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ORIGINAL RESEARCH

Premature Parental Cardiovascular Disease and Subclinical Disease Burden in the Offspring

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BACKGROUND: Offspring of parents with premature cardiovascular disease (CVD) have an increased risk of developing subclinical and clinical CVD. It is unclear whether this association differs by vascular beds in the offspring or by the age cut points used to define premature parental CVD.

METHODS AND RESULTS: Using 3 generations of Framingham Heart Study participants, we assessed prevalent coronary artery calcification, the progression of coronary artery calcification over 6.1 years (median), carotid intima media thickness and the ankle-brachial index in 1046 offspring of parents with premature CVD before age 70 years, in 1618 offspring with both parents free of CVD and in 923 offspring with parents with CVD after age 70 years. We used different age cut points (55, 60, 65, and 70 years) to define premature parental CVD. In multivariable-adjusted models, offspring of parents with premature CVD (onset before age 65 years) displayed greater odds for prevalent coronary artery calcification (odds ratio [OR], 1.81; 95% CI, 1.35–2.43), higher carotid intima media thickness (OR, 1.50; 95% CI, 0.92–2.44) and lower ankle-brachial index (OR, 1.89; 95% CI, 1.00–3.58). These associations were generally consistent across different age cut points used to define premature parental CVD. The association with the progression of coronary artery calcification was less consistent.

CONCLUSIONS: Parental premature CVD is associated with increased subclinical CVD burden in the offspring, with consistent relations across different vascular beds and for different age cut points used to define premature parental CVD. Future studies should evaluate whether screening for subclinical CVD traits is warranted in offspring with premature parental CVD.

Key Words: ankle-brachial index ■ coronary artery calcification ■ familial risk ■ intima media thickness ■ offspring ■ subclinical CVD

Cardiovascular disease (CVD) clusters in families, and offspring of parents with premature CVD have a higher risk of developing CVD themselves compared with offspring without such family history.[1,2] Clinical CVD is commonly preceded by subclinical alterations of the cardiovascular system, such as coronary artery calcification (CAC), an increased intima media thickness (IMT), or a reduced ankle-brachial index (ABI). These subclinical disease measures have prognostic significance with respect to the risk of new-onset CVD beyond established CVD risk factors.[3]

There is mounting evidence that presence of a family history of CVD, and particularly a family history of *premature* CVD, is associated with increased subclinical disease burden in the offspring, that is, a higher prevalence of CAC[4–7] or higher carotid IMT.[8,9] However, there is no universally accepted definition of what should be considered as premature CVD. Many different age cut points have been used to define premature CVD, for example, CVD before age 55 years,[5,6] before age 60 years,[9] or before age 65 years.[5,6]

The association between family history for CVD and offspring peripheral artery disease (PAD) is less clear

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CLINICAL PERSPECTIVE

What Is New?

- We assessed prevalent coronary artery calcification, the progression of coronary artery calcification over 6.1 years (median), carotid intima media thickness, and ankle-brachial index in 1046 offspring of parents with premature cardiovascular disease (CVD) before age 70 years, in 923 offspring with parental CVD after age 70 years, and in 1618 offspring with parents free of CVD.
- Age cut points of 55, 60, 65, and 70 years were used to define parental premature CVD.
- In multivariable-adjusted models and across different age cut points, offspring of parents with premature CVD displayed greater odds for prevalent coronary artery calcification, higher carotid intima media thickness, and lower ankle-brachial index.

What Are the Clinical Implications?

- Premature CVD in parents was associated with higher prevalence of multiple subclinical disease components representing different vascular territories in their offspring.
- Whether systematic screening for subclinical CVD components is warranted in offspring of parents with premature CVD should be evaluated in future studies.

Nonstandard Abbreviations and Acronyms

ABI	ankle-brachial index
ARIC	Atherosclerosis Risk in Communities
CAC	coronary artery calcification
CARDIA	Coronary Artery Risk Development in Young Adults
CVD	cardiovascular disease
FHS	Framingham Heart Study
ICA	internal carotid artery
IMT	intima media thickness
MESA	Multi-Ethnic Study of Atherosclerosis
PAD	peripheral artery disease

(particularly when potential confounders are taken into account), but parental PAD displayed a strong and consistent association with offspring PAD.[10,11]

While this prior evidence is intriguing, analyses on the subclinical disease burden in offspring of parents with premature CVD have focused usually on only 1 or in some cases on 2[6,12] vascular territories. Therefore, it is not well known whether the subclinical disease burden in the offspring (associated with premature parental CVD) is comparable across different vascular beds (such as the carotid, coronary, or peripheral arteries). Moreover, most prior studies modeled premature family history of CVD as a dichotomous trait (parental CVD below a certain age cut point versus no parental CVD). Therefore, it is not clear whether there is a graded association of premature parental CVD with offspring subclinical disease burden, depending on which age cut points have been used to define premature parental CVD.

