderly (Jorm, 1994), which included the proxy's assessment of the respondent's memory (excellent [0], very good [1], good [2], fair [3], and poor [4]), ability to perform five instrumental activities of daily living (managing money, taking medication, preparing hot meals, using phones, and shopping for groceries; range: 0–5), and the survey interviewer's assessment of whether the respondent was unable to complete the survey due to cognitive limitations (none [0], some [1], and prevents completion [2]). Proxy respondents with scores of 0–2 were classified as nonimpaired; 3–5 with CIND; and 6–11 with dementia (Crimmins et al., 2011; Jorm, 1994).

Exposure

We examined three measures of fertility history: the number of children ever born (no children, one child, two children, three children, four or more children), younger age at first birth (<20 years for women, <23 years for men), and older age at last birth (>35 years for women, >39 years for men). We used parity 0 as the reference group for analyses in which we evaluated parity as the exposure to align with biological explanations posited in the literature (Fox et al., 2018; C. P. Ryan et al., 2018). Gender-specific age cutoffs for younger age at first birth and older age at last birth were based on historical fertility schedules, as well as prior related work that used a UK-based sample (Read & Grundy, 2017). Respondents self-reported the number of children ever born by responding to the question, "How many children have (you fathered/you given birth to)?" Respondents were instructed to exclude miscarriages, stillbirths, adoptions, and step-children from their response. We constructed variables for age at first and last birth using the RAND HRS Family Respondent–Kid file (Bugliari et al., 2017), which provides information on family rosters, by subtracting the respondent's birth year from the birth year of their first- and last-born child, respectively. Kid records that implied extreme ages at birth (<13 years and >49 years) were excluded (n = 1,407) due to potential measurement error. We further excluded kid records that were inconsistent on key information (e.g., name, gender, age, relationship to HRS respondent; n = 10,017).

Covariates

We accounted for potential confounders of the association between each measure of fertility history and incident dementia. Sociodemographic confounders were selected for their documented association with dementia and were assessed at baseline in the year 2000. These confounders included age (continuous), gender (men, women), birth cohort (<1924, 1924–1930, 1931–1941, 1942–1947), whether the respondent was born outside of the United States, and whether the respondent was born in a southern region of the United States. We included mother's and father's educational attainment (≥8 years or otherwise), respondent's educational attainment (less than high school or General Educational Development, high-school graduate or some college, college and above), and marital status (married/partnered or not).

We also include a set of variables in our models that includes smoking status, select health behaviors, and medical conditions, all measured at baseline (i.e., 2000). While such measures may be considered as potential mediators between fertility history and incident dementia, we are particularly interested in whether our results are robust to their inclusion. We code smoking status as active smoker, former smoker, or never smoked. We included a continuous measure of body mass index (BMI) as well as continuous scores on the Center for Epidemiologic Studies—Depression scale to assess depressive symptomatology. Medical conditions were assessed by asking the respondent whether a medical practitioner had ever informed them of having a chronic condition (e.g., *Has a doctor ever told you that you have high blood pressure or hypertension?*). We included diabetes, hypertension, any heart condition (heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems), and stroke.

Missing covariate values were imputed using an iterative, nonparametric technique based on random forests. We implemented this technique using the missForest package in R (Stekhoven, 2011; Stekhoven & Bühlmann, 2012). This approach has the distinct advantage of accounting for nonlinearity in and interactions between the covariates, and has been shown to outperform commonly used imputation methods including parametric multivariate imputation by chained equations (Stekhoven & Bühlmann, 2012).

Statistical Analysis

Analyses were performed using R version 4.0.2 (R Core Team, 2020) and Stata version 14 (StataCorp, 2015). In all analyses, we used HRS-provided combined person-level and nursing home sampling weights to adjust for the complex survey design and allow estimates to be generalized to the U.S. population of community-dwelling and nursing home adults over the age of 50 (Ofstedal et al., 2005; Sonnega et al., 2014). Moreover, analyses were stratified by gender due to differences in the age patterns and risk of dementia for men and women and to account for potential differences in biological mechanisms linked to reproduction (e.g., Jasienska et al., 2017; Mielke, 2018). We computed unweighted frequencies and sample-weighted proportions to summarize the baseline characteristics of the analytic sample and used chi-squared tests to compare the baseline characteristics by gender.

