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Advanced Maternal Age and Its Association With Cardiovascular Disease in Later Life

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A B S T R A C T

Introduction: Fertility among women at advanced maternal age (AMA) is increasing at a rapid rate in the United States. Although much is known about the impact of older maternal age on the risk for proximate adverse pregnancy outcomes, it is unclear whether older maternal age affects subsequent health. The objective of this study was to evaluate whether AMA is associated with cardiovascular disease (CVD) later in life, adjusting for important social and health factors related to maternal age.

Methods: Data were obtained from the Nurses' Health Study II, a longitudinal prospective cohort study. We investigated whether women with an AMA first or subsequent birth were at higher risk for developing CVD (myocardial infarction or stroke) after age 42 than women without births at AMA. Cox proportional hazard models were estimated to evaluate this association, adjusting for demographic, fertility, and health characteristics.

Results: A total of 5,471 women (7.7%) in the sample had a first birth at an AMA and 1,282 (1.8%) developed CVD at age 42 or older. Women with first births at AMA had a 26% lower unadjusted hazard of CVD than women not at an AMA during their first birth (hazard ratio, 0.74; 95% confidence interval, 0.57–0.95). This association was attenuated (hazard ratio, 0.80; 95% confidence interval, 0.62–1.05) and no longer significant after adjustment for covariates; the modest association remained significant for women with any AMA birth.

Conclusions: We found no evidence that AMA births were associated with increased risk for developing CVD later in life in this sample.

Fertility among women of advanced maternal age (AMA; aged ≥35 years) is increasing at a rapid rate in the United States. Nearly 20% of births in 2019 were to women ages 35 and older (Martin, Brady, Osterman, & Driscoll, 2021). Although childbearing at older ages is not new, the high rate of first births to women with AMA is unprecedented. In 2018, 23% of births among women aged 35 to 39 were first births, up from 7% in 1955 (Martin, Hamilton, & Osterman, 2019; NVSS, 1957). With older maternal age, the risk increases for adverse pregnancy outcomes such as hypertensive disorders of pregnancy, low birth weight, preterm births, and cesarean birth (Correa-de-Araujo & Yoon, 2021; Frick, 2021; Haslinger et al., 2016; Joseph et al., 2005; Lean, Derricott, Jones, & Heazell, 2017; Moaddab et al., 2017). It is unclear, however, whether older maternal age affects a woman's subsequent health.

Cardiovascular disease (CVD) is the leading cause of death for U.S. women (Centers for Disease Control and Prevention, 2019). Complications of pregnancy may be important markers of future cardiovascular health. Women with pregnancy-induced hypertension are at increased risk for developing CVD at later ages (Tobias et al., 2017), with close to a four-fold increased risk of chronic hypertension, a four-fold increased risk of heart failure, an 80% increased risk of stroke, and double the risk of coronary heart disease (Coutinho, Lamai, & Nerenberg, 2018; Li et al., 2018). Women with gestational diabetes are not only at increased risk for developing type 2 diabetes, but also more likely to develop hypertension and CVD (Zhang et al., 2019). Other measures of reproductive history, including high parity

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(Stuart et al., 2018), history of stillbirth (Horn et al., 2019), short and long interpregnancy intervals (Ngo, Roberts, & Figtree, 2016), and small for gestational age and preterm births (Hauspurg, Ying, Hubel, Michos, & Ouyang, 2018) have been linked to cardiovascular risk.

The mechanisms linking pregnancy-related factors with future health are not understood fully. Adverse pregnancy outcomes such as hypertensive disorders of pregnancy, spontaneous preterm birth, and intrauterine growth restriction share similar yet diverse pathogenesis, although all involve inadequate placentation, inflammation, and vascular dysfunction (Lane-Cordova, Khan, Grobman, Greenland, & Shah, 2019); these factors may cause damage that accumulates over time and manifests later as CVD. Women with hypertensive disorders of pregnancy show increased biomarkers for CVD risk (Tanz et al., 2018; Veerbeek et al., 2015) and altered inflammatory pathways (Freeman et al., 2004) after delivery. Alternatively, pregnancy complications may result from an underlying predisposition to CVD that is unmasked through the physiological stress of pregnancy.