To address these open scientific questions, we explored different subclinical disease components representing different vascular beds (CAC and CAC progression, carotid IMT, ABI) in the offspring of parents with premature CVD. More specifically, we assessed whether these subclinical CVD measures in the offspring differ depending on the age cut point that is being used to define premature CVD in the parents (ie, ages 55, 60, 65, or 70 years).

We hypothesized that earlier age at onset of parental CVD is associated with a greater prevalence of subclinical disease components in the offspring as compared with offspring whose parents have CVD at a later age or who have no CVD at all.

METHODS

The data that support the observations reported in the present manuscript are available from the corresponding author upon reasonable request.

Study Sample

We used data from 3 generations from the FHS (Framingham Heart Study) for our investigation: The original cohort (initiated in 1948),[13] the offspring cohort (Generation 2; initiated in 1971)[14] and the third-generation cohort (Generation 3; initiated in 2002).[15] In the present analysis, we included participants from Generation 2 or Generation 3 as offspring, who had both parents in FHS original and Generation 2 cohorts, respectively, and with information available regarding their parental CVD status (n=5685; see Figure for details). Among the 5685 offspring, 2531 had available data on CAC, 1238 on carotid IMT measurement (Generation 2 only), and 3587 on ABI. These separate samples were used for the analyses for each subclinical disease trait (Figure). Offspring with just 1 parent in the FHS cohorts were not included because the CVD status of their other parent was not routinely ascertained.

For the present analysis, we focused on subclinical CVD components that have been assessed at the eighth examination cycle of the Generation 2 cohort (conducted between 2005 and 2008)[16] and at the first examination

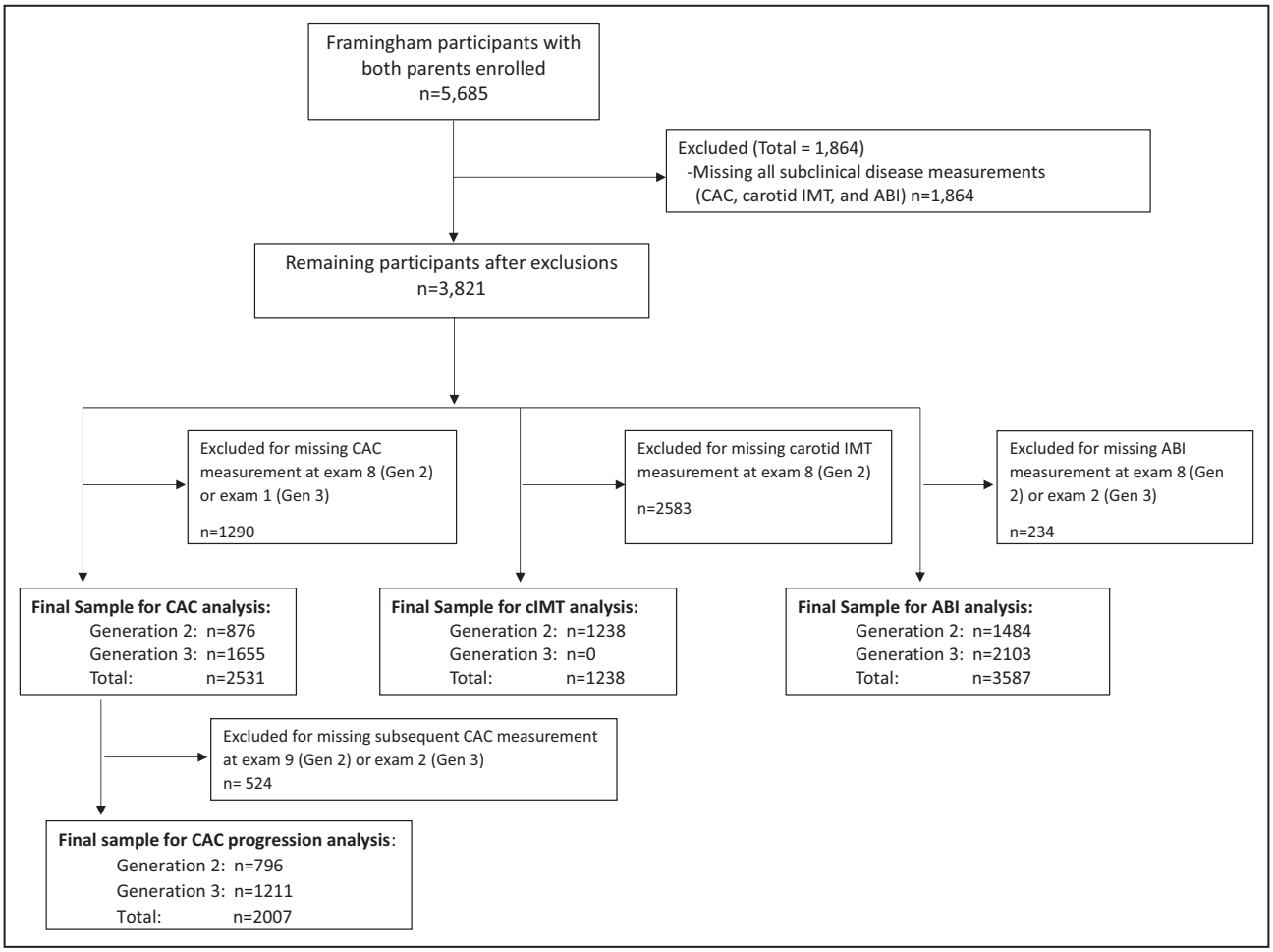

Figure. Derivation of the study sample.
ABI indicates ankle-brachial index; CAC, coronary artery calcification; IMT, intima media thickness.

