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FULL RESEARCH PAPER
CVD Risk Factors

Parental cardiovascular health predicts time to onset of cardiovascular disease in offspring

James M. Muchira [1,2]*, Philimon N. Gona[2], Mulubrhan F. Mogos[1], Eileen Stuart-Shor[2,3], Suzanne G. Leveille[2,3,4], Mariann R. Piano[1] and Laura L. Hayman[2,5]

[1]Center for Research Development and Scholarship, Vanderbilt University, School of Nursing, 461 21st Ave S, Nashville, TN 37240, USA; [2]College of Nursing and Health Sciences, University of Massachusetts Boston, 100 William T Morrissey Blvd, Boston, MA 02125, USA; [3]Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215, USA; [4]Harvard Medical School, 25 Shattuck St, Boston, MA 02115, USA; and [5]Division of Preventive & Behavioral Medicine, Department of Population & Quantitative Health Sciences, UMass Medical School, 368 Plantation Street, Worcester, MA 01605, USA

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Background Cardiovascular disease (CVD) risk factors are transmitted from parents to children. We prospectively examined the association between parental cardiovascular health (CVH) and time to onset of CVD in the offspring.

Methods and results The study consisted of a total of 5967 offspring–mother–father trios derived from the Framingham Heart Study. Cardiovascular health score was defined using the seven American Heart Association's CVH metrics attained at ideal levels: poor (0–2), intermediate (3–4), and ideal CVH (5–7). Multivariable-adjusted Cox proportional hazards regression models, Kaplan–Meier plots, and Irwin's restricted mean were used to examine the association and sex-specific differences between parental CVH and offspring's CVD-free survival. In a total of 71 974 person-years of follow-up among the offspring, 718 incident CVD events occurred. The overall CVD incidence rate was 10 per 1000 person-years [95% confidence interval (CI) 9.3–10.7]. Offspring of mothers with ideal CVH lived 9 more years free of CVD than offspring of mothers with poor CVH ($P < 0.001$). Maternal poor CVH was associated with twice as high hazard of early onset of CVD compared with maternal ideal CVH (adjusted Hazard Ratio 2.09, 95% CI 1.50–2.92). No statistically significant association was observed in the hazards of CVD-free survival by paternal CVH categories.

Conclusions We found that offspring of parents with ideal CVH had a greater CVD-free survival. Maternal CVH was a more robust predictor of offspring's CVD-free survival than paternal CVH, underscoring the need for clinical and policy interventions that involve mothers to break the intergenerational cycle of CVD-related morbidity and mortality.

Keywords Parents • Ideal cardiovascular health • Offspring • Cardiovascular disease • Survival

Introduction

Accumulating evidence from epidemiologic and experimental studies has supported the importance of both genomic and non-genomic intergenerational effects of parental health on offspring health.[1,2] However, non-genomic intergenerational effects on offspring's life expectancy as well as time to the onset of cardiovascular disease (CVD) is not well understood. Life expectancy in the USA has not exceeded 78.9 years since 2010 and is projected to have the lowest gains by 2030 compared to other developed countries due to CVD-related mortality.[3–5] To address the increasing morbidity and premature mortality from CVD and stroke, the American Heart Association (AHA) recommends that individuals attain ideal cardiovascular health (CVH) defined as the simultaneous presence of four ideal modifiable health behaviours [not smoking, normal body mass index (BMI), healthy diet, and being physically active] and three ideal health factors (normal blood pressure, cholesterol, and blood glucose).[6] Adhering to a healthy lifestyle such as engaging in physical activity, maintaining normal weight, and not smoking reduces the risk of CVD, increases the number of years lived free of CVD and life expectancy.[7–9]

* Corresponding author. Tel: +1-615-343-9878, Email: james.muchira@vanderbilt.edu

Studies have shown that cardiovascular risk factors are transmitted from parents to children via multiple mechanisms that involve genetic and shared-environmental (non-genomic) transmission across generations.[9,10] It is also known that CVD risk factors such as obesity, smoking, diabetes, and elevated blood pressure aggregate in families and are transmitted from parents to offspring.[11–15] Evidence also suggests that offspring of parents with longer lifespans are more likely to have lower CVD risk and longer life expectancy;[16] and that maternal exposures to deleterious health effects are transmitted to the offspring during the fetal life.[17–19] Therefore, we hypothesized that (i) offspring of parents with ideal CVH will have longer CVD-free survival regardless of offspring's sex and educational level and (ii) compared to paternal CVH, maternal CVH will have stronger positive association with offspring's CVD-free survival.