Research on the relationship between age at childbirth and subsequent health is limited. Given that maternal age is associated with conditions that increase the risk for CVD, such as hypertensive disorders of pregnancy and gestational diabetes, a link between age at pregnancy and future health is plausible (Correa-de-Araujo & Yoon, 2021; Haslinger et al., 2016; Joseph et al., 2005). In their recent review, Cooke and Davidge (2019) discuss emerging evidence from human studies and animal models that AMA affects maternal cardiovascular adaptions and that these effects may have implications beyond their influence on immediate adverse pregnancy outcomes.

Conversely, delayed fertility may be protective against future morbidities because the social characteristics of many women who delay first births, such as high levels of education, income, and protective health behaviors, are related to improved health (Delbaere et al., 2007; Klemetti, Gissler, Sainio, & Hemminki, 2016). The results of demographic research with an orientation toward biosocial influences indicate that initiation of childbearing at young ages (<20 years) is associated with increased morbidity and mortality in later life, whereas the initiation of childbearing at older ages may be associated with lower morbidity and mortality. These associations are attenuated with adjustment for health behaviors and social factors. They have been observed among men as well, which suggests the association may be due to social factors rather than biological mechanisms (Hanson, Smith, & Zimmer, 2015; Lacey, Kumari, Sacker, & McMunn, 2017; Read, Grundy, & Wolf, 2011).

The objective of this study was to evaluate whether AMA is a risk factor for CVD later in life, adjusting for important social and health factors, and to assess whether experience of adverse health conditions during pregnancy mediates the relationship between age at birth and future health. The higher propensity for developing health conditions during pregnancy may be indicative of suboptimal physiological adaptation to pregnancy among women with AMA, which may also impact health later in life. Data from the Nurses' Health Study (NHS) II, a longitudinal prospective cohort study, provided the opportunity to explore both objectives; comprehensive information was available about reproductive health as well as subsequent health conditions, and women were followed over a sufficient duration to observe CVD events in middle and older ages.

Methods

Data Source and Study Sample

Data for this analysis were obtained from the NHS II, a longitudinal prospective cohort study begun in 1989; 116,429 female nurses between the ages of 25 and 42 years were recruited in 14 states at baseline. Surveys administered every 2 years included health-related information as well as reproductive events. Since the initial recruitment, response rates have varied between 85% and 90% for each 2-year cycle.

Participants were eligible for inclusion in the present study if they reported a birth (live birth or stillbirth) of at least 20 weeks gestation and responded to either the 2001 or 2009 questionnaire ($n = 71{,}672$), which asked detailed questions about pregnancy outcomes. Women were excluded if they reported a first birth before age 18 ($n = 896$), were missing age at first birth (n=36), reported a CVD outcome (myocardial infarction or stroke) before their first birth ($n = 3$), or dropped out of the survey before age 42 ($n = 88$), yielding a final sample of 70,649 women.

Assessment of Exposure and Outcome

Age at birth was defined as a binary variable (AMA vs. not AMA), whether the first birth occurred when a woman was age 35 or above or less than 35. First births were of primary interest because they carry the highest risk for women with AMA and, as a result, may be more likely to be associated with future health (Gilbert, Nesbitt, & Danielsen, 1999; Kalayci, Ozdemir, Alkas, Cok, & Tarim, 2017). Sensitivity analyses compared woman with any AMA birth regardless of parity with those with no AMA births. This expanded definition provided a larger sample of women with AMA births for analyses. A full birth history was reported by participants in the 2001 and 2009 survey waves, including the year each pregnancy ended and length of pregnancy. Births were defined as pregnancies with a duration of 20 weeks or longer.