cycle of the Generation 3 cohort (conducted between 2002 and 2005[15]; except for ABI measurements, which were conducted at examination cycle 2). For the analysis related to change of CAC over time, we also used data from the subsequent examination cycles (examination cycle 9 of the Generation 2 cohort and examination cycle 2 of Generation 3, years 2008–2011).[17]

At each examination cycle, study participants were comprehensively examined by trained technicians and physicians using standardized protocols; detailed information about established cardiovascular risk factors and subclinical and clinical CVD events was obtained.

The Institutional Review Board of Boston University Medical Center approved the study protocols of all FHS cohorts, and all participants provided written informed consent.

Assessment of Subclinical Disease Components

Coronary artery calcification was assessed between June 2002 and April 2005[7] using a multidetector computed tomography, as described in detail elsewhere.[7] Multidetector computed tomographies were conducted in men and women aged ≥35 and ≥40 years, respectively.[7] Pregnant women and individuals weighing 320 pounds or more were excluded from the multidetector computed tomographies. To quantify the burden of CAC, an Agatston score, modified for multidetector computed tomography, was derived, as described previously.[7] A total of 2007 (796 in Generation 2 and 1211 in Generation 3) participants received a second computed tomography examination from 2008 to 2011.[17] The CAC score at baseline (at examination cycle 8, Generation 2 cohort; and at examination cycle 1, Generation 3 cohort, respectively) was modeled as a continuous trait (as Ln-CAC score+1) and as a binary trait (CAC of >0 versus 0). CAC progression was modeled as a continuous trait as well as a binary trait. The continuous CAC progression trait was calculated as the difference in the natural-logarithmically transformed CAC Agatston scores between serial examinations (eg, Ln-CAC score at follow-up examination—Ln-CAC score at baseline examination); thus, a

positive CAC progression trait indicated an increase in CAC score between successive examination cycles. Furthermore, CAC progression was modeled as a binary trait with a value of 1 indicating that there was any increase in CAC at the second CAC assessment as compared with the first CAC assessment.

Ultrasound of the carotid arteries was conducted at examination cycle 8 of the offspring cohort, as reported in detail elsewhere.[16] In brief, an ultrasound machine (model SSH-140A from Toshiba America Medical Systems) was used to visualize the common (7.5-MHz transducer) and internal (5-MHz transducer) carotid arteries. IMT was assessed at 3 different sites on each side: at the common carotid artery, at the carotid bulb, and at the proximal 2 cm of the internal carotid arteries (ICAs).[18] The maximum IMT near wall and far wall at each of the 3 locations on the left and on the right side, respectively, was assessed, providing 12 measurements in total. The 4 measurements at the common carotid artery were averaged to generate mean IMT–common carotid artery, and the 8 measurements at the ICA and the carotid bulb were averaged to generate mean IMT-ICA/bulb.[18] The carotid IMT variable as used in our present analysis was obtained as average (mean) of IMT–common carotid artery and IMT-ICA/bulb and was modeled as a continuous trait. Higher carotid IMT (binary trait) was defined as a ≥1 mm common carotid artery IMT or a standardized carotid IMT that met or exceeded the sex-specific 80th percentile in the sample.

ABI was determined as described in detail elsewhere.[19] In brief, in both arms and both ankles, systolic blood pressure was measured twice with an 8-MHz Doppler pen probe and an ultrasonic Doppler flow detector (Parks Medical Electronics, Inc., Aloha, OR).[19] The 2 blood pressure readings at each ankle were averaged. ABI was calculated by dividing the average systolic blood pressure of each ankle with the highest mean systolic blood pressure in the right or left arm.[19,20] The lower of the 2 ABI ratios (one for each leg) were used for analyses.[19] ABI was modeled as a continuous and as a binary trait (<0.90 versus ≥0.90).

Validation of CVD Events in the Parents

A panel of 3 physicians who reviewed all available data related to a suspected CVD event, including medical information from the participant's treating physician or the hospital and data that were obtained at the FHS research clinic, adjudicated CVD events. For the present analysis, we defined CVD events to include recognized myocardial infarction, stroke, and heart failure.

Statistical Analysis

We used different parental age cut points to define premature parental CVD (independent variable): CVD before the parental ages of 55, 60, 65, and 70 years, respectively.