Methods

Study population and design

Using the Framingham Heart Study (FHS), we conducted a prospective analysis examining the impact of parents' CVH on CVD-free survival among the offspring. The FHS comprises community-dwelling individual residents of Framingham, Massachusetts. The design and methods of FHS are described in detail elsewhere.[20,21] In brief, two multigenerational cohorts, the Original Cohort (parents) and Offspring Cohort are the longest-running cohorts of the FHS. The parents' cohort consisting of 5,209 participants aged 28–62 years was recruited and enrolled in 1948. The Offspring Cohort comprising of 5,124 children of the Original Cohort was recruited and enrolled in 1971. The offspring were aged 6–70 years of age at the baseline exam cycle.[20,21]

To be eligible for the present analysis, an offspring participant had to have both parents (mother and father) in the Original Cohort. Offspring and parent participants were linked using a unique family identifier in the datasets. Only the first occurrence of fatal or non-fatal CVD event at baseline year among the offspring was included. The final sample included 5,967 offspring–mother–father trios (1,989 offspring, 1,989 mothers, and 1,989 fathers; see Supplementary material online, *Figure S1* for sample exclusions). Data were obtained from the National Heart, Lung, and Blood Institute (NHLBI) Biologic Specimen and Data Repository Information Coordinating Center (https://biolincc.nhlbi.nih.gov/home/). Our study was approved by the Institutional Review Board at the University of Massachusetts Boston.

Study variables

A CVD event was defined using the FHS criteria and comprises manifestation of coronary heart disease, intermittent claudication, congestive heart failure, and stroke or transient ischaemic attack recorded in the events file.[21,22] Diagnosis of CVD in FHS is adjudicated by a three-physician panel based on medical records and physical examinations (Framingham Endpoint Review Committee) following recommended diagnostic criteria.[21,22] Framingham Heart Study examination cycles were conducted every 2–4 years by trained clinicians and researchers using standardized protocols and questionnaires. Clinical data were collected during onsite visits. Cardiovascular disease events were collected from the participant's primary care physicians, clinics, and nursing homes.[21] Framingham Heart Study continues surveillance of subjects to identify specific CVD events as they occur.[20,21] Each type of CVD event (coronary heart disease, intermittent claudication, congestive heart failure, stroke or transient ischaemic attack) for every study participant is recorded in the sequence of event file.

In the present study, we analysed incident CVD events recorded from 1971 through 31 December 2017. Participants who were alive and CVD-free by 31 December 2017 had their follow-up time right-censored on this date. Participants who withdrew or had missing follow-up data were censored on the date they were last seen or contacted. Ideal CVH was defined using AHA criteria: systolic/diastolic blood pressure (<120/<80 mmHg), fasting blood glucose (<100 mg/dL), total blood cholesterol (<200 mg/dL), BMI (<25 kg/m^2), and never smoked or quit in the last 12 months (Supplementary material online, *Table S1*).[23] A healthy diet was derived from recommended servings and combination of five food groups according to AHA criteria: (1) low-fat dairy products, (2) lean meats, (3) unsaturated fats, (4) vegetable and/or fruit intake, and (5) whole grain/cereals.[24] A healthy diet score was defined according to the attainment of the five recommended dietary components: 0–1 = poor, 2–3 = intermediate; and 4–5 = ideal (Supplementary material online, *Table S1*).[23] Owing to the design of physical activity data collection in the FHS, a method previously recommended for use in FHS was adopted to compute ideal physical activity based on hours spent per day on heavy, moderate, or slight activity and sedentary behaviour or sleeping.[25] Hours spent on each activity was multiplied by a weighted factor derived from estimated oxygen consumption for each intensity level to derive a physical activity score.[25] Physical activity weights were assigned as follows: sleeping (1.0), sedentary behaviours (1.1), slight activity (1.5), moderate activity (2.4), and heavy activity (5.0) (Supplementary material online, *Table S1*). Based on tertiles of physical activity scores, we collapsed the physical activity score into three categories: poor (<30), intermediate (30–33), and ideal physical activity levels (≥33) as used previously according to AHA criteria.[26,27]

A CVH score was derived from the seven CVH metrics according to AHA criteria (Supplementary material online, *Table S1*). According to these criteria, each CVH metric has a maximum of 2 points, with a total of 14 points for seven metrics. The score ranges from a minimum of 0 to a maximum of 14 (0, representing extremely poor CVH and 14, perfect ideal CVH score). Similar to others,[28,29] we analysed CVH scores grouped into three categories based on the sum of scores from the seven metrics: poor (0–4), intermediate (5–9), or ideal (10–14) CVH. Poor, intermediate, and ideal CVH represent attaining 0–2, 3–4, or 5–7 CVH metrics at ideal CVH metrics, respectively. Secondarily, we modelled CVH scores as ordinal CVH scores based on having 1, 2, 3, 4, 5, 6, and 7 ideal CVH metrics. Time to onset of CVD event (CVD-free survival time) for the offspring was calculated as the date of the onset of the first CVD event minus the baseline exam date (1971). Participants with no CVD event were censored at the end of the follow-up period on 31 December 2017.