The outcome of interest was CVD, defined as a composite variable of nonfatal and fatal myocardial infarction and stroke occurring between age 42 and age at return of the 2015 questionnaire. Participants reported a physician's diagnosis of a myocardial infarction or stroke on each biennial questionnaire. Medical records were obtained with participant consent to confirm diagnoses. Nonfatal myocardial infarction was confirmed according to the World Health Organization's criteria based on a combination of symptoms and changes in an electrocardiograph or presence of elevated cardiac specific enzymes (Rose, Blackburn, Gillum, & Prineas, 1982). Nonfatal stroke was confirmed using the National Survey of Stroke criteria of sudden onset of new focal neurological deficit persisting for 24 hours or longer, excluding causes owing to infection, traumatic injury, or malignancy (Walker, 1981). Deaths of participants were identified through a combination of reports of next of kin, postal authorities, and the National Death Index. Fatal myocardial infarction or stroke was determined by a review of autopsy records or if myocardial infarction or stroke was listed as the cause of death on the death certificate with evidence of prior CVD from medical records. Age of onset was determined from date of diagnosis recorded in medical records or the death certificate.

Statistical Analyses

Participants were eligible to contribute to the analysis from age 42 until report of incident CVD event (nonfatal or fatal myocardial infarction or stroke), death from any cause, or the date of their latest questionnaire return (at which time participants ranged in age from 53 to 71 years), whichever came first. Age 42 was selected as the start of the observation period because it was the oldest age of enrollment at baseline and prevents left censoring of the data. It is also an age when most women have completed childbearing and before the typical onset of CVD.

Multivariable Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between age at first birth and risk of CVD. Age is used as the time scale for all models. Multivariable models were adjusted for a priori selected covariates including demographic, fertility, and health characteristics. Demographic characteristics were race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Asian), parents' and spouses' highest education (high school or less, college education, graduate education, education unknown/missing), marital status at age 42 (married, divorced/separated, widowed, never married), and birth cohort (1945–1949, 1950–1954, 1955–1959, 1960–1965). Parents' and spouse's education served as indicators of each participant's socioeconomic status in this homogeneous sample of nurses. There is both theoretical and empirical evidence of a link between parents' education and adulthood health (Huang et al., 2019). The survey did not include measures of participants' highest education level and income was measured only once during the survey rounds with considerable missing data. Fertility characteristics included infertility before age 35 based on self-reported attempts to conceive for 12 or more months without success (yes/no), parity (continuous), and menopause before age 51 (yes/no). Health characteristics were body mass index at age 42 (underweight/normal weight, overweight, obese), family history of diabetes (yes/no), family history of hypertension (yes/no), and smoking status at age 42 (never smoker, former smoker, current smoker). Occurrence of gestational diabetes, gestational hypertension, and preeclampsia during any pregnancy were evaluated as potential mediators in the relationship between age at birth and future CVD risk. The proportional hazard assumption was upheld based on Schoenfeld residual tests. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

This analysis was deemed exempt from review by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board because it involved a secondary analysis of existing, de-identified data.

Results

Participants were followed for a mean of 20.2 years (ranging from <1.0 year to 28.7 years). Of the 70,649 women with eligible births, 647 (0.92%) experienced myocardial infarction and 569 (0.81) experienced stroke during the follow-up period. Table 1 shows the characteristics of study participants by age at first birth. In total, 5,451 women (7.7%) had a first birth at age 35 or older. Women with first births at AMA were more likely to experience infertility before age 35. Women's general health status also differed by AMA status. Women with AMA were less likely to have overweight or obesity at age 42, have an immediate family member with diabetes, or smoke at age 42. Demographic characteristics also differed by AMA status. Women with AMA were less likely to be White and more likely to be Asian or Hispanic. They were more likely to have parents and spouses with a graduate-level education, and to not marry by age 42. They were also more likely to be from later birth cohorts. Women with AMA first births were more likely to have a history of gestational diabetes and gestational hypertension, but were no more likely to have a history of preeclampsia/toxemia than women without AMA.