We used generalized estimating equation models (accounting for relatedness among participants), adjusting for established CVD risk factors, including age, sex, body mass index, current smoking, diabetes mellitus, the total/high-density lipoprotein cholesterol ratio, systolic blood pressure, and antihypertensive medication to relate premature parental CVD (independent variable) to each subclinical disease measure (dependent variable). In sensitivity analyses, we additionally adjusted the multivariable model for the intake of lipid-lowering medications and for "cohort type" (to account for the fact that CAC and ABI were assessed in 2 different FHS cohorts), respectively.

Premature parental CVD was modeled as a binary variable using different age cut points (separate models for each cut point as detailed above; using offspring with both parents free of any CVD as the referent group). Furthermore, we performed an analysis with "any parental CVD" as exposure variable and added "age of onset of parental CVD" as a covariate to obtain an effect estimate for the association of age of onset of parental CVD with the subclinical disease measures of interest. This analysis estimates the decrease in odds of offspring subclinical disease components for every year increment in parental age of CVD onset.

In secondary analyses, we modeled parental CVD as an ordinal variable, coded as follows: "1"=parental CVD before age 55 years in at least 1 parent; "2"=parental CVD between ages 55 and <60 years in at least 1 parent; "3"=parental CVD between ages 60 and <65 years in at least 1 parent; "4"=parental CVD between ages 65 and <70 years in at least 1 parent; "5"=parental CVD age ≥70 years in at least 1 parent; "6"=no parental CVD. We also repeated our main analyses using mutually exclusive parental CVD age categories. These were coded thus: parental CVD before age 55 years; between ages 55 and <60 years; between ages 60 and <65 years; between ages 65 and <70 years; and parental CVD age ≥70 years; offspring with parents free of CVD served as referent category. In these secondary analyses, each offspring contributed to only 1 category using the earliest parental CVD age, even if both parents had any CVD.

Binary outcomes (dependent variables; CAC >0 versus CAC=0; any CAC progression versus no CAC progression; ABI <0.9 versus ≥0.9; higher IMT, as defined above) were compared between offspring with and without premature CVD (independent variable) using logistic regression accounting for familial relations and adjusting for the covariates as defined above.

To assess potential interactions of parental CVD with sex, we added a sex*parental CVD interaction term in multivariable models using the parental age at

Table 1. Baseline Characteristics of the Sample, Stratified by Parental CVD Age Groups

	All Offspring*	No Parental CVD	Parental CVD† Age <55 y	Parental CVD† Age 55 to <60 y	Parental CVD† Age 60 to <65 y	Parental CVD† Age 65 to <70 y	Parental CVD† Age ≥70 y
	n=3587	n=1618	n=267	n=249	n=231	n=299	n=923
Age, y	52.4±13.1	46.6±10.9	53.8±13.2	56.3±12.6	55.0±13.3	56.7±13.4	61.5±10.1
Body mass index, kg/m^2	27.5±5.5	26.8±5.3	27.5±5.1	28.8±5.6	28.8±6.3	28.0±5.8	28.5±5.5
Systolic blood pressure, mm Hg	122±16	117±15	124±14	124±16	124±17	125±16	125±17
Total/HDL cholesterol ratio	3.7±1.3	3.7±1.3	3.7±1.2	3.8±1.3	3.8±1.4	3.6±1.3	3.5±1.0
Total cholesterol, mg/dL	190±35	190±35	188±36	191±38	193±37	187±35	190±37
Triglycerides, mg/dL	96 (68, 140)	90 (66, 133)	101 (72, 151)	106 (72, 148)	103 (75, 152)	98 (68, 144)	99 (73, 140)
Hypertension treatment, n (%)	867 (24)	205 (13)	91 (34)	94 (38)	74 (32)	103 (35)	339 (37)
Lipid-modifying treatment, n (%)	777 (22)	181 (11)	89 (33)	82 (33)	73 (32)	102 (34)	297 (32)
Current smoking, n (%)	415 (12)	192 (12)	32 (12)	29 (12)	35 (15)	27 (9)	89 (10)
Diabetes mellitus, n (%)	245 (7)	62 (4)	31 (12)	20 (8)	19 (8)	28 (9)	90 (10)
Coronary artery calcium score, Agatston units	0.0 (0, 34)	0.0 (0, 1.2)	0.8 (0, 100)	4.5 (0, 92)	1.2 (0, 80)	0 (0, 60)	2.0 (0, 112.5)
Coronary artery calcium score (>0)	985 (43)	295 (29)	82 (51)	91 (57)	83 (56)	101 (49)	333 (55)
Ankle-brachial index ratio‡	1.17 (1.11, 1.23)	1.18 (1.13, 1.24)	1.16 (1.09, 1.22)	1.16 (1.09, 1.22)	1.17 (1.09, 1.23)	1.16 (1.11, 1.23)	1.16 (1.10, 1.22)
Ankle-brachial index ratio (<0.9)‡	76 (2.1)	16 (1.0)	12 (4.5)	10 (4.0)	12 (5.2)	4 (1.3)	22 (2.4)
Carotid IMT,§ mm	1.38 (1.01, 1.86)	1.23 (0.96, 1.70)	1.36 (0.97, 1.92)	1.55 (1.07, 1.95)	1.57 (1.05, 2.02)	1.48 (1.02, 1.89)	1.38 (1.01, 1.86)
High carotid IMT (≥1 mm or >80th percentile),§ n (%)	247 (20)	41 (15)	22 (20)	31 (26)	26 (28)	32 (22)	95 (20)
Proportion of offspring with both parents with premature CVD, n (%)	103 (2.9)	…	32 (12.0)	28 (11.2)	23 (10.0)	20 (6.7)	…