Statistical analysis

Descriptive statistics were used to generate a frequency table for the sample characteristics and the distribution of CVH metrics. The outcome variable was time to onset of CVD (CVD-free survival) while the independent variable was the parental CVH score (ideal, intermediate, poor). Sex-specific analyses were performed, for example, differences in median as well as mean survival times for daughters and sons of mothers with ideal CVH (or poor CVH) vs. daughters and sons of fathers with ideal (or poor CVH). Median survival times and 95% confidence intervals (CIs) derived from Kaplan–Meier (K–M) plots for offspring were stratified by the parent's CVH score (ideal, intermediate, poor) as well as by each of the parent's CVH metric. We used Irwin's restricted mean to assess mean differences and generate 95% CI for CVD-free survival time of offspring stratified by sex and parents by sex. Irwin's restricted mean is similar to the area under the K–M survivor plots and computes survival time restricted to the longest follow-up.[30] Restricted mean has more robust

and clinically interpretable results for between-group differences and has been used for survival analysis using cohort participants.[30–32] We then used two-sided *z*-tests to assess the mean differences in offspring CVD survival time stratified by sex and by parent's sex and CVH status. Kaplan–Meier curves together with the logrank test were used to analyse CVD-free survival time. The K–M curves were stratified by parent's (mother and father) CVH categories and offspring sex (son and daughter). After confirming the veracity of the proportionality of hazards using Schoenfeld Residuals,[33] the Cox proportional hazards regression model was used to model the CVD hazards associated with categories of CVH score (poor, intermediate, ideal) with the ideal category serving as the referent category. Both parent-specific (only maternal or paternal) and combined parents (both maternal and paternal) Cox proportional hazard regression models were fitted to account for the combined mother–father effect on the offspring. The Cox proportional hazard regression models were adjusted for baseline characteristics for offspring: age, sex, and education level to account for potential confounding. To assess the stability of survival analyses derived from categorical CVH score, sensitivity analyses for CVD-free survival were performed using the ordinal CVH score as well as with each of the seven CVH metrics as the main predictor variables to generate K–M plots and Cox proportional hazard regression models. We also performed sub-analysis of age-matched parents and offspring as well as using three age-group categories for the offspring: ≤25, 26–<40, and ≥40 years. Statistical analysis was conducted using Stata version 14.2 (StataCorp LLC, College Station, TX, USA). A *P*-value ≤0.05 was considered statistically significant.

Results

Descriptive statistics

A total of 1,989 offspring were paired using a unique family identity variable in the datasets with 1,989 mothers and 1,989 fathers, with a total of 5,967 offspring–mother–father trios. At baseline exams, offspring's age was similar by sex (daughters vs. sons; 32.5 vs. 32.9 $P = 0.293$). Other sample characteristics and the prevalence of CVH metrics are shown in *Table 1*. The proportion of fathers and sons attaining 5–7 metrics at ideal levels was lower than that of mothers and daughters, respectively ($P < 0.001$, *Table 1*).

There was a total of 718 incident CVD events over 71,974 person-years among offspring resulting in an overall CVD incidence rate (IR) of 10 per 1000 person-years (95% CI 9.3–10.7). Out of 718 incident CVD events among the offspring, 31 events were deaths due to CVD, with the majority ($n = 23$, 74%) of deaths due to sudden or non-sudden coronary heart disease (Supplementary material online, *Table S2*). Sons had a higher IR for CVD than the daughters (17.6 vs. 12.4, per 1000 person-years, respectively, $P < 0.001$, *Table 2*). Sons of mothers with poor CVH had the highest IR for CVD compared with sons of fathers with poor CVH (*Table 2*). A similar pattern was observed for IRs for the daughters stratified by parent's CVH by sex (*Table 2*). The IR for CVD among the sons was higher than the daughters even after stratifying by averaged parental CVH (data not shown).

Time to onset of cardiovascular disease event

The median time to incident CVD for offspring was 26 years (95% CI 25–28; *Table 2*). Daughters had a longer CVD-free survival time than the sons. Offspring of mothers (son/daughter) with ideal CVH and intermediate CVH lived 9 more years free of CVD than offspring with poor CVH (27 vs. 18 years, $P < 0.001$, *Figure 1*). However, there were no statistically significant differences in median time lived free of CVD for offspring by paternal CVH status. The mean survival times obtained using the area under the K–M plots showed similar results in that sons or daughters of mothers with ideal CVH lived longer free of CVD compared with sons of fathers with ideal CVH. Maternal poor CVH was associated with 5 less years of CVD-free survival than paternal poor CVH ($P < 0.001$). Cardiovascular disease-free survival times stratified by individual CVH metrics of parents are presented in Supplementary material online, *Table S3*. Parental ideal physical activity, total cholesterol, blood pressure, BMI, and blood glucose were among the CVH metrics associated with the longest CVD-free survival among the offspring (up to 29 years).