Cox proportional hazard models assessed the HR by AMA status and whether any difference in hazard remained when

Table 1
Characteristics of Participants by AMA Status at First Birth

Participant Characteristics	<35 Years ($n = 65,179$)	≥35 Years ($n = 5,471$)	p Value of Difference by AMA Status
Mean age at first birth	26.2 (3.8)	37.5 (2.5)	NA
Fertility characteristics			
Infertility before age 35 (%)	20.1	25.6	<.001
Total parity, as of 2009 (%)			<.001
1	13.3	50.5	
2–3	76.4	48.3	
≥4	10.3	1.2	
Mean age of menopause onset	50.2 (4.3)	50.7 (3.7)	<.001
Health characteristics			
BMI, age 42 (%)			<.001
Underweight	1.4	1.7	
Normal weight	53.7	56.9	
Overweight	25.2	23.2	
Obese	18.6	16.8	
Missing BMI	1.1	1.4	
Family history of diabetes (%)	42.5	39.4	<.001
Family history of hypertension (%)	52.8	53.0	.10
Smoking status at age 42 (%)			<.001
Never smoker	66.4	64.1	
Former smoker	23.8	28.2	
Current smoker	9.6	7.4	
Missing smoking status	0.3	0.2	
Demographic characteristics			
Race/ethnicity (%)			<.001
White, non-Hispanic	93.9	91.5	
Black, non-Hispanic	1.2	1.2	
Asian, non-Hispanic	1.1	2.3	
Hispanic	1.6	2.1	
Parents' highest education, combined (%)			
High school or less	9.4	7.5	<.001
College education	57.4	53	
Graduate education	19.4	25.4	
Education missing	13.8	14.0	
Spouse's highest education (%)			<.001
High school or less	16.7	11.6	
College education	46.2	42.8	
Graduate education	25.8	35.3	
Education missing	11.4	10.3	
Marital status, age 42 (%)			<.001
Married	80.6	75.4	
Divorced/separated	18.1	14.6	
Widowed	0.5	0.2	
Never married	0.8	9.8	
Birth cohort (%)			<.001
1945–1949	18.7	11.1	
1950–1954	32.8	32.4	
1955–1959	31.1	37.7	
1960–1965	17.3	18.8	
Pregnancy conditions			
Gestational diabetes	4.8	7.3	<.001
Gestational hypertension	6.4	8.4	<.001
Preeclampsia/toxemia	7.4	7.6	0.41

Abbreviations: AMA, advanced maternal age; BMI, body mass index.
Note: Values are means (standard deviation) for continuous variables or percentages for categorical variables. Values of polytomous variables may not sum to 100% owing to rounding. The p values are based on t-statistics for continuous variables and χ^2 analyses for categorical variables.

Table 2
Cox Proportional Hazard Models of Time to Cardiovascular Disease

Variable	Unadjusted			Adjusted*		
	Hazard Ratio	95% CI	*p* Value	Hazard Ratio	95% CI	*p* Value
AMA at first birth	0.74	0.57–0.95	.02	0.80	0.62–1.05	.11
Race/ethnicity						
White, non-Hispanic	*Ref.*			*Ref.*		
Black, non-Hispanic	1.56	1.04–2.34	.03	1.15	0.76–1.73	.51
Asian, non-Hispanic	0.61	0.32–1.18	.14	0.78	0.39–1.56	.48
Hispanic	0.57	0.31–1.03	.06	0.59	0.33–1.07	.08
Parents' highest education, combined						
High school or less	1.32	1.11–1.58	<.001	1.20	1.00–1.44	.05
College education	*Ref.*			*Ref.*		
Graduate education	0.89	0.76–1.04	.15	1.08	0.91–1.27	.39
Education unknown/missing	1.27	1.08–1.49	<.001	1.17	0.99–1.39	.07
Spouse's highest education						
High school or less	1.30	1.11–1.52	<.001	1.16	0.99–1.37	.07
College education	*Ref.*			*Ref.*		
Graduate education	0.80	0.68–0.93	<.001	0.89	0.76–1.05	.16
Education unknown/missing	1.58	1.34–1.85	<.0001	1.24	1.04–1.48	.02
Marital status, age 42						
Married	*Ref.*			*Ref.*		
Divorced/separated	1.59	1.39–1.81	<.0001	1.29	1.12–1.5	<.001
Widowed	1.48	0.74–2.96	.27	1.06	0.53–2.14	.87
Never married	1.13	0.68–1.88	.65	1.00	0.59–1.7	.99
Birth cohort						
1945–1949	1.20	1.04–1.38	.01	1.18	1.02–1.37	.03
1950–1954	*Ref.*			*Ref.*		
1955–1959	0.81	0.69–0.95	.01	0.84	0.72–0.99	.04
1960–1965	0.79	0.62–1.01	.06	0.80	0.62–1.04	.09
Infertility before age 35	1.15	1.00–1.31	.05	1.10	0.95–1.26	.20
Parity	0.94	0.89–1	.05	0.87	0.77–0.98	.02
Menopause onset at age 51 or older	0.76	0.68–0.85	<.0001	0.84	0.72–0.99	.04
BMI, age 42						
Normal weight/underweight	*Ref.*			*Ref.*		
Overweight	1.53	1.33–1.75	<.0001	1.52	1.32–1.76	<.0001
Obese	2.26	1.97–2.59	<.0001	2.15	1.86–2.48	<.0001
Family history of diabetes	1.25	1.12–1.4	<.001	1.08	0.96–1.22	.21
Family history of hypertension	1.33	1.19–1.5	<.0001	1.26	1.11–1.42	<.001
Smoking status, age 42						
Never smoker	*Ref.*			*Ref.*		
Former smoker	1.02	0.88–1.18	.79	0.97	0.83–1.12	.66
Current smoker	2.64	2.29–3.04	<.0001	2.36	2.03–2.74	<.0001