Data are presented as mean±SD or median (Q1, Q3), unless otherwise noted. CVD indicates cardiovascular disease; HDL, high-density lipoprotein; and IMT, intima media thickness.
*For the characteristics displayed in Table 1, we used the largest subsample (the ABI sample) of the "base sample" of participants with at least one subclinical disease measurement.
†Offspring with 2 parents with any CVD (with father and mother belonging to different parental CVD age groups) were counted only once using the earlier parental CVD age.
‡Ankle-brachial index in Generation 3 was measured at examination cycle 2.
§Carotid IMT was measured in the Generation 2 cohort only.

Table 2. Association of Parental CVD at Different Ages With Offspring Coronary Artery Calcification (CAC), Modeled as a Continuous and as a Binary Trait

Exposure (Number Exposed/Total N)	Offspring CAC (Continuous); Age- and Sex-Adjusted Model			Offspring CAC (Continuous); MV-Adjusted Model		
	Estimate*	95% CI	*P* Value	Estimate*	95% CI	*P* Value
No parental CVD	Ref.			Ref.		
Parental CVD before age 55 y (171/1475)	0.584	0.236 to 0.931	0.001†	0.459	0.130 to 0.787	0.006†
Parental CVD before age 60 y (342/1629)	0.590	0.309 to 0.871	<0.001†	0.476	0.207 to 0.745	0.001†
Parental CVD before age 65 y (481/1650)	0.506	0.259 to 0.753	<0.001†	0.387	0.144 to 0.630	0.002†
Parental CVD before age 70 y (636/1579)	0.374	0.138 to 0.611	0.002†	0.267	0.036 to 0.499	0.024†
Parental CVD age ≥70 y (516/1459)	0.219	−0.061 to 0.498	0.126	0.155	−0.114 to 0.425	0.258
Exposure (Number Exposed/Total N)	**Offspring CAC (Binary); Age- and Sex-Adjusted Model**			**Offspring CAC (Binary); MV-Adjusted Model**		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
No parental CVD	1.00 (Ref.)			1.00 (Ref.)		
Parental CVD before age 55 y (171/1475)	1.98	1.32–2.95	0.001†	1.80	1.22–2.66	0.003†
Parental CVD before age 60 y (342/1629)	2.06	1.50–2.83	<0.001†	1.87	1.37–2.56	<0.001†
Parental CVD before age 65 y (481/1650)	2.04	1.53–2.72	<0.001†	1.81	1.35–2.43	<0.001†
Parental CVD before age 70 y (636/1579)	1.65	1.25–2.17	<0.001†	1.48	1.11–1.96	0.007†
Parental CVD age ≥70 y (516/1459)	1.46	1.06–2.00	0.020†	1.34	0.97–1.86	0.073

The multivariable-adjusted (MV) model included age, sex, body mass index, current smoking, diabetes mellitus, the total/high-density lipoprotein cholesterol ratio, systolic blood pressure and antihypertensive medication. The binary CAC variable was defined as CAC score of >0 vs 0. CVD indicates cardiovascular disease.

*The effect estimate indicates the change in the dependent variable (CAC score) for the selected parental CVD age category as compared with the referent category of "No parental CVD." Participants could contribute to parental CVD age categories in separate models using different age cut points (for parental CVD). For example, an offspring with a parental CVD age of 59 y could contribute to each of separate models estimating the effect for parental CVD at age <60, <65 and <70 y. This strategy maximizes statistical power for each model with a specific parental CVD age cut point.

†indicate $P<0.05$.

onset of CVD cut point that yielded the most statistically significant associations for each subclinical disease measure in the offspring.

RESULTS

Baseline characteristics in the overall sample, stratified by parental CVD age group and stratified by sex are provided in Table 1 and in Table S1, respectively. Among 3587 offspring in the ABI sample (the largest subsample among offspring with information on parental CVD status and at least 1 subclinical disease trait; Figure), 1046 offspring had at least 1 parent with premature CVD. Specifically, 267, 249, 231, and 299 offspring had a parent with premature CVD below the age of 55 years, between ages 55 and <60 years, between ages 60 and <65 years, and between ages 65 and <70 years, respectively. A total of 1618 offspring had both parents free of CVD, and 923 offspring had parents with a CVD event after the age of 70 years.

