ORIGINAL RESEARCH

Adolescent Childbirth Is Associated With Greater Framingham Risk Scores for Cardiovascular Disease Among Participants of the IMIAS (International Mobility in Aging Study)

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***Background*—**Previous studies observe associations between lifetime parity and cardiovascular disease, but relatively fewer investigate age at first childbirth (AFB). Herein, we examine the association of AFB with a summary cardiovascular risk measure (Framingham Risk Score [FRS]).

***Methods and Results*—**As part of the IMIAS (International Mobility in Aging Study), data were collected in 2012 among 1047 women, aged 65 to 74 years, from Canada, Albania, Colombia, and Brazil. FRSs were calculated to describe cardiovascular risk profiles, and linear regression analyses were performed, adjusting for early life and socioeconomic variables. Women with an AFB of <20 years were compared with women with an AFB of 20 to 24, 25 to 29, and ≥30 years, as well as nulliparous women. We also compared FRS between combinations of AFB and parity categories: nulliparous women, parity 1 to 3 combined with AFB <20 years, parity ≥4 with AFB <20 years, parity 1 to 3 with AFB ≥20 years, and parity ≥4 with AFB ≥20 years. Women with an AFB of <20 years had a higher mean FRS compared with all other AFB groups. Compared with the lowest AFB risk group (25–29 years), women with an AFB of <20 years had a 5.8-point higher mean FRS (95% confidence interval, 3.4–8.3 points). Nulliparous women presented the lowest mean FRS in all analyses. The analysis comparing combinations of AFB and parity categories showed no meaningful differences in FRS between women who had 1 to 3 childbirths and those who had ≥4 childbirths within the stratum of AFB <20 years, and in the stratum of AFB ≥20 years.

***Conclusions*—**Our analyses suggest that nulliparity and AFB, rather than increasing parity, drive the association with cardiovascular disease risk. **(*J Am Heart Assoc*. 2017;6:e007058. DOI: 10.1161/JAHA.117.007058.)**

Key Words: age at first birth • cardiovascular disease risk factors • epidemiology • Framingham Risk Scores • global health

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide.[1] Women's reproductive health is increasingly recognized as an important contributing factor to CVD risk.[2–6] Previous studies document associations of greater lifetime parity,[2,7] early age at menarche,[3,8] and early age at menopause[4] with CVD; however, findings are not always consistent.[9,10] Age at first childbirth (AFB) is much less studied. In this article, we focus on 2 aspects of women's reproductive health (AFB and parity) as determinants of CVD risk in an international sample of postmenopausal women.

Numerous studies observe associations between an early AFB, especially adolescent childbirth, and all-cause mortality,[11–14] and a few observe associations between AFB and CVD risk factors, CVD events, and CVD mortality.[6,15–18] Parity has been examined more thoroughly than AFB,[2,4,19–22] including as part of 2 systematic reviews on women's cardiovascular health.[4,19] In those studies reporting statistically significant associations, typically nulliparous and multiparous women are at greater risk of CVD.[4,19,21] Yet, AFB may confound observed associations between parity and CVD, because AFB is closely linked with parity.[18] Women with early AFB tend to have more children.[23,24] For example, in 1 study of middle-aged women from Brazil, those who gave birth as adolescents were twice as likely to have ≥3 children across

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Received June 30, 2017; accepted September 11, 2017.

Clinical Perspective

What Is New?

- To the best of our knowledge, this is the first study to demonstrate, in postmenopausal women from multiple global settings, that adolescent childbirth is related to greater overall cardiovascular risk, as measured by the Framingham Risk Score, compared with women who gave birth at later ages, and compared with nulliparous women.

What Are the Clinical Implications?

- Adolescent childbirth may serve as a cardiovascular disease risk marker; women who were adolescent mothers may benefit from earlier and increased cardiovascular screening to reduce the incidence of cardiovascular events.

their lifetimes compared with women whose first childbirth was during adulthood.[23]

AFB may influence CVD through pathways that range from the purely physiological to the social and behavioral.[15,17] On one end of the spectrum, pregnancy-related physiological changes may differ in adolescent compared with adult women.[25–29] For example, adolescent pregnant women may be exposed to physiological changes accompanying pregnancy, such as insulin resistance, that irreversibly influence cardiovascular health earlier in life. These changes contribute to longer exposure durations and, thus, greater overall CVD risk compared with women who have children later in life.[15,30] In addition, well-conducted prospective studies document greater weight gain and retention among pregnant adolescents compared with adult pregnant women, likely contributing to later-life obesity and cardiometabolic diseases.[25,26] On the other end of the spectrum, associations between AFB and CVD may be entirely social. The age at which a woman gives birth likely has long-lasting consequences on educational attainment, career opportunities, family relations, and family support.[31–33] The accumulation of adversities during a woman's life course potentially accelerates aging and increases metabolic and cardiovascular risk through mechanisms such as multisystem dysregulation (eg, greater allostatic load).[34,35]

By using data from the IMIAS (International Mobility in Aging Study), we investigate the relationship between self-reported AFB, lifetime parity, and the Framingham Risk Score (FRS), a summary measure of CVD risk. Because of previous research on lifetime parity and CVD, we aim to disassociate the effects of AFB from parity. This cohort of community-dwelling older adults is unique in that it allows for examination of the hypothesized association (ie, early childbirth is associated with greater CVD risk) in 5 diverse settings with widely differing levels of exposures and outcome.