Abbreviations: AMA, advanced maternal age; BMI, body mass index; CI, confidence interval; Ref., reference group.
Note: Women with missing BMI and smoking values imputed to reference category.
* All covariates in the table are included in the adjusted model.

adjusting for covariates. They were also computed for each covariate individually. Women with AMA had a 26% lower hazard of CVD than women without AMA at first birth (HR, 0.74; 95% CI, 0.57–0.95) in the unadjusted model (Table 2). After adjustment for demographic, fertility, and health characteristics, the association between AMA and lower risk of CVD was attenuated and no longer statistically significant (HR, 0.80; 95% CI, 0.62–1.05).

Several covariates were associated with CVD hazard in the adjusted models. Higher education levels of the women's parents, parity, and being members of later birth cohorts were associated with lower hazard of CVD. Being divorced or separated, having a higher body mass index, smoking, a family history of hypertension, and earlier age of menopause were associated with increased hazard for CVD. Associations were also noted in the unadjusted model between race, spouses' education, infertility before age 35, and family history of diabetes, but the hazard of CVD was not significant for these factors after adjustment for other covariates.

We also assessed differences in the hazard of time to CVD outcome (myocardial infarction or stroke) by AMA status at any birth as a sensitivity analysis. In the analytical sample, 26% of women ($n = 18{,}540$) had AMA at any birth. The results of the Cox proportional hazard models demonstrated a lower hazard for CVD among women with any AMA births, but the association was not strong. Women with AMA at any birth had a 26% lower hazard of CVD compared to women who never had a birth with AMA in the unadjusted model (HR, 0.74; 95% CI, 0.64–0.85) (results not shown). The HR for AMA status at any birth increased to 0.85 (95% CI, 0.71–0.97) after adjusting for demographic, health, and fertility covariates and remained statistically significant.

Pregnancy conditions—gestational diabetes, gestational hypertension, and preeclampsia/toxemia—were added individually to the adjusted model to test for potential mediating effects in the relationship between AMA at first birth and CVD (Table 3). Experience of gestational hypertension or preeclampsia/toxemia, but not gestational diabetes, was significantly associated with increased risk for CVD. The coefficient for AMA was stable after inclusion of these variables, providing no evidence of mediation.

Discussion

The results of our survival analyses indicate that women with AMA first births did not have a greater risk of developing CVD

Table 3
Test for Mediating Effect of Pregnancy Conditions on Relationship between AMA and Cardiovascular Disease

Variables	Hazard Ratio	95% CI	*p* Value
Adjusted without mediators			
AMA at first birth	0.80	0.62–1.05	.11
Gestational diabetes			
AMA at first birth	0.80	0.61–1.05	.11
Gestational diabetes	1.03	0.79–1.35	.83
Gestational hypertension			
AMA at first birth	0.79	0.61–1.03	.08
Gestational hypertension	1.69	1.41–2.04	<.0001
Preeclampsia/toxemia			
AMA at first birth	0.81	0.62–1.05	.11
Preeclampsia/toxemia	1.55	1.29–1.86	<.0001

Abbreviations: AMA, advanced maternal age; CI, confidence interval.
Note: Models include adjustment for all demographic, fertility, and health covariates.