A relatively small proportion of offspring (103/3587=2.9 % in the base sample) had both parents with premature CVD (Table 1). Therefore, the number (1 or both) or the sex (mother/father) of the parent with premature CVD was not analyzed separately in the present analysis. Rather, we focused on the potential impact of different age cut points used to define premature parental CVD on the association with presence of subclinical CVD in the offspring. Our sample had a better cardiovascular risk profile and lower mean values for most subclinical disease measures as compared with offspring with no parents or only 1 parent in the FHS (Table S2).

Association of Premature Parental CVD With CAC and With CAC Progression

Premature parental CVD was consistently associated with CAC, modeled as a continuous or binary variable (Table 2), across all age cut points of premature parental CVD that we evaluated. The strengths of association (effect estimates in Table 2) were comparable for the parental CVD onset age thresholds of 55, 60, and 65 years, but was slightly attenuated when age <70 years was used to define premature parental CVD. A relatively similar pattern of association was observed when we used mutually exclusive parental CVD age categories and when each offspring contributed only once to a category using the first (earlier) parental CVD event (Table S3). We also observed an association with offspring CAC, when parental CVD age was modeled as an ordinal variable (Table S3).

Table 3. Association of Parental CVD at Different Ages With Offspring CAC Progression, Modeled as a Continuous and a Binary Trait

Exposure (Number Exposed/Total N)	Offspring CAC Progression (Continuous); Age- and Sex-Adjusted Model			Offspring CAC Progression (Continuous); MV-Adjusted Model		
	Estimate*	95% CI	*P* Value	Estimate*	95% CI	*P* Value
No parental CVD	Ref.			Ref.		
Parental CVD before age 55 y (101/875)	0.118	−0.123 to 0.359	0.337	0.065	−0.171 to 0.301	0.589
Parental CVD before age 60 y (195/958)	0.146	−0.045 to 0.338	0.134	0.084	−0.104 to 0.272	0.381
Parental CVD before age 65 y (272/963)	0.212	0.059 to 0.406	0.009†	0.168	−0.001 to 0.337	0.051
Parental CVD before age 70 y (375/951)	0.112	−0.037 to 0.282	0.131	0.081	−0.076 to 0.238	0.311
Parental CVD age ≥70 y (312/888)	−0.039	−0.208 to 0.129	0.647	−0.067	−0.232 to 0.100	0.430
Exposure (Number Exposed/Total N)	**Offspring CAC Progression (Binary); Age- and Sex- Adjusted Model**			**Offspring CAC Progression (Binary); MV-Adjusted Model**		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
No parental CVD	1.00 (Ref.)			1.00 (Ref.)		
Parental CVD before age 55 y (101/875)	1.65	1.01–2.72	0.047†	1.48	0.89–2.44	0.128
Parental CVD before age 60 y (195/958)	1.65	1.10–2.49	0.016†	1.48	0.98–2.23	0.063
Parental CVD before age 65 y (272/963)	1.90	1.32–2.72	0.001†	1.69	1.17–2.43	0.005†
Parental CVD before age 70 y (375/951)	1.55	1.10–2.18	0.013†	1.42	1.00–2.01	0.047†
Parental CVD age ≥70 y (312/888)	1.23	0.85–1.80	0.274	1.19	0.81–1.76	0.375

The multivariable-adjusted (MV) model included age, sex, body mass index, current smoking, diabetes mellitus, the total/HDL cholesterol ratio, systolic blood pressure and antihypertensive medication. CAC indicates coronary artery calcification; and CVD, cardiovascular disease. Continuous CAC progression was defined as (ln_CAC second CAC assessment—ln_CAC first CAC assessment); binary CAC progression as any progression (if the difference ln_CAC second CAC assessment—ln_CAC first CAC assessment was >0).

*The effect estimate indicates the change in the dependent variable (ln_CAC second CAC assessment—ln_CAC first CAC assessment) for the selected parental CVD age category as compared with the referent category of "No parental CVD." Participants could contribute to parental CVD age categories in separate models using different age cut points (for parental CVD), as detailed in the legend to Table 2.

†indicate $P<0.05$.

Premature parental CVD was less consistently associated with CAC progression, with mainly parental CVD age <65 years providing some evidence for association with CAC progression (Table 3; Table S4).

There were slight differences in the cardiovascular risk profile between those with CAC data available only at baseline and those with serial CAC measurements; participants with a single-time-point CAC measurement had lower mean serum total cholesterol levels, a greater proportion of antihypertensive medication use (25% versus 21%), and a higher proportion of current smokers (15% versus 8%). However, repeating the analysis using data from the second CAC assessment for cross-sectional associations with premature parental CVD revealed results similar to those reported in Table 2 (data not shown).