We used cause-specific hazard ratios (csHRs) derived from cause-specific Cox regression models to separately evaluate the association between each measure of fertility history and incident dementia. The cause-specific hazard function obtained from a Cox regression model can be defined at time t as the instantaneous rate of failure due to event k conditional on survival to time t and among individuals who are event-free. Attained age was used as the underlying timescale due to its strong association with incident dementia, with respondent's age at baseline defined as entry time; exit time was defined as age at incident dementia or censoring (i.e., death or study end). Such an approach implicitly adjusts for age in our analyses.

We first estimated a base model adjusted for birth cohort to examine associations between the exposure and incident dementia. We then estimated a fully adjusted model that accounted for race/ethnicity, birth place, education, parental education, partnership status, smoking status, BMI, depressive symptomology, and medical comorbidities. Models were estimated with robust standard errors clustered at the household level to adjust for the nonindependence of observations in the same household.

We separately analyze each of the three measures of fertility history as key independent variables in our models, but also include an analysis that contains all three measures in the same model. This latter approach accounts for the positive correlations between younger age at first birth and parity. Models that include younger age at first birth and older age at last birth as exposures are restricted to individuals with a parity of one or higher (n = 13,743).

One caveat of the Cox regression model is that it assumes independent or noninformative censoring (Cox, 1972; Kalbfleisch & Prentice, 2011). That is, individuals who remain under follow-up are considered to have the same risk for incident dementia as those no longer being followed irrespective of their circumstances (e.g., censoring, lost to follow-up, or death). However, whereas individuals who are censored or lost to follow-up may still be at risk for dementia, decedents who die prior to incident dementia should no longer be considered at risk—and this event should not be treated as noninformative. To address concerns related to modeling the semicompeting risk of death and how it may alter estimates between the association of fertility history and incident dementia, we conducted a parallel analysis in which we used the Fine and Gray model (Fine & Gray, 1999) to calculate subdistribution hazard ratios (sdHRs) derived from the subdistribution hazard function. The subdistribution hazard function can be defined at time t as the instantaneous risk of event k

among individuals who have not experienced event k prior to time t.

In the presence of competing risks, cause-specific hazard models and subdistribution hazard models provide different measures of association. Specifically, the csHR can be interpreted as a quantity that reflects a causal association whereas the sdHR may be best suited for quantifying predictive relationships (Noordzij et al., 2013). Due to these discrepancies, and in accordance with recommendations specified in prior work (Grambauer et al., 2010; Latouche et al., 2013), we report results from both analyses.

Results

Descriptive statistics of the analytic sample at baseline overall and by gender are shown in Table 1. Of the 15,361 respondents in the analytic sample, 28.2% were between the ages 65 and 74 years; 8,875 (56.0%) were women; 86.3% self-reported their race as non-Hispanic White; nearly 75% attained a high-school diploma or higher; and 11.5% of respondents reported zero births. Among men, 19.8% had a younger age at first birth (<23 years) and 17.1% had an older age at last birth (>39 years). Among women, 17.7% were younger than 20 years during their first birth, and 19.6% were over 35 years at their last birth. We noted differences in several baseline characteristics by gender as indicated by results from chi-squared tests. These included, for example, age, race/ethnicity, respondent's education, smoking status, and all three fertility history exposures.

The 15,361 respondents who comprised the analytic sample contributed 173,282 person-years (median [interquartile range] length of follow-up: 13.0 [7.0–16.0] years) of follow-up over the study period. Over the 173,282 person-years of follow-up, 3,208 cases of all-cause dementia were observed yielding a crude incidence rate of 18.5/1,000 person-years. There were 2,030 cases of all-cause dementia among women (crude incidence rate: 19.9/1,000 person-years) and 1,178 cases were observed among men (crude incidence rate: 16.6/1,000 person-years).

Parity

Table 2 presents csHRs and 95% confidence intervals (CIs) obtained from cause-specific Cox regression models evaluating the association between parity and incident dementia. Corresponding CIs that include 1 are not considered statistically significant at the 5% level. In Model 1, we observed an increased risk of incident dementia among both men and women with high parity (having four or more children) compared with those who had no children (csHR for men is 1.33 [1.02, 1.73] and csHR for women is 1.31 [1.11, 1.55]). After adding the full set of covariates to the model (Model 2), the association between higher parity and incident dementia no longer held for both genders (csHR for men: 1.12 [0.85, 1.48]; csHR for women: 1.09 [0.92, 1.28]).