(myocardial infarction and stroke) than women without AMA. They had a 20% lower hazard of experiencing CVD during the follow-up period than women who were younger at first birth after adjusting for demographic, fertility, and health characteristics, but the difference was not significant. The HR for AMA status at any birth was lower than for women who completed childbearing before age 35. It also was attenuated after adjusting for demographic, health, and fertility covariates, but remained significant, suggesting a modest 15% lower risk of CVD.

CVD was a rare outcome in the sample: less than 1% of women experienced myocardial infarction and less than 1% experienced stroke by the end of the observation period. The low incidence of CVD was expected given age-specific rates of these conditions among the general population (Benjamin et al., 2019). The oldest members of the cohort were observed until age 71, and the mean age by the end of follow-up was 62 years.

Among women in the study sample, 8% had a first birth at age 35 and older (AMA) and 26% had any birth with AMA. Women differed in fertility, health, and demographic characteristics by AMA status at first birth. The findings are consistent with those described in prior literature; women with AMA had more protective health behaviors and higher levels of education and household income than women with births at younger ages (Bayrampour & Heaman, 2011; Joseph et al., 2005). Despite protective characteristics, women with AMA are more likely to have fertility histories associated with increased risk, such as experience of infertility and gestational hypertension and diabetes, also evident in the NHS II sample (Haslinger et al., 2016; Joseph et al., 2005; Moaddab et al., 2017). The higher percentage of births with AMA among women from more recent birth cohorts was also expected given the shift toward delayed childbearing over time.

Covariates included demographic, fertility, and health characteristics. Their association with the hazard of CVD was in the expected direction given prior research findings, supporting the validity of the finding observed for AMA and CVD. Higher socioeconomic status, as indicated by education levels of the women's parents, was associated with a lower hazard of CVD (Clark, DesMeules, Luo, Duncan, & Wielgosz, 2009), whereas being divorced or separated increased the risk (Wong et al., 2018). A higher body mass index and smoking were associated with higher risk for CVD outcomes in the sample (Kondo, Nakano, Adachi, & Murohara, 2019; Wilson, D'Agostino, Sullivan, Parise, & Kannel, 2002). Earlier age of menopause was also associated with increased risk for CVD outcomes. The association between menopause (Atsma, Bartelink, Grobbee, & van der Schouw, 2006) and CVD is well-documented, whereas the association between infertility and CVD is supported by emerging research linking certain types of infertility with risk for CVD (Park, Wei, Minissian, Bairey Merz, & Pepine, 2015; Verit, Yildiz Zeyrek, Zebitay, & Akyol, 2017). Associations were also noted in the unadjusted model between spouses' education and infertility before age 35 and parity, but the hazard of CVD was not significant for these variables after adjustment for other covariates.

Findings related to race were unexpected. Black women were not at increased risk for CVD outcomes in the sample after adjusting for covariates, despite higher rates of CVD among Black women in the general population (Brothers, Fadel, & Keller, 2019). This finding is likely due to the very small number of Black women in the NHS II cohort (1.2%) and the overall homogeneity of the sample regarding other characteristics.

Our findings that AMA status was not associated with increased risk for future CVD run counter to the hypothesis that AMA may be a risk factor for developing CVD later in life. This hypothesis was based on research demonstrating that AMA is associated with an increased risk for adverse health conditions during pregnancy, such as hypertensive disorders of pregnancy (Haslinger et al., 2016; Joseph et al., 2005; Moaddab et al., 2017). The higher propensity for developing health conditions may be indicative of suboptimal physiological adaptation to pregnancy among older women (Cooke & Davidge, 2019), so we presumed that maladaptation could also impact health later in life. Experience of health conditions during pregnancy also increases the risk for future CVD (Tobias et al., 2017), potentially acting as a mediator between age at birth and CVD outcomes.