Methods

The IMIAS

Data were collected as part of the IMIAS, a prospective cohort study of community-dwelling older adults, conducted at 5 sites: Tirana (Albania), Natal (Brazil), Manizales (Colombia), Kingston (Ontario, Canada), and Saint-Hyacinthe (Quebec, Canada). Albania, Colombia, and Brazil are considered middle-income countries and, on average, have lower educational attainment, lower human development indexes, and higher income and gender inequalities compared with Canada.[36]

The IMIAS cohort was established in 2012 and contains 2002 community-dwelling older adults, aged 65 to 74 years at the time of recruitment. Approximately 200 women were enrolled at each of the 5 sites. Participants with ≥4 errors on the orientation scale of the Leganes Cognitive Test, a screening tool for dementia in populations with low levels of education,[37,38] were excluded (0 in Kingston, 1 in Saint-Hyacinthe and Tirana each, 2 in Manizales, and 5 in Natal). These participants were excluded because they were likely unable to complete the study protocols. Of the 2002 participants recruited to IMIAS, 1047 are women.

Recruitment and Study Procedures

In Manizales, ≈82% of the older adults are covered in the public healthcare network, and the populations of Brazil, Albania, and Canada have universal healthcare coverage, facilitating affordable access to healthcare providers for most older adults. Because high proportions of older adults in these contexts are registered in the public health system, we recruited through primary care centers. In Tirana, Natal, and Manizales, participants were randomly selected from the population registered at neighborhood health centers and invited to participate in the study. Response rates were >90% in Tirana, Manizales, and Natal. Ethics' committees at the 2 Canadian universities did not allow direct contact with potential participants. Canadian participants were, thus, invited by a letter from their healthcare provider, encouraging them to contact our field coordinator if they were interested in participating in the study. In Saint-Hyacinthe and Kingston, 30% of the invited subjects contacted the field coordinator. Of them, 95% participated in the study. Comparisons of the population sampled in Canada with census data suggest that participants recruited in Saint-Hyacinthe are representative of the population of that city, whereas those in Kingston are slightly better educated than the general population of older adults of that city.

Unless otherwise requested, interviews were conducted at the participants' homes. Study questionnaires and supporting materials were available in all local languages and administered by interviewers who were trained according to the same

protocol and standards. Anthropometric measures and blood samples were also obtained at baseline. Blood samples were analyzed for several cardiovascular and metabolic biomarkers. Analyses were conducted at the Medical School University Hospital at Tirana (Tirana, Albania); Multilab Laboratory and Alvaro Laboratorios (Natal, Brazil); Caldas University Hospital (Manizales, Colombia); Kingston General Hospital (Kingston, Ontario, Canada); and the Honoré Mercier Hospital (Saint-Hyacinthe, Quebec, Canada). More details on the study sites, populations, and recruitment can be found in the study by Zunzunegui et al.[39] Of the 1047 women who participated in the IMIAS baseline data collection, cardiometabolic data from blood samples were available for 908 (87%). Complete data on all covariates included in this study (see measures below) were available for 892 women (85%), or 98% of those with FRS data.

Human Subjects

Institutional review for this project was obtained from the relevant organizations at each site: the Institute of Public Health in Albania, the Federal University of Rio Grande do Norte in Brazil, the University of Caldas in Colombia, the University of Montreal Hospital Research Centre, and Queen's University in Canada. Written informed consent was obtained from all participants.

Primary Outcome Measure

FRSs are based on the Framingham Heart Study, a long-term cardiovascular cohort study, ongoing in Framingham, MA.[40] Several FRSs have been developed to estimate the CVD, coronary heart disease, and stroke risk of an individual. We use 10-year laboratory-based CVD risk equations based on sex, age, systolic blood pressure, treatment for hypertension, total and high-density lipoprotein cholesterol, smoking, and diabetes mellitus status.[41]

Blood pressure was measured 3 times after at least 5 minutes of rest using a validated automated blood pressure device. The mean value of the second and third systolic blood pressure measurements was used to inform the Framingham equation. As part of the survey, participants were requested to show the interviewer all containers of medication that they used; these were recorded. A participant was considered to be taking antihypertensive medication when either antihypertensive medication was presented or the participant self-reported using antihypertensive medication. Cholesterol and glycosylated hemoglobin measures were obtained through a blood sample collected by a trained phlebotomist. Participants were considered to have diabetes mellitus based on a high glycosylated hemoglobin level (≥6.5%),[42] antidiabetic medication, and/or self-reported diabetes mellitus. The latter was determined by an affirmative response to the question "Has a physician or nurse ever told you that you have diabetes mellitus (ie, high blood glucose levels)?" Smoking and age were self-reported.

Exposure Variables

AFB and parity were self-reported. We operationalized AFB into 5 categories: <20 years, 20 to 24 years, 25 to 29 years, ≥30 years, and nulliparous women. Most studies examining AFB and CVD events have defined their youngest age group as <20 years.[6,18] Because we hypothesize that younger AFB is associated with greater CVD risk, we treated AFB <20 years as the reference group. To dissociate between AFB and parity when examining the association with FRS, we additionally conducted analyses in which we compared FRS according to combinations of AFB and parity categories. We categorized women into 5 groups: nulliparous women, parity 1 to 3 combined with AFB <20 years, parity ≥4 combined with AFB <20 years, parity 1 to 3 combined with AFB ≥20 years, and parity ≥4 combined with AFB ≥20 years. These parity categories were selected on the basis of previous work suggesting that parity is associated with CVD in a J-shaped manner, with the lowest risk observed among women with 2 births.[21]

Covariates

Age and study site

The trained interviewer recorded these data.