Younger Age at First Birth

Table 3 presents results examining the relationship between younger age at first birth and incident dementia. In Model 1, which only adjusts for birth cohort, both men and women with a younger age at first birth experience higher risk of incident dementia (csHR for men: 1.32 [1.12, 1.57]; csHR for women: 1.69 [1.49, 1.92]). However, these observed hazards were attenuated after adding sociodemographic and health controls (Model 2) and were no longer significant at the 5% level, although for women, the csHR remained somewhat elevated (csHR: 1.11 [0.96, 1.27]).

Older Age at Last Birth

Table 4 presents csHRs and 95% CIs obtained from cause-specific Cox regression models evaluating the association between older age at last birth and incident dementia. In Model 1, we observe some suggestion of elevated risks for both men and women with older ages at last birth (csHR for men: 1.15 [0.97, 1.35]; csHR for women: 1.11 [0.99, 1.25]). However, after adding sociodemographic and health controls (Model 2), we observe no differences in incident dementia by age at last birth.

Parity and Age at Birth

Including all three measures of parity, age at first birth, and age at last birth in the same model does not substantially alter our results (Table 5). Whereas higher parity and younger age at first birth are associated with incident dementia in Model 1, adding sociodemographic and health covariates attenuates observed relationships (Model 2), which parallels findings from models that analyzed each fertility history measure separately.

Subdistribution Hazard Ratios

As a complementary analysis, we estimated sdHRs for which we present results in Supplementary Tables S1–S4. These results largely parallel findings from analyses that estimate csHRs. However, in models assessing the relationship between older age at last birth and incident dementia, we observed an increased hazard for women, but not men (Supplementary Table S3), as well as after adjusting for final parity (Supplementary Table S4). After fully adjusting for all covariates (Supplementary Table S3; Model 2), a 1-year increase in the age at last birth was associated with a hazard of 1.12 (1.00, 1.26).

Discussion

In our study that uses nationally representative, population-based data from the United States, we find no strong evidence of an association between three commonly used measures of fertility history and incident dementia after adjusting for confounders and while accounting for the

Table 1. Descriptive Characteristics of the Analytic Sample at Baseline (n = 15,361) Overall and by Gender

	Overall n = 15,361		Men n = 6,486		Women n = 8,875	
Characteristic	n	%	n	%	n	%
Age*						
51–64 years	6,719	49.3	2,855	52.7	3,864	46.6
65–74 years	4,856	28.2	2,140	27.6	2,716	28.7
75–84 years	2,974	18.1	1,202	16.4	1,772	19.4
≥85 years	812	4.4	289	3.3	523	5.3
Gender						
Male	6,486	44.0	6,486	100.0	0	0.0
Female	8,875	56.0	0	0.0	8,875	100.0
Race/ethnicity*						
NH White	12,420	86.3	5,356	87.0	7,064	85.7
NH Black	1,994	8.8	730	8.0	1,264	9.4
Hispanic	944	4.9	397	5.0	547	4.9
Foreign born	1,237	7.2	515	7.2	722	7.2
Southern born	5,241	30.7	2,108	29.9	3,133	31.4
Father's education*						
<8 years	4,956	29.3	2,039	28.1	2,917	30.2
≥8 years	10,405	70.7	4,447	71.9	5,958	69.8
Mother's education*						
<8 years	4,186	24.2	1,669	22.4	2,517	25.6
≥8 years	11,175	75.9	4,817	77.6	6,358	74.4
Education*						
<HS or GED	4,402	25.5	1,906	26.0	2,496	25.2
HS or some college	8,119	53.9	3,054	48.1	5,065	58.6
≥College	2,840	20.5	1,526	25.9	1,314	16.3
Married/partnered*	10,186	64.3	5,233	77.6	4,953	53.8
Smoking status*						
Never	6,309	40.6	1,789	28.6	4,520	50.1
Former	6,805	43.8	3,670	55.1	3,105	34.9
Active	2,247	15.6	997	16.3	1,250	15.0
Body mass index*	15,361	27.2 (0.05)[a]	6,486	27.6 (0.07)[a]	8,875	26.9 (0.07)[a]
Center for Epidemiologic Studies—Depression score*	15,361	1.5 (0.02)[a]	6,486	1.2 (0.02)[a]	8,875	1.7 (0.02)[a]
Diabetes*	2,168	12.9	1,026	14.4	1,142	11.7
Hypertension	7,116	43.9	2,931	43.0	4,185	44.5
Heart disease*	3,238	19.8	1,675	23.6	1,563	16.8
Stroke	1,015	6.2	469	6.5	546	5.9
Parity*						
0	1,618	11.5	685	12.0	933	11.1
1	1,533	10.2	628	10.1	905	10.3
2	4,090	28.1	1,797	29.1	2,293	27.2
3	3,466	22.5	1,489	22.7	1,977	22.4
≥4	4,654	27.7	1,887	26.1	2,767	29.0
Younger age at first birth*	2,770	18.7	1,215	19.8	1,555	17.7
Older age at last birth*	2,600	18.5	1,002	17.1	1,598	19.6