Our findings are, nevertheless, not fully surprising given prior demographic research suggesting lower morbidity and mortality among women with later births. This research indicates that early parenthood may be associated with increased morbidity and mortality owing to biosocial influences, such as lower income, more negative health behaviors, and social strain, which could accelerate biological aging (Hanson et al., 2015; Lacey et al., 2017; Read et al., 2011). The association of age at first birth with future CVD risk was attenuated in the NHS II sample with introduction of demographic factors into the model. This attenuation supports the idea that social factors may explain the relationship between age at first birth and future health. If additional measures of socioeconomic status were available for inclusion as covariates, such as participants' education and income levels, attenuation may have been even greater. We tested for potential mediation between AMA status and CVD outcomes by pregnancy conditions (gestational hypertension, gestational diabetes, and preeclampsia) because these conditions are more frequent among women with AMA and increase the risk of future CVD (Coutinho et al., 2018; Li et al., 2018; Zhang et al., 2019). No evidence of a mediating effect was present, also supporting the notion that social factors may partially explain the relationship between age at first birth and future health.

Grundy and Tomasini (2005) posited that delayed fertility may be associated with lower rates of morbidity and mortality owing to a selection effect: the ability to conceive at older ages may be indicative of slower aging and better overall health. This supposition may be the reason why the hazard is reduced for women with any AMA birth. Our finding that women in the sample with AMA first births had menopause onset at later ages than women with earlier births also supports this association. Both the work of Gundy and Tomasini and the present study are limited by use of an older cohort of women to examine the relationship between age at birth and future health. In the years since these cohorts had births, assisted reproductive technologies have improved and become much more widely used (Sunderman et al., 2019). As a result, women with AMA births may increasingly include women with subfertility or infertility who are able to conceive through use of medical interventions, altering the selection effect that previously limited later births to healthier women.

Women who gave birth in the NHS II cohort differ from current cohorts of women in other important ways. The rate of first births to women age 35 to 39 increased 78% between 1990 (when many women in the sample where in their reproductive years) and 2017 (Martin & Arafeh, 2018; Ventura, Hamilton, & Sutton, 2003). Findings from this study may not reflect current associations between pregnancy timing and future health. The tradeoff related to selection of an older cohort was necessary given the need for longitudinal data to assess the relationship between pregnancy timing and future health outcomes that do not typically occur until older ages. Delayed fertility has traditionally been associated with protective social factors and health behaviors, as many women delay childbearing for educational and employment reasons (Delbaere et al., 2007; Goisis, Remes, Barclay, Martikainen, & Myrskyla, 2017; Klemetti et al., 2016). This association also may be diminished as more women delay fertility for a variety of reasons, including waiting to be financially secure, and as rates of delayed fertility increase for groups who are traditionally at higher risk of CVD, including Black women and women with comorbidities. In fact, shifts to delayed fertility have been greatest among Black women in the past three decades (Lo, Mission, & Caughey, 2013), and births among older Black women are known to be at particularly high risk (Schempf, Branum, Lukacs, & Schoendorf, 2007). These trends are not accounted for in our data. We were further limited by the low number of Black women in the sample.

Other limitations are related to age of enrollment, which ranged from 25 to 42 years old. At the end of the follow-up period, the oldest participants were in their late 60s to early 70s, but the youngest participants were only in their early 50s. Many younger women in the cohort did not reach ages at which myocardial infarction and stroke are most likely to occur. In fact, we observed that fewer than 1% of participants born after 1960 had a CVD outcome by the end of the study period compared to more than 3% of women born before 1950. As a result, there is differential censoring by age at enrollment, with much of the variability in outcome limited to the oldest women in the study. Limited socioeconomic status data also constrained our full understanding of the role of social factors in interpreting the low risk of CVD for women with AMA first births.

Despite these limitations, this study is the first, to our knowledge, that comprehensively examined the relationship between age at birth and future risk for CVD. The large sample size and availability of confounders are key strengths.

Implications for Practice and/or Policy

We found no evidence that AMA at first or any birth increases a woman's risk for developing CVD later in life among the cohort of nurses in the NHS II. Additional research is needed with more diverse cohorts to confirm that there is no association among the general population or among women with underlying health problems.

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