Childhood social and economic adversity

On the basis of a previous validation study with the IMIAS data,[43] a participant was considered to have experienced childhood social adversity if she reported parental alcohol or drug abuse, witnessing physical violence in the family, and/or physical abuse during childhood. A participant was considered to have experienced childhood economic adversity if she reported poor economic status, hunger, or unwanted parental unemployment. Childhood adversities were self-reported and pertained to the first 15 years of life.[43]

Education and income

Educational level was categorized into tertiles (low, medium, and high) of self-reported years of education. Because of the large difference in years of education between the research sites, these tertiles were determined site specifically as follows: Kingston, <15, 15 to 17, and ≥18 years; Saint-Hyacinthe, <11, 11 to 12, and ≥13 years; Tirana, <8, 8 to 12, and ≥13 years; and Latin American sites, <4, 4 to 5, and ≥6 years. Participant income level was site specific and classified

into 3 categories (poor, middle, and middle high/high), as follows: Canadian sites, annual income of <20 000, 20 000 to 40 000, >40 000 CAD; Latin American sites, monthly income of <1 minimum salary, 1 minimum salary, and ≥2 minimum salaries; and Albania, annual income of <1000, 1000 to 2000, and ≥2000 USD.

Statistical Analyses and Conceptual Framework

We explored the population characteristics of the sample with descriptive statistics. In bivariate analyses, we used 2-sample independent *t* tests for dichotomous variables and ANOVA for polytomous variables to examine associations between population characteristics and FRS.

Figure 1 depicts our conceptual framework with relevant citations supporting each arrow in the model.[6,15–17,44–52] Directed acyclic graphs were used to establish the minimum confounders required for the multivariate analyses. With linear regression models, we examined the covariate-adjusted associations between AFB, parity, and FRS. The models were built in a step-wise manner based on our conceptual framework. Accordingly, participant age and study site were considered as confounders in all models. Childhood social and economic adversities were included as dichotomous variables in the second model, whereas educational level and income were added to the third model. We consider the covariates added in the first 2 models as likely confounders. The third model is exploratory. The covariates added in the last model may confound the association between AFB and CVD risk, but may also be on the pathway between AFB and CVD risk, in which case their inclusion in the model would entail overadjustment. For example, an environment with lower educational opportunities may predispose women to have children at a young age. At the same time, having a child at a young age may also influence future educational and professional opportunities. In the analyses of the combined AFB and parity categories, we statistically adjust only for the likely confounders (age, study site, and childhood adversities) because the third model is more exploratory.

Finally, sensitivity analyses were conducted to assess the robustness of our findings, because not all study participants agreed to have laboratory measures taken. For 139 women, we could not calculate a 10-year CVD score using the laboratory FRS equations. We, thus, ran an analysis with the office-based FRS, using body mass index (height and weight were measured in the study) instead of cholesterol measures and self-reported diabetes mellitus or presence of antidiabetic medication in lieu of glycosylated hemoglobin level. Data for these analyses were available for 1039 participants (99% of IMIAS women). We also examined AFB according to whether the participant did or did not have laboratory data; there were no significant differences according to missingness.

Regression diagnostics were performed to examine the validity of all linear regression models. This included performing log-transformed analyses because of the right-skewed distribution of the FRS. Data were analyzed with Stata, version 14.

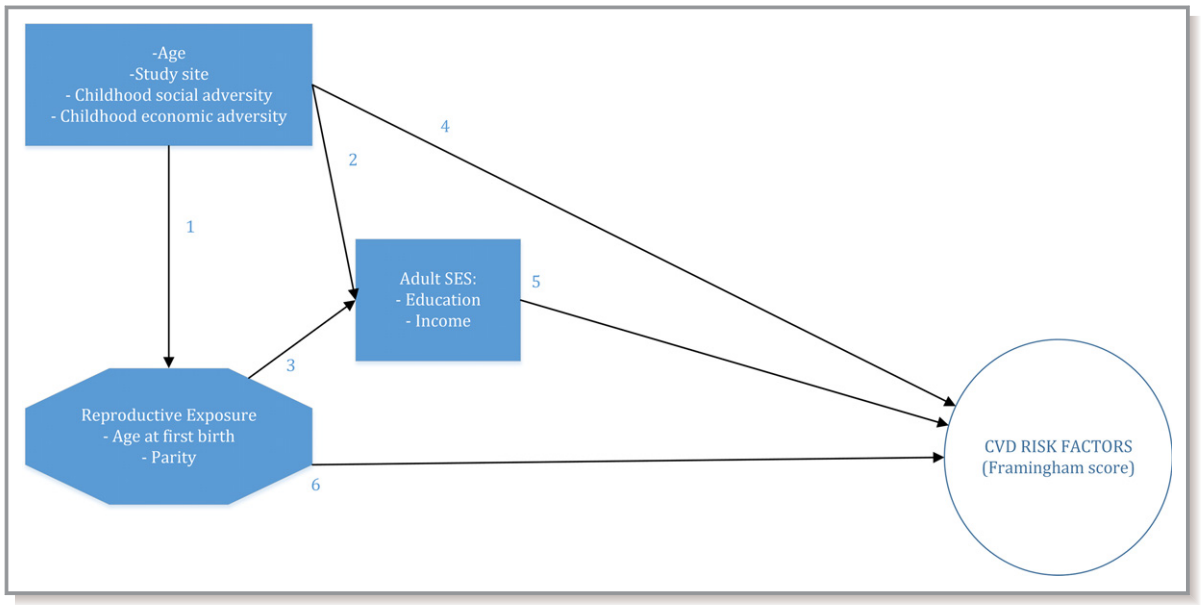

Figure 1. Conceptual framework. The references corresponding to each arrow (a previously published association) are indicated as follows: (1) references 45 and 46; (2) reference 45; (3) reference 45; (4) references 47 to 50; (5) references 44, 51, and 52; and (6) references 6 and 15 to 17. AFB indicates age at first childbirth; CVD, cardiovascular disease; FRS, Framingham Risk Score; and SES, socioeconomic status.