Association of Premature Parental CVD With Offspring Carotid IMT

Premature parental CVD displayed a relatively consistent pattern of association with offspring carotid IMT in most models across most parental CVD age cut points (Table 4), with the strongest associations being observed when age <60 and age <65 years were used to define premature parental CVD and when carotid IMT was modeled as a continuous trait (Table 4). When we used mutually exclusive parental CVD age categories and each offspring contributed to only 1 parental CVD group (based on the earliest parental CVD event), only the association of parental CVD between ages 55 and <60 years with offspring carotid IMT and the association of parental CVD, modeled as an ordinal variable, were statistically significant (Table S5).

Association of Premature Parental CVD With Offspring ABI

Premature parental CVD was relatively consistently associated with offspring ABI in age- and sex- adjusted models (Table 5). However, the association of premature parental CVD with offspring ABI (modeled as continuous and as binary trait) became statistically nonsignificant upon multivariable adjustment for most parental CVD age categories, except for the association of parental CVD before the age of 55 years, when ABI was modeled as a binary trait (Table 5 and Table S6).

Additional adjustment for lipid-lowering medication and for "cohort type" (to account for the fact that CAC and ABI were assessed in 2 different FHS cohorts) in

Table 4. Association of Parental CVD at Different Ages With Offspring Carotid IMT, Modeled as a Continuous and as a Binary Trait (Higher Carotid IMT)

Exposure (Number Exposed/Total N)	Offspring Carotid IMT (Continuous); Age- and Sex-Adjusted Model			Offspring Carotid IMT (Continuous); MV-Adjusted Model		
	Estimate*	95% CI	*P* Value	Estimate*	95% CI	*P* Value
No parental CVD	Ref.			Ref.		
Parental CVD before age 55 y (112/391)	0.123	−0.018 to 0.263	0.086	0.081	−0.051 to 0.214	0.230
Parental CVD before age 60 y (233/512)	0.180	0.067 to 0.293	0.002†	0.124	0.019 to 0.230	0.021†
Parental CVD before age 65 y (328/607)	0.174	0.076 to 0.271	0.001†	0.123	0.029 to 0.216	0.010†
Parental CVD before age 70 y (474/753)	0.153	0.066 to 0.240	0.001†	0.109	0.026 to 0.192	0.010†
Parental CVD age ≥70 y (485/764)	0.075	−0.010 to 0.161	0.084	0.063	−0.022 to 0.147	0.145
Exposure (Number Exposed/Total N)	**Offspring Carotid IMT (Binary); Age- and Sex-Adjusted Model**			**Offspring Carotid IMT (Binary); MV-Adjusted Model**		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
No parental CVD	1.00 (Ref.)			1.00 (Ref.)		
Parental CVD before age 55 y (112/391)	1.35	0.74–2.46	0.325	1.09	0.57–2.12	0.789
Parental CVD before age 60 y (233/512)	1.74	1.06–2.86	0.028†	1.49	0.88–2.51	0.137
Parental CVD before age 65 y (328/607)	1.76	1.12–2.78	0.014†	1.50	0.92–2.44	0.101
Parental CVD before age 70 y (474/753)	1.65	1.09–2.51	0.019†	1.41	0.90–2.19	0.133
Parental CVD age ≥70 y (485/764)	1.13	0.74–1.73	0.564	1.07	0.69–1.67	0.750

The multivariable-adjusted (MV) model included age, sex, body mass index, current smoking, diabetes mellitus, the total/high-density lipoprotein cholesterol ratio, systolic blood pressure, and antihypertensive medication. CVD indicates cardiovascular disease; and IMT, intima media thickness. Higher carotid IMT was defined as an increase of the common carotid artery IMT ≥1 mm OR standardized carotid IMT that met or exceeded the sex-specific 80th percentile in the sample.

*The effect estimate indicates the change in the dependent variable (carotid IMT in millimeters) for the selected parental CVD age category as compared with the referent category of "No parental CVD." Participants could contribute to parental CVD age categories in separate models using different age cut points (for parental CVD), as detailed in the legend to Table 2.

†indicate $P<0.05$.

our multivariable-adjusted models did not substantially change the results for the association of parental CVD age with any of the subclinical disease measures (data not shown).

Association of "Any Parental CVD" (Parental CVD at Any Age) With Offspring Subclinical Disease Components

We observed an association of "any parental CVD" with offspring CAC, carotid IMT and ABI (Tables 6 and 7). The variable "age of onset of parental CVD" also reached statistical significance or was borderline statistically significant in its association with these subclinical disease components (Tables 6 and 7). We observed that older parental age of onset for CVD was associated with lower odds of subclinical disease components in the offspring (inverse effect estimates and odds ratios <1 associated with "age of onset of parental CVD" for CAC, CAC progression, and carotid IMT—positive associations with offspring ABI [continuous]).

There was no evidence for a statistically significant parental CVD×sex interaction for any of the subclinical disease measures (for models using the age cut point for parental CVD that yielded the most statistically significant associations; data not shown).