Table 1 Baseline sample characteristics of offspring and parents at baseline exam

Characteristics	Daughters	Sons	Mothers	Fathers
Age, mean (SD)	32.5 (9.4)	32.9 (9.5)	40.8 (7.5)	43.4 (8.1)
Education level, *n* (%)				
<High school	53 (5.1)	45(4.8)	728 (39.3)	872 (46.6)
High school	342(32.9)	279 (29.4)	615 (33.2)	463 (24.8)
Some college	324 (31.1)	234 (24.7)	145 (7.8)	160 (8.6)
≥College grad	322 (30.9)	390 (41.1)	367 (19.8)	376 (20.1)
CVD risk factors,[a] *n* (%)				
HTN	80 (7.7)	195 (20.6)	519 (27.2)	822 (42.2)
Obesity	79 (7.6)	121 (12.8)	270 (14.2)	247 (12.7)
Smoking	437 (42.2)	441 (46.8)	793 (41.8)	1467 (76.1)
Unhealthy diet	894 (87.1)	818 (86.7)	1355 (71.8)	1473 (76.9)
High cholesterol	111 (10.7)	134 (14.1)	516 (27.8)	595 (31.2)
Inactivity/sedentary	147 (14.3)	158 (16.7)	405 (21.2)	584 (30.0)
High blood glucose	8 (0.8)	16 (1.7)	9 (0.5)	20 (1.1)
CVH score,[b] *n* (%)				
Poor CVH	39 (4.0)	96 (10.5)	107 (5.8)	366 (19.4)
Intermediate CVH	571 (58.3)	739 (80.5)	1323 (72.3)	1416 (75.1)
Ideal CVH	369 (37.7)	83 (9.0)	401 (21.9)	104 (5.5)

Data are displayed as mean (standard deviation) for continuous variables and *n* (%) for categorical variables.
CVD, cardiovascular disease; CVH, cardiovascular health; HTN; hypertension (systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90 mmHg) (see Supplementary material online, *Table S1*); SD, standard deviation.
[a]CVD risk factors and units defined using 'poor' category in respective CVH metric (see criteria for CVH metrics Supplementary material online, *Table S1*).
[b]Poor, intermediate, and ideal CVH represent attaining 0–2, 3–4, and 5–7 CVH metrics at ideal levels, respectively. Offspring $n = 1,989$, mothers $n = 1,989$; fathers $n = 1,989$; baseline exam year for parents is 1948, for offspring, 1971.

Survival curves and Cox proportional hazards regression analyses

The K–M plots show that offspring of parents (mother or father) with ideal CVH had longer CVD-free survival than offspring of parents with poor or intermediate CVH (*Figure 2A* and *B*). However, sex-specific differences in CVD-free survival were observed between sons and daughters vs. mothers and fathers (*Figure 2*). Accounting for the effects of age, sex, and level of education, the hazard ratio (HR) for incident

Table 2 Cardiovascular disease events, survival time, and incidence rate cardiovascular disease in offspring

Attribute	Offspring measures		
	Overall	Daughters	Sons
Time(yrs) to incident CVD, median (95% CI)	26 (25–28)	29 (27–30)	25 (24–26)
Total CVD events,[a] *n* (%)	718 (36.1)	301 (28.9)	417 (44.0)
Person-years of follow-up	71,974	39,618	32,356
CVD incidence rate[b]			
Offspring (both sexes)	10.0 (9.3–10.7)	7.6 (6.8–8.5)	12.9 (11.7–14.2)
Offspring of mothers with poor CVH	26.5 (21.1–33.3)	17.7 (11.9–26.5)	34.7 (26.3–45.8)
Offspring of fathers with poor CVH	12.3 (10.5–14.4)	10.3 (8.2–13.0)	14.9 (12.0–18.5)

CI, confidence interval; CVD, cardiovascular disease; CVH, cardiovascular health.
[a]CVD events include myocardial infarction, angina pectoris, coronary insufficiency, cardiovascular accident/stroke, transient ischaemic attack, cerebral embolism, intracerebral haemorrhage, subarachnoid haemorrhage, coronary heart disease, intermittent claudication, and congestive heart failure (CHF).
[b] Incidence rate computed per 1000 person-years and 95% CI.