Results

Sample Characteristics

Table 1 presents the participant characteristics according to AFB categories. Adolescent childbirth was much more prevalent in the Latin American study sites compared with the Albanian and Canadian sites. Of the 188 women who reported a first childbirth at <20 years old, 68.1% were from the Latin American sites. Women who were <20 years old at first childbirth had an overall higher prevalence of childhood economic and social adversity when compared with older AFB categories, especially the 25 to 29 years category. Young AFB women tended to have lower educational attainment and more often fell into the low-income category. Women with a young AFB were also more likely to have given birth to ≥4 children (75.5%, compared with 37.6% of women with an AFB of 20–24 years, 13.1% of women with an AFB of 25–29 years, and 5.4% of women with an AFB of ≥30 years).

FRS by Sample Characteristics

The average FRS was 19.5 (SD, 13.1), with the lowest mean in Kingston and the highest mean in Tirana. Higher mean FRS scores indicate greater CVD risk. Older ages, childhood economic adversity, low education, younger AFB, and higher parity were significantly associated with higher mean FRS. No

Table 1. Distribution (or Means) of Sample Characteristics by AFB (N=905)*

Characteristics	AFB, y				Nulliparous Women (N=100)
	<20 (N=188)	20–24 (N=355)	25–29 (N=169)	≥30 (N=93)	
Study site, N (%)					
Kingston (Ontario, Canada)	23 (12.2)	48 (13.5)	49 (29.0)	27 (29.0)	25 (25.0)
Saint-Hyacinthe (Quebec, Canada)	11 (5.9)	71 (20.0)	54 (32.0)	18 (19.4)	28 (28.0)
Tirana (Albania)	26 (13.8)	106 (29.9)	32 (18.9)	11 (11.8)	13 (13.0)
Manizales (Colombia)	75 (39.9)	71 (20.0)	18 (10.7)	17 (18.3)	17 (17.0)
Natal (Brazil)	53 (28.2)	59 (16.6)	16 (9.5)	20 (21.5)	17 (17.0)
Age, mean (SD), y	69.2 (2.9)	69.1 (2.9)	69.3 (2.8)	68.9 (2.7)	68.8 (2.7)
Childhood economic adversity, N (%)†					
No	92 (48.9)	192 (54.1)	109 (64.9)	51 (54.8)	61 (61.0)
Yes	96 (51.1)	163 (45.9)	59 (35.1)	42 (45.2)	39 (39.0)
Childhood social adversity, N (%)†					
No	126 (67.0)	267 (75.2)	128 (76.2)	70 (75.3)	81 (81.0)
Yes	62 (33.0)	88 (24.8)	40 (23.8)	23 (24.7)	19 (19.0)
Education site specific, N (%)‡					
Low	114 (60.6)	144 (40.6)	53 (31.4)	27 (29.0)	34 (34.0)
Medium	54 (28.7)	129 (36.3)	56 (33.1)	28 (30.1)	31 (31.0)
High	20 (10.6)	82 (23.1)	60 (35.5)	38 (40.9)	35 (35.0)
Income, N (%)§					
Poor	81 (43.6)	115 (32.7)	57 (34.3)	28 (31.1)	30 (30.3)
Middle	85 (45.7)	168 (47.7)	73 (44.0)	41 (45.6)	44 (44.4)
High	20 (10.8)	69 (19.6)	36 (21.7)	21 (23.3)	25 (25.3)
Parity, N (%)‖					
Nulliparous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	100 (100.0)
1–3	46 (24.5)	221 (62.4)	146 (86.9)	88 (94.6)	0 (0.0)
≥4	142 (75.5)	133 (37.6)	22 (13.1)	5 (5.4)	0 (0.0)

AFB indicates age at first childbirth.
*AFB is missing for 3 participants.
†One missing value.
‡Site specific, for women only (no laboratory included).
§Twelve missing values.
‖Two missing values.

Table 2. FRS by Sample Characteristics (N=908)

Characteristics	N	Mean	SD	*P* Value
Study site				
Kingston (Ontario, Canada)	172	13.7	8.2	<0.001
Saint-Hyacinthe (Quebec, Canada)	183	14.3	8.3	
Tirana (Albania)	188	27.7	14.4	
Manizales (Colombia)	198	18.0	10.8	
Natal (Brazil)	167	23.6	16.1	
Age in 2 categories, y				
64–69	498	17.6	11.9	<0.001
70–74	410	21.8	14.1	
Childhood economic adversity*				
No	507	18.5	12.7	0.012
Yes	400	20.7	13.6	
Childhood social adversity*				
No	674	19.7	13.5	0.546
Yes	233	19.0	11.9	
Education site specific†				
Low	372	21.0	13.5	<0.001
Medium	301	20.2	14.1	
High	235	16.2	10.3	
Income‡				
Poor	313	18.5	12.1	0.218
Middle	412	20.2	13.5	
High	171	19.7	14.1	
AFB, y§				
<20	188	23.2	14.9	<0.001
20–24	355	20.8	13.8	
25–29	169	16.3	10.5	
≥30	93	17.7	11.7	
Nulliparous	100	14.8	9.0	
Parity‖				
Nulliparous	100	14.8	9.0	<0.001
1–3	501	19.0	12.5	
≥4	302	21.8	14.6	

AFB indicates age at first childbirth; and FRS, Framingham Risk Score.
*One missing value.
†Site specific, for women only.
‡Two missing values.
§Three missing values.
‖Five missing values.

large differences in FRS were observed between individuals with or without childhood social adversities or between individuals with current low, middle, or high incomes in the bivariate analyses (Table 2).