Notes: GED = General Educational Development; HS = high school; NH = non-Hispanic. Weighted percentages and unweighted frequencies presented.
[a]Weighted mean and linearized standard errors shown.
*p < .05, chi-squared or t test for null hypothesis of no between-gender differences.

semicompeting risk of death. In crude models, we find that high parity (having four or more children) and younger age at first birth (<23 for men and <20 for women) are associated with an increased risk of incident dementia. However, these associations did not persist after adjusting for sociodemographic and health covariates, including education, smoking, and health conditions. Further analysis shows that most of this attenuation occurs after adjusting for sociodemographic covariates, including measures of the respondent's education and parental education. Our findings suggest that measures of fertility history are absorbed through more proximate determinants

Table 2. Associations Between Parity and Incident Dementia in Models Stratified by Gender, csHR, and 95% CI

	Model 1		Model 2	
Characteristic	Men *n* = 6,486	Women *n* = 8,875	Men *n* = 6,486	Women *n* = 8,875
Parity				
0 (reference)	1.00	1.00	1.00	1.00
1	1.16 (0.85, 1.59)	0.99 (0.80, 1.22)	1.13 (0.82, 1.56)	0.96 (0.78, 1.18)
2	0.92 (0.70, 1.20)	1.04 (0.88, 1.24)	1.01 (0.77, 1.32)	1.12 (0.95, 1.33)
3	1.04 (0.79, 1.37)	0.98 (0.82, 1.16)	1.16 (0.89, 1.53)	0.98 (0.82, 1.17)
≥4	1.33 (1.02, 1.73)	1.31 (1.11, 1.55)	1.12 (0.85, 1.48)	1.09 (0.92, 1.28)
Cohort				
born <1924	1.02 (0.83, 1.26)	0.94 (0.79, 1.11)	0.81 (0.64, 1.02)	0.78 (0.65, 0.93)
born 1924–1930	1.13 (0.93, 1.38)	1.01 (0.86, 1.19)	1.00 (0.82, 1.22)	0.95 (0.81, 1.12)
born 1931–1941 (reference)	1.00	1.00	1.00	1.00
born 1942–1947	0.96 (0.69, 1.32)	0.94 (0.68, 1.31)	1.00 (0.73, 1.38)	0.96 (0.69, 1.33)
Race/ethnicity				
NH White (reference)			1.00	1.00
NH Black			1.71 (1.39, 2.10)	1.99 (1.73, 2.29)
Hispanic			1.26 (0.92, 1.73)	1.61 (1.30, 1.99)
Foreign born			1.21 (0.93, 1.57)	1.09 (0.90, 1.31)
Southern born			1.36 (1.16, 1.58)	1.22 (1.09, 1.36)
Father's education				
<8 years			1.06 (0.89, 1.26)	0.96 (0.84, 1.10)
≥8 years (reference)			1.00	1.00
Mother's education				
<8 years			0.95 (0.79, 1.14)	1.08 (0.94, 1.24)
≥8 years (reference)			1.00	1.00
Education				
<HS or GED			2.14 (1.83, 2.49)	1.77 (1.59, 1.97)
HS or some college (reference)			1.00	1.00
≥College			0.80 (0.66, 0.97)	0.67 (0.56, 0.80)
Married/partnered			0.98 (0.82, 1.17)	1.00 (0.90, 1.10)
Smoking status				
Never (reference)			1.00	1.00
Former			1.01 (0.86, 1.18)	0.99 (0.90, 1.10)
Active			1.36 (1.07, 1.73)	1.19 (1.00, 1.41)
Body mass index			0.98 (0.96, 1)	0.99 (0.98, 1.00)
Center for Epidemiologic Studies—Depression score			1.10 (1.06, 1.15)	1.10 (1.07, 1.12)
Diabetes			1.50 (1.25, 1.79)	1.45 (1.26, 1.66)
Hypertension			1.03 (0.90, 1.18)	1.08 (0.98, 1.20)
Heart disease			1.00 (0.86, 1.17)	1.02 (0.91, 1.15)
Stroke			1.59 (1.26, 2.01)	1.35 (1.14, 1.61)