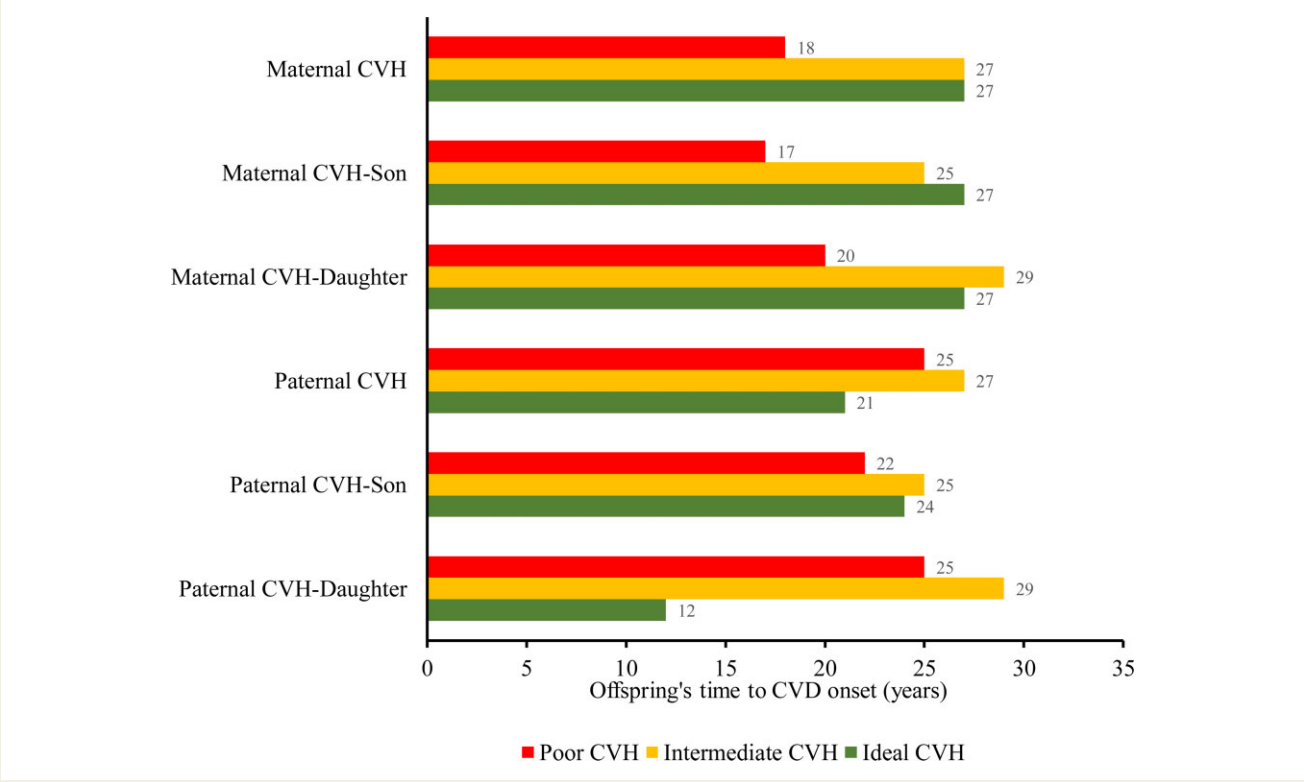

Figure 1 Offspring median cardiovascular disease-free survival time using parents' cardiovascular health status. Ideal, intermediate, and poor cardiovascular health = attaining 6–7, 3–5, and 0–2 metrics at ideal levels, respectively; time to cardiovascular disease for offspring cardiovascular health's time to onset of cardiovascular disease independent of parent's cardiovascular health; maternal, used to refer to both sons and daughters of mothers unless where specified, and likewise for paternal. For instance, maternal cardiovascular health indicates the median cardiovascular disease-free survival time of the offspring (son or daughter or both, where applicable) stratified by cardiovascular health status of the mother. CVD, cardiovascular disease; CVH, cardiovascular health.

CVD decreased with increasing CVH score but was not statistically significant by paternal CVH. Using the ordinal CVH variable (1–7 CVH score), each additional increase in maternal CVH score was associated with 11% lower hazard for CVD (adjusted HR 0.89, 95% CI 0.82–0.97; $P = 0.008$) and 9% lower hazard for CVD for paternal CVH (adjusted HR 0.93, 95% CI 0.86–1.00, $P = 0.057$). However, for the three-level CVH score (poor, intermediate, ideal), HR for offspring CVD survival time was not statistically significant by paternal CVH (for both offspring