AFB and FRS

Table 3 presents the results of the multivariate models based on our conceptual model. Young AFB was positively associated with FRS. Statistically adjusting for age, study site, and childhood adversities, women with an AFB of <20 years had 3.1 points higher mean FRS (95% confidence interval [CI], 1.0–5.3) compared with women with an AFB of 20 to 24 years, 5.6 points higher mean FRS (95% CI, 3.1–8.2) compared with women with an AFB of 25 to 29 years, 3.9 points higher mean FRS (95% CI, 1.0–6.8) compared with women with an AFB of ≥30, and 6.7 points higher mean FRS (95% CI, 3.8–9.6) compared with nulliparous women (model 2) (Table 3). The association was only slightly attenuated in model 3, although the sample size also decreased. The results of model 3 are visually presented in Figure 2.

The association between AFB and FRS differed by study site (Table 4). For the Canadian sites, adjusting for age, study site, and childhood adversities, women with an AFB of <20 years had a higher mean FRS compared with all other groups, but only significantly so when compared with women with an AFB of ≥30 years (3.7 points; 95% CI, 0.1–7.3 points). Young AFB was strongly associated with higher FRS in Natal; compared with women with an AFB of 25 to 29 years, women with an AFB of <20 years had 11.5 (95% CI, 3.1–19.9) points higher mean FRS. In Tirana, we observed a J-shaped association: those with an AFB of <20 years had 8.7 (95% CI, 1.4–16.0) points higher mean FRS compared with those with an AFB of 25 to 29 years, but 2.6 (95% CI, −12.5 to 7.4) points lower mean FRS compared with those with an AFB of ≥30 years. In both Tirana and Natal, mean FRS scores of the AFB <20 years group were also high compared with the nulliparous category (9.8 points in Tirana and 16.3 points in Natal; $P<0.01$). For Manizales, women with a young AFB had a higher FRS compared with the other groups, but this difference was small and not statistically significant.

Parity, AFB, and FRS

Table 5 presents results for the combined AFB and parity categories, compared with nulliparous women, adjusted for study site, age, and childhood adversities. Although all parous groups have a higher mean FRS compared with nulliparous women, the difference between those with low parity (1–3) and high parity (≥4) is small when we examine across equal AFB groups (0.2 points in the 2 AFB ≥20 groups and 1.1 in the 2 AFB <20 groups). In contrast, there is a stark difference in mean FRS between the <20 versus ≥20 years AFB groups when we examine across equal parity categories. In the 1 to 3 parity category, women with an AFB of <20 years had 3.1 points higher mean FRS compared with women with an AFB of ≥20. In the ≥4 parity category, the difference between the 2 AFB groups is 4.0 points (Table 4).

Table 3. Linear Regression Models Presenting the Association of AFB With FRSs, Progressively Adjusting for Childhood and Adulthood Socioeconomic Risk Covariates

	Age and Site Only (Model 1)			Age, Site, and Childhood Adversities (Model 2)			Age, Site, Childhood Adversities, Education, and Income (Model 3)		
Variable	(N=905)			(N=904)			(N=892)		
Categories of AFB, y									
<20	Ref			Ref			Ref		
20–24	−3.15	−5.26	−1.03	−3.14	−5.26	−1.01	−2.92	−5.09	−0.76
25–29	−5.64	−8.19	−3.10	−5.63	−8.19	−3.07	−5.29	−7.93	−2.65
≥30	−3.91	−6.84	−0.99	−3.90	−6.84	−0.96	−3.12	−6.15	−0.08
Nulliparous	−6.67	−9.55	−3.79	−6.65	−9.55	−3.75	−6.19	−9.15	−3.23
Age (centered), y	0.89	0.62	1.16	0.89	0.62	1.16	0.89	0.61	1.16
Research site									
Kingston (Ontario, Canada) (ref)	Ref			Ref			Ref		
Saint-Hyacinthe (Quebec, Canada)	1.44	−0.99	3.87	1.42	−1.02	3.86	1.74	−0.83	4.32
Tirana (Albania)	13.53	11.09	15.98	13.57	11.09	16.06	14.09	11.53	16.64
Manizales (Colombia)	2.76	0.31	5.20	2.76	0.31	5.21	2.90	0.29	5.51
Natal (Brazil)	8.69	6.16	11.21	8.72	6.16	11.29	9.37	6.70	12.03
Childhood economic adversity (no=ref)				−0.19	−1.81	1.42	−0.34	−1.98	1.31
Childhood social adversity (no=ref)				0.20	−1.61	2.01	0.12	−1.70	1.95
Education site specific									
Low (ref)							Ref		
Medium							−0.30	−2.14	1.53
High							−2.40	−4.48	−0.33
Income									
Poor (ref)							Ref		
Middle							−1.76	−3.64	0.12
High							0.09	−2.34	2.52
Constant	17.61			17.62			18.60		

Data are given as B (95% confidence interval). AFB indicates age at first childbirth; FRS, Framingham Risk Score; and Ref, reference.

Sensitivity Analysis

The sensitivity analysis using the office-based FRS yielded results that were consistent with the results of the laboratory-based FRS (Table 6); women <20 years at first childbirth had the greatest mean FRS across all models. We also performed a log-transformed analysis because of the right-skewed nature of the FRS measure, and these analyses yielded similar results, with slightly different effect sizes. For ease of interpretation, we only present the nontransformed model (log-transformed results are available on request).

Discussion

To the best of our knowledge, this is the first study to demonstrate, in postmenopausal women from multiple global settings, that adolescent childbirth is related to higher mean cardiovascular risk, as measured by FRS, compared with women who gave birth at later ages, and compared with nulliparous women. This association remained even after statistical adjustment for socioeconomic variables that may be on the pathway between AFB and FRS. Nulliparous women had the lowest average FRS. Among parous women, women with an AFB of 25 to 29 years had the lowest average FRS.