Note: CI = confidence interval; csHR = cause-specific hazard ratio; GED = General Educational Development; HS = high school; NH = non-Hispanic.

of incident dementia, prompting questions as to whether the previously observed relationships between fertility history and incident dementia in the literature (e.g., Bae et al., 2020; Yoo et al., 2020)—which, to our knowledge, have not accounted for the semicompeting risk of death—may be largely due to the health and social correlates of childbearing patterns that are often stratified along axes of socioeconomic status and race/ethnicity.

We observed suggestive evidence that later age at last birth might be associated with increased risk of dementia for women, although this finding was not consistent across the two analytical approaches we used. That said, the positive association we find contrasts with other studies that suggest a protective effect of later age at last birth on later-life health. For example, prior research from both contemporary and historical populations finds that that later ages at last birth are associated with postreproductive longevity (Gagnon et al., 2009; Sun et al., 2015) and longer telomere length (Latour et al., 2020). Assuming our finding can be replicated in other populations, these conflicting results merit further investigation.

Table 3. Associations Between Younger Age at First Birth and Incident Dementia in Models Stratified by Gender, csHR, and 95% CI

	Model 1		Model 2	
Characteristic	Men *n* = 5,801	Women *n* = 7,942	Men *n* = 5,801	Women *n* = 7,942
Younger age at first birth	1.32 (1.12, 1.57)	1.69 (1.49, 1.92)	1.00 (0.84, 1.19)	1.11 (0.96, 1.27)
Cohort				
born <1924	1.04 (0.84, 1.29)	0.94 (0.78, 1.12)	0.85 (0.67, 1.70)	0.79 (0.66, 0.95)
born 1924–1930	1.14 (0.93, 1.40)	1.05 (0.88, 1.24)	1.03 (0.84, 1.26)	0.97 (0.82, 1.15)
born 1931–1941 (reference)	1.00	1.00	1.00	1.00
born 1942–1947	1.03 (0.74, 1.44)	1.00 (0.72, 1.40)	1.06 (0.76, 1.47)	1.00 (0.71, 1.40)
Race/ethnicity				
NH White (reference)			1.00	1.00
NH Black			1.77 (1.44, 2.20)	1.97 (1.69, 2.29)
Hispanic			1.25 (0.93, 1.70)	1.54 (1.23, 1.92)
Foreign born			1.12 (0.86, 1.48)	1.16 (0.95, 1.41)
Southern born			1.35 (1.15, 1.60)	1.23 (1.90, 1.38)
Father's education				
<8 years			1.04 (0.86, 1.24)	0.99 (0.86, 1.15)
≥8 years (reference)			1.00	1.00
Mother's education				
<8 years			0.94 (0.77, 1.15)	1.03 (0.89, 1.20)
≥8 years (reference)			1.00	1.00
Education				
<HS or GED			2.22 (1.88, 2.61)	1.73 (1.54, 1.94)
HS or some college (reference)			1.00	1.00
≥College			0.80 (0.65, 0.98)	0.68 (0.56, 0.82)
Married/partnered			1.00 (0.83, 1.22)	1.01 (0.91, 1.12)
Smoking status				
Never (reference)			1.00	1.00
Former			1.06 (0.89, 1.25)	1.04 (0.93, 1.16)
Active			1.46 (1.14, 1.86)	1.21 (1.01, 1.44)
Body mass index			0.99 (0.97, 1.01)	0.99 (0.98, 1.00)
Center for Epidemiologic Studies—Depression score			1.09 (1.05, 1.14)	1.09 (1.07, 1.12)
Diabetes			1.51 (1.26, 1.80)	1.38 (1.19, 1.60)
Hypertension			0.99 (0.86, 1.14)	1.14 (1.02, 1.27)
Heart disease			0.99 (0.85, 1.16)	1.01 (0.89, 1.15)
Stroke			1.58 (1.26, 1.98)	1.38 (1.15, 1.66)