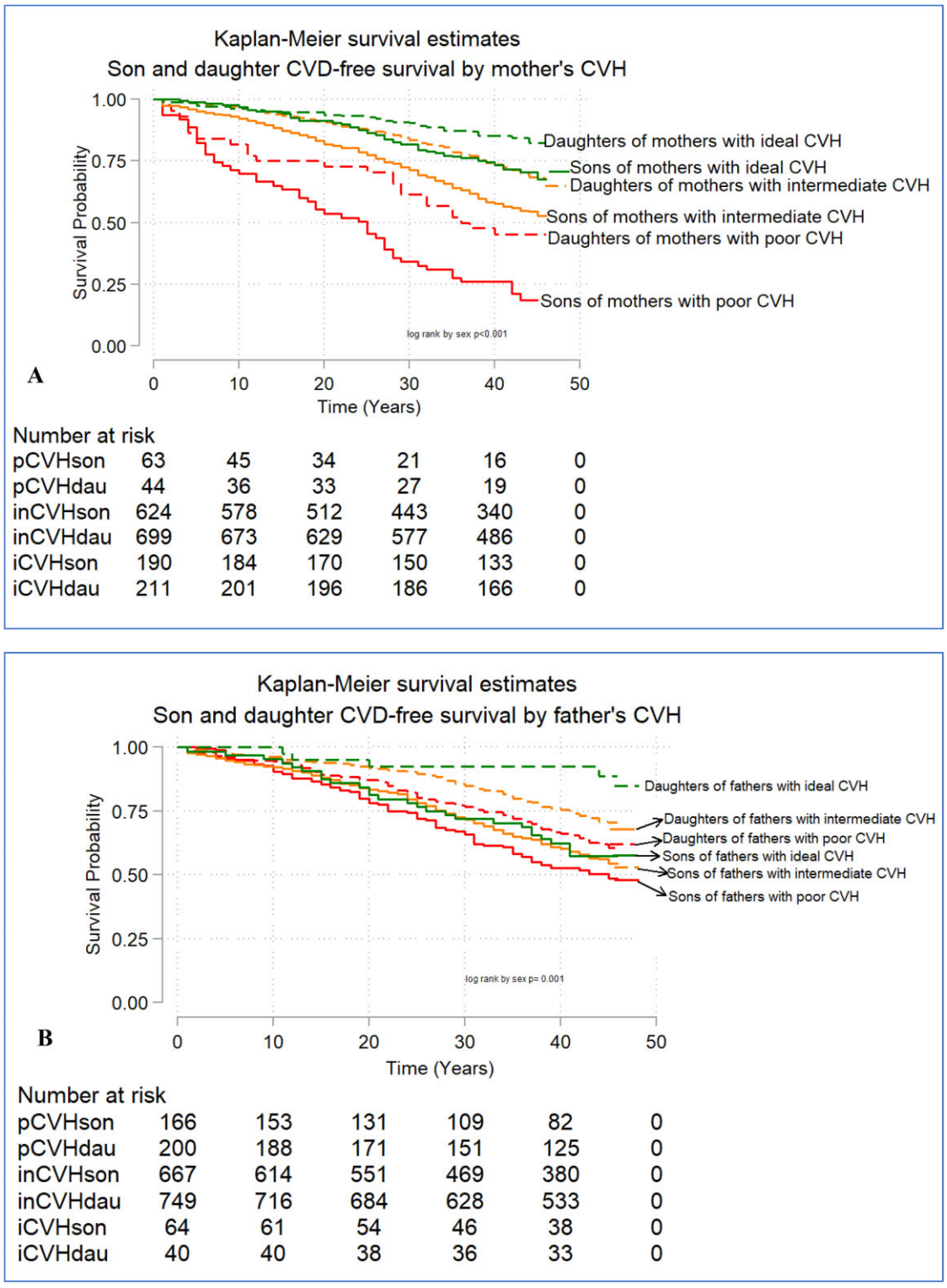

Figure 2 Kaplan–Meier plots showing cardiovascular disease-free survival by parent's cardiovascular health status: (*A*) son/daughter by mother cardiovascular health and (*B*) son/daughter by father cardiovascular health. Maternal and paternal cardiovascular health scores are computed as follows: ideal, intermediate, and poor cardiovascular health for attaining 5–7, 3–4, and 0–2 metrics at recommended levels, respectively. CVD, cardiovascular disease; CVH, cardiovascular health; dau, daughter; iCVH, ideal CVH; inCVH, intermediate CVH; pCVH, poor CVH.