We also attempted to dissociate parity from AFB in examining the association with CVD risk. The analyses in which we used combination categories of AFB and parity allowed us to investigate differences related to parity for women in the same AFB category, and differences related to AFB for women in the same parity category. We observed small differences between women with a parity of 1 to 3 compared with women with a parity of ≥4 within equivalent

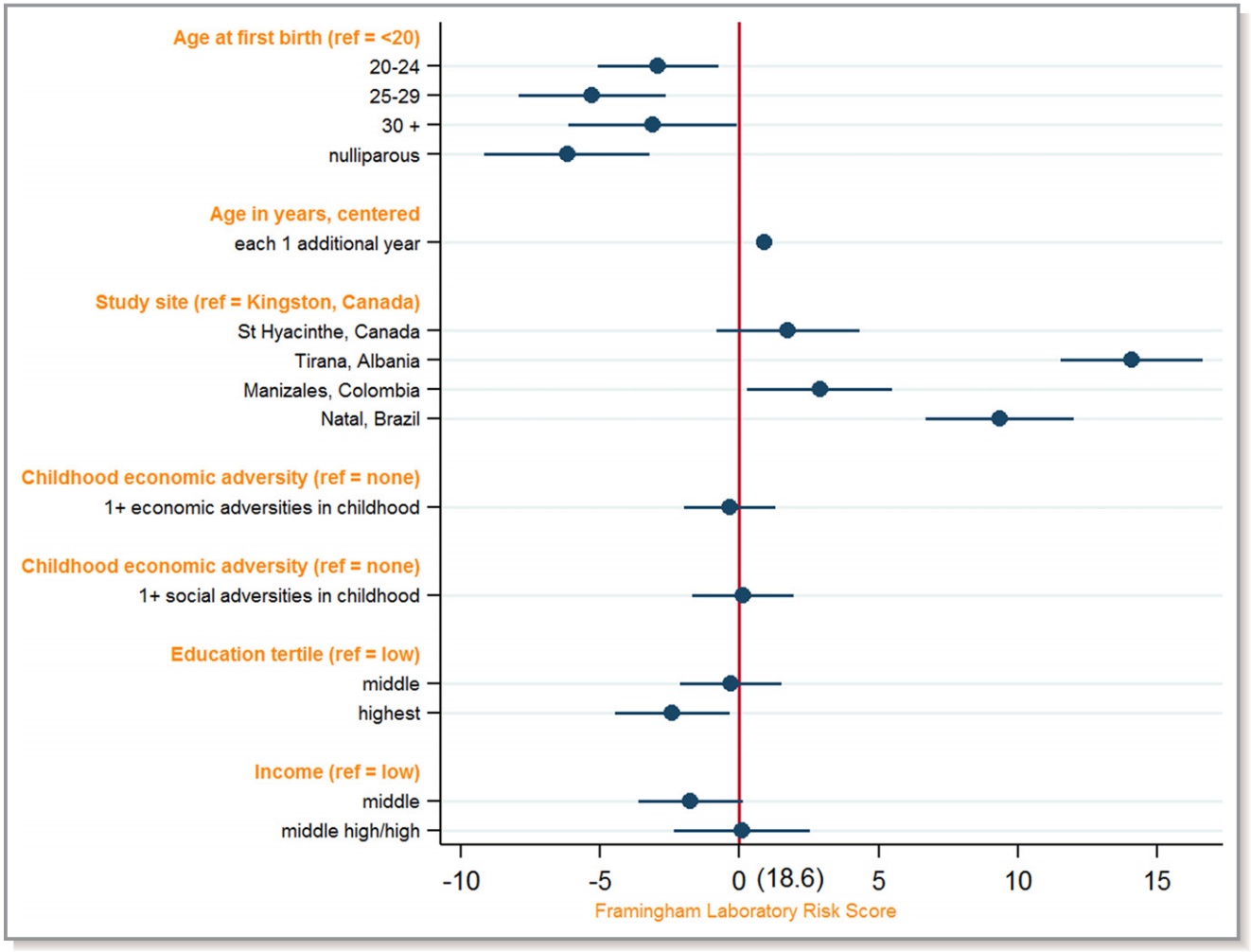

Figure 2. Association of age at first childbirth (AFB) and Framingham Risk Score (FRS); visualization of model 3 is displayed in Table 3. N=892. Ref indicates reference.

AFB categories. We observed large differences between women with an AFB of <20 years compared with women with an AFB of ≥20 years within the same parity categories. All 4 AFB/parity categories had a higher mean FRS when compared with nulliparous women, suggesting that both AFB and nulliparity, but not increasing parity, drives the association with FRS.

Comparison With Other Studies

This is the first study to examine the association between adolescent childbirth and FRS as a measure of cardiovascular risk. As a result, we cannot compare our results with other studies examining the same outcome. Instead, we can compare our results with a limited number of studies examining the association between AFB and other CVD (risk) outcomes. Other studies observed positive associations with young AFB and overweight status,[44] high blood pressure,[16,53,54] and diabetes mellitus–related mortality.[55] In previous work using IMIAS data, we reported statistically significant associations between AFB ≤18 years and participant-reported physician-diagnosed high blood pressure (odds ratio, 2.1) and diabetes mellitus (odds ratio, 1.9), and a marginal association with stroke (odds ratio, 1.9; *P*=0.06).[24] Of 3 studies[56–58] analyzing AFB and metabolic syndrome, another summary measure of CVD that includes many of the components that are also accounted for in the FRS, 2 observed a positive association of young AFB with metabolic syndrome.[56,57] In a recent analysis of the 1958 British birth cohort study, the authors observed a relationship between adolescent childbirth and many metabolic parameters assessed individually: higher body mass index, waist:hip ratio, blood pressure, triglycerides, glycosylated hemoglobin, and lower high-density lipoprotein cholesterol.[6] Finally, we recently conducted a systematic review on AFB and CVD events and mortality. The study findings were relatively consistent when young AFB was defined as 20 years or younger and pointed towards increased risk for CVD for women with a young AFB.[18]