Notes: CI = confidence interval; csHR = cause-specific hazard ratio; GED = General Educational Development; HS = high school; NH = non-Hispanic. Birth cohort excluded from table for brevity.

This study is one of a handful that investigates the relationship between fertility history and cognitive outcomes among both *men and women* using population-based data. As stated previously, there has been much recent research that focuses on the role of fertility history for women's health and longevity. While the focus on women is often motivated by biological mechanisms particular to female physiology, the reality is that data on men's reproductive histories are not commonly collected. In the United States, commonly used population-based surveys such as the National Health and Nutrition Examination Survey, as well as epidemiologic cohorts such as the Women's Health Initiative, are increasingly used to study reproductive history exposures but are limited to women (Shadyab et al., 2017; Shirazi et al., 2020). The omission of men leads to a missed opportunity to deepen our understanding of potential mechanisms and targets for intervention. For example, in at least two studies that have studied the relationship between fertility history and cognitive health among men and women, observed relationships are often similar for both genders (Read & Grundy, 2017; Saenz et al., 2019), suggesting that biological explanations on their own are insufficient.

Strengths of this study include the use of a large, nationally representative sample of men and women with up to 16 years of follow-up, ascertainment of dementia status using validated criteria, and mortality coverage that is essentially complete. The cohorts included in our study

Table 4. Associations Between Older Age at Last Birth and Incident Dementia in Models Stratified by Gender, csHR, and 95% CI

	Model 1		Model 2	
Characteristic	Men *n* = 5,801	Women *n* = 7,942	Men *n* = 5,801	Women *n* = 7,942
Older age at last birth	1.15 (0.97, 1.35)	1.11 (0.99, 1.25)	0.99 (0.84, 1.17)	1.03 (0.92, 1.15)
Cohort				
born <1924	1.03 (0.83, 1.28)	0.91 (0.77, 1.09)	0.85 (0.67, 1.07)	0.79 (0.66, 0.95)
born 1924–1930	1.16 (0.95, 1.42)	1.02 (0.86, 1.21)	1.03 (0.83, 1.26)	0.97 (0.81, 1.14)
born 1931–1941 (reference)	1.00	1.00	1.00	1.00
born 1942–1947	1.01 (0.73, 1.41)	0.97 (0.69, 1.35)	1.06 (0.76, 1.47)	0.99 (0.71, 1.39)
Race/ethnicity				
NH White (reference)			1.00	1.00
NH Black			0.99 (0.84, 1.17)	1.03 (0.92, 1.15)
Hispanic			1.78 (1.44, 2.21)	1.99 (1.71, 2.32)
Foreign born			1.26 (0.93, 1.70)	1.54 (1.23, 1.92)
Southern born			1.12 (0.86, 1.48)	1.15 (0.94, 1.39)
Father's education				
<8 years			1.04 (0.86, 1.24)	0.99 (0.85, 1.15)
≥8 years (reference)			1.00	1.00
Mother's education				
<8 years			0.94 (0.77, 1.15)	1.03 (0.89, 1.20)
≥8 years (reference)			1.00	1.00
Education				
<HS or GED			2.22 (1.88, 2.61)	1.76 (1.58, 1.97)
HS or some college (reference)			1.00	1.00
≥College			0.80 (0.65, 0.98)	0.68 (0.56, 0.82)
Married/partnered			1.00 (0.83, 1.22)	1.01 (0.91, 1.12)
Smoking status				
Never (reference)			1.00	1.00
Former			1.06 (0.90, 1.25)	1.04 (0.93, 1.16)
Active			1.46 (1.14, 1.86)	1.21 (1.01, 1.45)
Body mass index			1.09 (1.05, 1.14)	1.09 (1.07, 1.12)
Center for Epidemiologic Studies—Depression score			0.99 (0.86, 1.14)	1.14 (1.02, 1.27)
Diabetes			1.51 (1.26, 1.80)	1.37 (1.18, 1.59)
Hypertension			0.99 (0.86, 1.14)	1.14 (1.02, 1.27)
Heart disease			1.00 (0.85, 1.16)	1.02 (0.90, 1.16)
Stroke			1.58 (1.26, 1.98)	1.39 (1.16, 1.66)