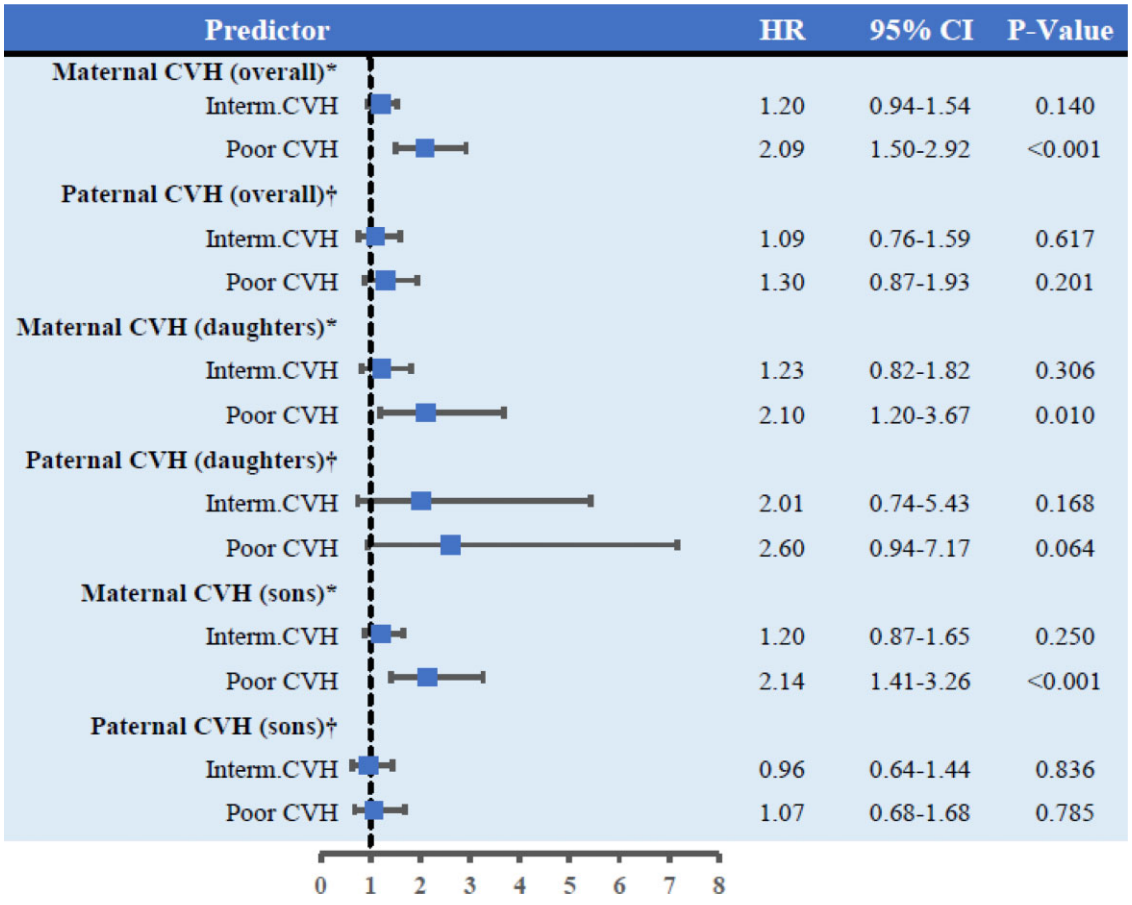

Figure 3 Cardiovascular disease hazard ratios for offspring's incident cardiovascular disease predicted by parental cardiovascular health status. CI, confidence interval; CVH, cardiovascular health; HR, adjusted hazard ratio; interm, intermediate; 'overall' refers to both sons and daughters; *referent category is maternal ideal cardiovascular health; †referent category is paternal ideal cardiovascular health; 'overall' models adjusted for offspring's age at exam 1, sex, education level; sex-specific models adjusted for age at exam 1 and education level; offspring's hazard ratio is computed from parental cardiovascular health status (ideal, intermediate, or poor cardiovascular health). Parental cardiovascular health is the independent variable; offspring cardiovascular disease risk is the dependent variable, for instance, 'maternal cardiovascular health (daughters)' refers to daughters of mothers with poor and intermediate cardiovascular health vs. ideal cardiovascular health.

sexes, and by sex-specific analyses—*Figure 3*). The HR for offspring CVD survival remained more robustly associated with maternal than paternal CVH for age-matched analyses as well as by offspring age groups ≤25, 26–<40, and ≥40 years (Supplementary material online, *Table S4*). Sensitivity analyses using each of the seven CVH metrics (Supplementary material online, *Table S2*) revealed quantitatively similar findings as above. The effect of parental CVH on offspring's event-free survival (sample consisting all events—both CVD and non-CVD events) did not show different results. Sex-specific K–M plots for each CVH metric revealed that maternal CVH was associated with longer CVD-free survival than paternal CVH (data not shown).

Discussion

The main findings from this study are (i) offspring of mothers with ideal CVH lived longer free of CVD than offspring of mothers with poor and intermediate CVH; (ii) maternal CVH was more predictive of offspring's time to onset of CVD than paternal CVH; and (iii) the CVD IR was higher for sons than daughters and among offspring of mothers with poor CVH (<2 CVH metrics at ideal levels). These findings highlight the significant role of maternal CVH on offspring CVD risk.

Time-to-event association using a wide range of parental CVH metrics and their offspring's life lived free of CVD has not been studied previously. Most studies on time-to-event analysis have focused on hospitalized individuals, whereas our study was conducted among a community-dwelling population (non-hospitalized individuals). Therefore, our findings are more generalizable to real-life experiences and the community settings. Our study shows that offspring of parents with ideal CVH (having 5–7 CVH metrics at ideal levels) are more likely to have a later onset, if any, of CVD events compared to those with poor or intermediate CVH. Our research supports the continued emphasis on primary prevention efforts and build upon previous studies that have shown that ideal CVH is

inversely associated with incident CVD;[29,34] and parent's achievement of ideal CVH predicts child attainment of individual CVH metrics such as BMI.[10,15]

An important finding related to our study is that maternal CVH status was more predictive of offspring's (sons and daughters) time lived free of CVD than paternal CVH. Paternal CVH status was weakly or not significantly associated with CVD survival times for both the sons and the daughters. The relationship between offspring–mother vs. offspring–father relationships for CVD risk factors has been previously investigated, but those studies show mixed results. A FHS study examining the association between parental timing (age of onset) of CVD showed that maternal age at onset of CVD was more predictive of offspring age at onset of CVD than paternal age.[35] Another study showed that maternal BMI was more strongly associated with their children's BMI than paternal BMI at every child's age from age 1–3.5 years.[36] Another study that prospectively followed offspring for 6 and 9 years after pregnancy showed a strong association between offspring and maternal adverse cardiovascular profiles, suggesting transmission of CVD risk factors from mothers to offspring postpartum.[10] A population-based Nordic study, however, found similar father–offspring and mother–offspring associations of cardiovascular risk factors.[14] The study was, however, cross-sectional in nature and therefore not possible to glean time trends of parent–offspring relationships of the examined CVD risk factors. Based on findings from current and previous studies on maternal/paternal-child CVD risk factors, we can conclude that maternal CVH is superior in predicting offspring CVD-free than paternal CVH.