Table 4. Linear Regression Models Presenting the Association of AFB With FRS by Study Site, Adjusting for Childhood Socioeconomic Risk Covariates

Variable	Canadian Sites (N=353)			Tirana (Albania) (N=188)			Manizales (Colombia) (N=198)			Natal (Brazil) (N=165)		
Categories of AFB, y												
<20	Ref			Ref			Ref			Ref		
20–24	−1.43	−4.55	1.70	−1.14	−7.23	4.96	−0.82	−4.35	2.71	−10.42	−15.93	−4.91
25–29	−2.91	−6.08	0.26	−8.69	−16.02	−1.37	−0.97	−6.56	4.61	−11.47	−19.88	−3.06
≥30	−3.71	−7.31	−0.11	2.58	−7.39	12.55	−1.37	−7.12	4.37	−8.02	−15.65	−0.40
Nulliparous	−3.47	−7.00	0.06	−9.83	−19.25	−0.41	−2.33	−8.09	3.42	−16.33	−24.51	−8.16
Age (centered), y	0.59	0.26	0.92	0.90	0.21	1.58	0.72	0.21	1.22	2.15	1.29	3.00
Research site (Kingston [Ontario, Canada]=ref)*	0.97	−0.75	2.70									
Childhood economic adversity (no=ref)	0.05	−1.81	1.91	−1.16	−5.34	3.02	0.20	−3.10	3.49	1.11	−3.79	6.01
Childhood social adversity (no=ref)	1.76	−0.16	3.69	−0.05	−6.12	6.03	−0.58	−4.36	3.20	−2.32	−7.12	2.48
Constant	15.40			30.95			18.61			30.88		

Data are given as B (95% confidence interval). AFB indicates age at first childbirth; FRS, Framingham Risk Score; and Ref, reference.
*Only for Canadian site analysis. Coefficient shown is for Saint-Hyacinthe (Quebec, Canada).

In our analysis that compared combination categories of AFB and parity, we found an association between FRS and AFB, and between FRS and nulliparity, but not between FRS and greater lifetime parity. Although we do not know of any other studies that examined parity in relation to FRS, 10 studies[57–66] have examined associations between parity and metabolic syndrome. Nine studies[58–66] observed a positive association between parity and metabolic syndrome. Of these 9 studies, 5[59–61,64,66] did not adjust for the participants' AFB. AFB is closely linked with parity[23,24]; by not adjusting for AFB, differences in FRS may mistakenly be attributed to parity when, in fact, AFB is driving the association. The results from our analyses, in which we report on associations within strata of parity and AFB, suggest that it is AFB, and not increasing parity, that is associated with FRS. The 4 remaining studies[58,62,63,65] that still observed a positive association between parity and metabolic syndrome all adjusted for AFB, but as a continuous linear variable. This may result in residual confounding by AFB if there is a reverse J-shaped association of AFB and CVD risk.

Table 5. Linear Regression Model Presenting the Association of Combinations of AFB and Parity Categories With FRSs

Variable	B	95% CI	
Parity and age			
Nulliparous (N=100)	Ref		
Parity 1–3, AFB <20 y (N=46)	5.74	1.66	9.82
Parity ≥4, AFB <20 y (N=142)	6.82	3.71	9.93
Parity 1–3, AFB ≥20 y (N=455)	2.62	0.08	5.15
Parity ≥4, AFB ≥20 y (N=160)	2.78	−0.22	5.77
Age (centered), y	0.88	0.60	1.15
Research site			
Kingston (Ontario, Canada) (ref)	Ref		
Saint-Hyacinthe (Quebec, Canada)	1.46	−0.97	3.89
Tirana (Albania)	13.87	11.43	16.32
Manizales (Colombia)	3.03	0.50	5.57
Natal (Brazil)	8.93	6.27	11.59
Childhood economic adversity (no=ref)	−0.07	−1.69	1.56
Childhood social adversity (no=ref)	0.25	−1.56	2.06
Constant	10.78		

N=903. AFB indicates age at first childbirth; CI, confidence interval; FRS, Framingham Risk Score; and Ref, reference.

Mechanisms

Pregnancy has been described as a physiological "stress" test.[67] Although some of the nulliparous women in our sample may have miscarried or terminated pregnancies, as a group, they would have experienced dramatically lower mean levels of pregnancy-related complications and no, or much shorter, durations of stress tests on the body. These findings potentially explain the lower mean FRSs observed in the nulliparous group. Common pregnancy complications, such as gestational diabetes mellitus and hypertensive disorders, may

Table 6. Linear Regression Models Presenting the Association of AFB With Office-Based FRSs, Progressively Adjusting for Childhood and Adulthood Socioeconomic Risk Covariates