Note: CI = confidence interval; csHR = cause-specific hazard ratio; GED = General Educational Development; HS = high school; NH = non-Hispanic.

also had heterogeneous childbearing experiences, allowing us to exploit variation in both fertility timing and parity. Moreover, we used a methodological approach that accounts for the semicompeting risk of death, which allowed us to obtain more precise estimates of the association between fertility history and incident dementia. In survival or time-to-event analysis, it is common for researchers to invoke the assumption of noninformative censoring (Cox, 1972; Kalbfleisch & Prentice, 2011), which, in this context, would imply that decedents who die over the study period without dementia and dementia-free respondents who survive through the end of the study period share the same risk of dementia. Not accounting for the semicompeting risk of death could inflate the cumulative incidence of dementia and result in incorrect conclusions.

Our study has some limitations. Although we included several confounders in our models, our observed relationships may suffer from additional selection or omitted variable bias, and therefore causal inference is limited. Future analyses may consider using alternative empirical approaches to gain more traction on this limitation. For example, two recently created polygenic scores for fertility behavior (Barban et al., 2016) could be employed using Mendelian randomization or alternative genetically informed designs.

The HRS does not contain reliable information on menarche, menopause, breastfeeding, fetal loss, and puberty (for men), so we did not look at alternative measures of reproductive history, including the reproductive period, nor did we test hypotheses related to exogenous estrogen exposure

Table 5. Associations Between Three Fertility Exposures and Incident Dementia in Models Stratified by Gender, csHR, and 95% CI

	Model 1		Model 2	
Characteristic	Men *n* = 5,801	Women *n* = 7,942	Men *n* = 5,801	Women *n* = 7,942
Parity				
1 (reference)	1.00	1.00	1.00	1.00
2	0.79 (0.62, 1.00)	1.07 (0.90, 1.28)	0.89 (0.69, 1.14)	1.17 (0.98, 1.40)
3	0.88 (0.69, 1.13)	0.97 (0.81, 1.17)	1.03 (0.80, 1.32)	1.02 (0.85, 1.23)
≥4	1.09 (0.85, 1.38)	1.24 (1.03, 1.48)	1.00 (0.78, 1.29)	1.13 (0.95, 1.35)
Younger age at first birth	1.28 (1.07, 1.52)	1.66 (1.46, 1.89)	0.99 (0.83, 1.18)	1.11 (0.96, 1.27)
Older age at last birth	1.08 (0.91, 1.29)	1.09 (0.96, 1.23)	0.97 (0.81, 1.16)	1.03 (0.91, 1.16)
Cohort				
born <1924	1.06 (0.86, 1.32)	0.94 (0.79, 1.12)	0.86 (0.68, 1.08)	0.79 (0.66, 0.95)
born 1924–1930	1.16 (0.95, 1.42)	1.03 (0.87, 1.23)	1.03 (0.84, 1.26)	0.97 (0.82, 1.15)
born 1931–1941 (reference)	1.00	1.00	1.00	1.00
born 1942–1947	1.04 (0.75, 1.46)	1.01 (0.72, 1.42)	1.07 (0.77, 1.48)	1.00 (0.71, 1.40)
Race/ethnicity				
NH White (reference)			1.00	1.00
NH Black			1.76 (1.42, 2.19)	1.96 (1.68, 2.28)
Hispanic			1.23 (0.91, 1.68)	1.52 (1.22, 1.91)
Foreign born			1.14 (0.86, 1.49)	1.16 (0.95, 1.41)
Southern born			1.36 (1.16, 1.60)	1.23 (1.09, 1.39)
Father's education				
<8 years			1.03 (0.86, 1.24)	0.99 (0.85, 1.14)
≥8 years (reference)			1.00	1.00
Mother's education				
<8 years			0.94 (0.77, 1.15)	1.03 (0.89, 1.20)
≥8 years (reference)			1.00	1.00
Education				
<HS or GED			2.21 (1.88, 2.61)	1.72 (1.53, 1.94)
HS or some college (reference)			1.00	1.00
≥College			0.8 (0.65, 0.98)	0.68 (0.56, 0.82)
Married/partnered			1.00 (0.82, 1.22)	1.01 (0.90, 1.12)
Smoking status				
Never (reference)			1.00	1.00
Former			1.05 (0.89, 1.24)	1.04 (0.93, 1.16)
Active			1.46 (1.14, 1.86)	1.21 (1.01, 1.44)
Body mass index			0.99 (0.97, 1.01)	0.99 (0.98, 1.00)
Center for Epidemiologic Studies—Depression score			1.09 (1.05, 1.14)	1.09 (1.07, 1.12)
Diabetes			1.51 (1.26, 1.80)	1.38 (1.19, 1.61)
Hypertension			0.99 (0.86, 1.14)	1.14 (1.02, 1.27)
Heart disease			1.00 (0.86, 1.16)	1.02 (0.90, 1.15)
Stroke			1.58 (1.26, 1.98)	1.39 (1.16, 1.67)