Accumulating evidence from systematic reviews and meta-analyses show a strong association between parental smoking or alcohol consumption and occurrence of congenital heart disease (defects) among the offspring.[37,38] Zhang *et al.*[38] conducted a meta-analysis to examine the association between parental alcohol consumption and the risk of congenital heart defects among the offspring. Their study showed that offspring exposed to maternal alcohol consumption was associated with increased risk of Tetralogy of Fallot (odds ratio 1.20; 95% CI 1.08–1.33).[38] Others found that increased risk of congenital heart defects was associated with maternal active smoking [risk ratio (RR) 1.25, 95% CI 1.16–1.34] and passive smoking (RR 2.24, 95% CI 1.81–2.77) as well as paternal smoking (RR 1.74, 95% CI 1.48–2.06).[37] These are important findings given that congenital heart disease, which is the most common congenital anomaly, increases the risk for future CVD in adulthood by over three-fold.[39] These studies suggest that phenotypic expression of CVD among the offspring greatly depends on their parents' phenotype, and most importantly, the need for preventive interventions before or during pregnancy to reduce parental-induced plasticity of CVD risk early in child's life.

Several mechanisms have been proposed as possible underpinnings for intergenerational transmission of phenotypes from parents to offspring. As highlighted in a recent AHA scientific statement, children observe and acquire health behaviours, including patterns of dietary intake and physical activity behaviours, within the family environment they share with parents and/or caregivers.[40] Particularly during early childhood, role modelling of health behaviours by primary caregivers (fathers and mothers) has been shown to be a major contributor to parent–offspring concordance of selected behaviours.[40] Also, Vernon *et al.*[41] reported that among patients ($n = 695$) with the diagnosis of ST-segment elevation myocardial infarction, 25% did not have the standard modifiable cardiovascular risk factors such as hypertension, diabetes mellitus, hypercholesterolaemia, or smoking. These findings suggest a complex interplay of biological, behavioural, or environmental factors and support intergenerational studies that further integrate these factors addition to traditional CVD risk factors.

Fetal life, however, is an important time where initial environmental 'programming' of the fetal phenotype occurs through complex interactions of maternal health factors such as caloric excess, protein deprivation, among others and involve epigenetic mechanisms such as DNA methylation.[2,17] A large cohort study involving over 2 million live births showed that children born from mothers with diabetes before and during pregnancy had double the risk of early onset of CVD beginning as early as <10 years of age.[13] Previously, pregnancy-induced hypertension has been shown to be associated with increased blood pressure among the offspring.[11] Animal studies have shown that phenotypes such as obesity and glucose intolerance are transmitted via the matrilineal inheritance involving complex factors and interaction of metabolic, epigenetic, and mitochondrial mechanisms while patrilineal inheritance is primary as a result of epigenetic mechanisms leading to sex differences in transmission of phenotypes.[18,19] Therefore, maternal transmission of phenotypes to offspring may be stronger than paternal influence due to intrauterine maternal environmental factors and amplified when mothers are the primary caregivers.[1,2,40] This underscores that parents, and most importantly, mothers and the primary caregivers are the likely gatekeepers of the children's health.[40]

Strengths/limitations

The FHS is a well-known prospective cohort study which has meticulously collected multigenerational CVD-related data. The systematic collection of data using a standard protocol is a major strength in that it enables unbiased comparison of one generation to the next using a wide range of CVH metrics and over an extended period with subsequent events recorded. However, we note a potential limitation in that technologies for detection of CVD have dramatically improved over time; hence earlier cohorts or exams (for parents or offspring) may have experienced a different sensitivity and specificity of CVD diagnosis. This difference could be a source of bias due to time-dependent differential misclassification. The FHS addressed this limitation by involving a panel of three physicians to review available data to ascertain CVD diagnosis. Another limitation is that FHS participants are predominantly white, making it impossible to stratify analyses by race or ethnic backgrounds. Our study might have underestimated the actual contribution of parental CVH on offspring CVD-free survival due to right truncation of follow-up times, a situation which assumes that offspring participants with missing follow-up data or who were free of CVD at the end of follow-up were to remain in the same event-free status.[42] However, the K–M plots and Cox proportional hazards regression models account for the fact that censored event times represent the lower limit of survival time.

Conclusion

Our findings provide strong evidence that offspring of parents with ideal CVH have a longer CVD-free survival. Our study demonstrates

that maternal CVH is a stronger predictor of offspring time to onset of incident CVD than paternal CVH. These findings give impetus for targeting family-based interventions using a life-course approach for prevention of CVD involving mothers and children and the need for policies that value and reimburse family-centred primary prevention across the continuum of community-based programmes, primary care, and specialty cardiology care. Optimizing CVH among women of reproductive age and mothers with young children has the potential to break the intergenerational cycle of preventable high CVD morbidity and mortality, especially among the historically at-risk populations or families.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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