Variable	Age and Site Only (N=1039)			Age, Site, and Childhood Adversities (N=1038)			Age, Site, Childhood Adversities, Education, and Income (N=1022)		
Categories of AFB, y									
<20	Ref			Ref			Ref		
20–24	−2.34	−4.65	−0.03	−2.21	−4.53	0.11	−1.89	−4.26	0.48
25–29	−5.41	−8.14	−2.68	−5.14	−7.88	−2.40	−4.57	−7.42	−1.73
≥30	−3.48	−6.67	−0.29	−3.30	−6.49	−0.10	−2.44	−5.75	0.88
Nulliparous	−7.14	−10.31	−3.95	−6.83	−10.02	−3.64	−6.31	−9.60	−3.02
Age (centered), y	1.22	0.92	1.52	1.22	0.93	1.52	1.22	0.92	1.52
Research site									
Kingston (Ontario, Canada) (ref)	Ref			Ref			Ref		
Saint-Hyacinthe (Quebec, Canada)	1.99	−0.62	4.61	1.93	−0.69	4.56	2.63	−0.18	5.43
Tirana (Albania)	11.87	9.23	14.51	11.89	9.21	14.58	12.34	9.56	15.12
Manizales (Colombia)	−0.01	−2.69	2.68	0.05	−2.64	2.74	0.53	−2.36	3.42
Natal (Brazil)	9.92	7.28	12.56	9.58	6.89	12.28	10.26	7.44	13.08
Childhood economic adversity (no=ref)				0.90	−0.89	−2.68	0.61	−1.21	2.43
Childhood social adversity (no=ref)				1.36	−0.62	3.34	1.35	−0.66	3.35
Education site specific*									
Low (ref)							Ref		
Medium							−1.38	−3.39	0.64
High							−3.11	−5.38	−0.83
Income									
Poor (ref)							Ref		
Middle							−1.18	−3.28	0.92
High							1.16	−1.51	3.83
Constant	22.37			21.54			22.45		

Data are given as B (95% confidence interval). AFB indicates age at first childbirth; FRS, Framingham Risk Score; and Ref, reference.
*Site specific, for women only (no laboratory included).

reveal latent chronic disease or initiate a cascade of pathophysiological processes contributing to CVD.[68] Preeclampsia, in particular, may be associated with increased later-life risk of CVD.[69] Meta-analysis on the topic reports that women who experienced preeclampsia have nearly 3 times the risk of developing hypertension later in life and approximately double the risk of cardiovascular and cerebrovascular events.[69] It is unclear whether preeclampsia represents an independent causal risk factor for CVD by inducing systematic endothelial damage that manifests later in life or whether preeclampsia and CVD share a common underlying risk factor.[69] Early childbearing is a risk factor for preeclampsia.[70] Preeclampsia may, therefore, be on the pathway between early childbearing and CVD risk later in life.

Our findings warrant future research investigating the pathways that may explain the observed associations. Selection mechanisms, and mediation through physiological and social pathways, could explain the observed association between AFB and FRS. There may be unobserved characteristics in childhood and puberty, such as a risk-seeking personality that "selects" women into both adolescent pregnancies and risky health behaviors; these negatively influence lifetime cardiovascular health.[33,71] Alternatively, or in combination, greater gain and retention of body weight, fewer career opportunities, higher stress levels, preeclampsia and other pregnancy complications, smaller social networks, and less social support are examples of possible mediators between early AFB and higher FRSs.[25,26,31–33,69] The lack of a uniform association across the study sites supports the possibility of social factors mediating the observed associations. Possibly, different familial, social, and governmental support across study sites may alter the association between AFB and FRS.

Limitations

Study participants were asked to report retrospectively about the reproductive exposures of AFB and parity, which may have introduced recall bias. However, both are major life events that are unlikely to have been forgotten. Furthermore, all study participants passed the orientation scale of the Leganes cognitive test for dementia, limiting the possibility that cognitive decline influenced recall.[37,38] More important, selective survival may have influenced our results, likely reducing the strength of association observed.[72–74] If exposure of early AFB is associated with higher CVD risk, a larger proportion of high-risk individuals may have "selected out" of the sample by not surviving to recruitment. Sampled women were between 64 and 75 years; in places like Natal, Brazil, these women have nearly doubled their life expectancy at birth.[74]

The FRS equation that we used is typically used to predict 10-year CVD risk in a clinical setting for individual patients with no CVD diagnosed. Our analyses examining the association of AFB, parity, and cardiovascular risk, measured by FRS, used a sample that contained participants with and without CVD. We are not unique in using the FRS as a composite measure of CVD risk; a similar approach was also taken by the CARMELA (Cardiovascular Risk Factor Multiple Evaluation in Latin America) study when assessing prevalent cardiovascular risk in a population of ≈11 500 participants from 7 Latin American cities.[75] Although it is inappropriate to interpret the FRSs obtained in these analyses for prediction purposes, the FRS does provide a useful and elegant composite measure of the classic risk factors for CVD. Finally, laboratory-based FRSs were not available for 13% of the women who participated in the study. However, the sensitivity analyses with office-based FRS, which were available for >99% of study participants, revealed markedly similar results.

Conclusions

Adolescent childbirth was frequent in our sample of older adults, especially among those from Latin America. Adolescent childbearing remains an issue of global importance, with an estimated 11% of births worldwide occurring among adolescents.[76] Besides the known risks of adolescent childbirth (eg, delivery complications and stillbirth),[76] our study suggests that young AFBs are associated with long-term CVD risk. As highlighted above, more work is needed to carve out the pathways by which AFB is associated with CVD. Although we cannot accredit causal inference, at the least, young AFB can serve as a risk marker. Identification of this higher-risk group could prove useful for clinicians, because women who were adolescent mothers may benefit from earlier and increased cardiovascular screening to reduce the incidence of CVD events. The clear dissociation of AFB and elevated parity in the association with CVD suggests that nulliparity and AFB, rather than increasing parity, drive the association with CVD risk. This finding provides a possible explanation for the conflicting results that have been reported in the literature to date on parity and CVD.

Acknowledgments

We thank Dr Maria-Victoria Zunzunegui for critical review of the article and the entire IMIAS (International Mobility in Aging Study) research team, without whom this study would never have been possible.

Sources of Funding

This study was supported by the Canadian Institutes of Health Research and by the Fogarty International Center of the National Institutes of Health (award R21TW010466). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Canadian Institutes of Health Research.

Disclosures

None.

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J Am Heart Assoc. 2017;6:e007058; originally published November 1, 2017;
doi: 10.1161/JAHA.117.007058
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980