Note: CI = confidence interval; csHR = cause-specific hazard ratio; GED = General Educational Development; HS = high school; NH = non-Hispanic.

or pregnancy-induced changes in immunological function. It is possible that alternative measures would be more sensitive to the hypothesized mechanisms put forward in the literature.

Our measure of fertility history only considers biological children. However, if the pathways linking fertility history and incident dementia are more closely related to parenthood, rather than physiological influences of pregnancy, than our omission of nonbiological children may bias results. Given increasing family complexity in the United States, a more nuanced picture of the family environment may shed additional light on the mechanisms at play (Kalmijn, 2013; Seltzer & Bianchi, 2013; Suanet et al., 2013). We also did not consider how work demands, which are often difficult to balance with family responsibilities, might interact with fertility histories to contribute to changes in dementia risk (Ice et al., 2020).

We assessed dementia on the basis of cognitive tests and proxy reports rather than clinical diagnoses. In prior studies

using the HRS, researchers have demonstrated that cognitive tests and proxy reports correctly classify 74% and 86% of respondents, respectively (Crimmins et al., 2011). Thus, the concern of misclassification cannot be ignored. We also acknowledge that although the survey instrument was administered in both English and Spanish, measures for respondents whose first language is not English may also be misclassified. Further, despite the breadth of available information in the HRS, data quality concerns have been noted in the RAND HRS Family Respondent–Kid level file—which was used to construct variables for age at first and last birth—in which approximately 3% of the parent–child cases are duplicates (RAND Data Alert, 2018). To remedy this matter, we excluded records that implied extreme ages at birth and removed records that were inconsistent on key information. Future questionnaires should consider collecting this information directly from participants, if possible.

Finally, we recognize that the time elapsed between our exposures and outcome spans a long interval that includes both the reproductive period and midlife. While biologically oriented hypotheses often predict a direct association between measures of fertility history and later-life health (at least for women), there may be several mediating factors that link measures of fertility history with incident dementia, as described above. However, as we are strictly interested in the association between fertility history and incident dementia, we do not further parse the role of these covariates. Thus, future work that tests mediational hypotheses may be warranted.

Conclusion

Sex and gender differences in dementia are well documented with women facing greater dementia risk (Mielke, 2018). Although the specific pathways linking female sex and gender to increased dementia risk remain poorly understood, it is widely speculated that the processes that result in disparate outcomes span pregnancy and parenthood over the life course. In our analysis, we observed an association between measures of fertility history and incident dementia that largely did not persist after adjusting for key risk factors. Elucidating the social and biological pathways that increase dementia risk among women remains a critical etiological question with important implications for population health and equality.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

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Conflict of Interest

None declared.

Author Contributions

A. Gemmill conceptualized the study, interpreted all statistical analyses, wrote the original draft, and revised the paper. J. Weiss conceptualized the study, performed and interpreted all statistical analyses, wrote the original draft, and revised the paper.

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