DISCUSSION

Using data from 3 generations of the FHS, we assessed the association of parental CVD occurrence at different ages with presence of subclinical disease measures in different vascular beds in their offspring. In our principal analysis, we investigated whether the use of different age cut points to define parental CVD affected the strength and statistical significance of these associations. Additionally, we estimated the effect of "age of onset of parental CVD" (modeled as a continuous variable) on subclinical disease components in the offspring (Tables 6 and 7).

Principal Observations

Our main observations were as follows: First, premature parental CVD was strongly associated with prevalent CAC and higher IMT (or mean), irrespective of which age cut point was used to define premature parental CVD. Second, premature parental CVD was less consistently associated with CAC progression in

Table 5. Association of Parental CVD at Different Ages With Offspring ABI Modeled as a Continuous and as a Binary Trait

Exposure (Number Exposed/Total N)	Offspring ABI (Continuous); Age- and Sex- Adjusted Model			Offspring ABI (Continuous); MV-Adjusted Model		
	Estimate*	95% CI	*P* Value	Estimate*	95% CI	*P* Value
No parental CVD	Ref.			Ref.		
Parental CVD before age 55 y (267/1885)	−0.019	−0.040 to 0.002	0.072	−0.015	−0.035 to 0.006	0.162
Parental CVD before age 60 y (516/2134)	−0.022	−0.040 to -0.005	0.014†	−0.016	−0.034 to 0.001	0.063
Parental CVD before age 65 y (744/2340)	−0.020	−0.036 to −0.004	0.014†	−0.014	−0.030 to 0.002	0.083
Parental CVD before age 70 y (1002/2437)	−0.015	−0.031 to 0.000	0.055	−0.010	−0.025 to 0.006	0.217
Parental CVD age ≥70 y (923/2358)	−0.008	−0.024 to 0.009	0.362	−0.004	−0.020 to 0.012	0.603
Exposure (Number Exposed/Total N)	**Offspring ABI (Binary); Age- and Sex-Adjusted Model**			**Offspring ABI (Binary); MV-Adjusted Model**		
	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
No parental CVD	1.00 (Ref.)			1.00 (Ref.)		
Parental CVD before age 55 y (267/1885)	3.04	1.49–6.18	0.002†	2.73	1.29–5.80	0.009†
Parental CVD before age 60 y (516/2134)	2.76	1.45–5.26	0.002†	1.95	0.98–3.85	0.055
Parental CVD before age 65 y (744/2340)	2.73	1.49– 5.01	0.001†	1.89	1.00–3.58	0.050
Parental CVD before age 70 y (1002/2437)	2.06	1.13–3.74	0.018†	1.48	0.80–2.76	0.213
Parental CVD age ≥70 y (923/2358)	1.24	0.64–2.42	0.519	0.98	0.47–2.04	0.961

The multivariable-adjusted (MV) model included age, sex, body mass index, current smoking, diabetes mellitus, the total/high-density lipoprotein cholesterol ratio, systolic blood pressure and antihypertensive medication. ABI indicates ankle-brachial index; and CVD, cardiovascular disease. The binary ABI variable compared ABI <0.90 vs ≥0.90.

*The effect estimate indicates the change in the dependent variable (ABI, a ratio) for the selected parental CVD age category as compared with the referent category of "No parental CVD." Participants could contribute to parental CVD age categories in separate models using different age cut points (for parental CVD), as detailed in the legend to Table 2.

†indicate *P*<0.05.

the offspring over a median time of 6.1 years. Third, several parental CVD age groups were associated with offspring ABI in age- and sex-adjusted models, but only parental CVD before the age of 55 years was associated with offspring ABI (binary trait) upon multivariable adjustment. Fourth, we observed statistically significant inverse associations of "age of onset of parental CVD" (continuous variable) with offspring CAC and offspring carotid IMT; and obtained evidence for a positive association of "age of onset of parental CVD" with offspring ABI (continuous); this indicates that the prevalence of offspring subclinical disease burden decreases with increasing age of onset of parental CVD.

Comparison With the Literature

Association of Parental CVD With CAC in the Offspring

The association of parental CVD and CAC in the offspring has been assessed in different population-based studies, wherein different cut points were used to define CAC prevalence and to define premature parental CVD.[5–7,21] In the CARDIA (Coronary Artery Risk Development in Young Adults) study, a history of premature stoke or myocardial infarction in any parent, but particularly in the father (defined as an event before age 55 years), was associated with a higher prevalence of offspring CAC >0 as compared with offspring with no history of premature parental CVD in White participants.[6] In MESA (Multi-Ethnic Study of Atherosclerosis), a consistent association of premature parental coronary heart disease (CHD; before age 55 and 65 years in fathers and mothers, respectively) with CAC was observed.[5] In the Dallas Heart Study, a premature family history of myocardial infarction was associated with greater odds of prevalent CAC in men <45 years and in women <55 years, but not in participants above these age cut points (effect modification by age).[4]

In prior analyses, FHS investigators have reported that premature parental CVD (<55 years in fathers and <65 years in mothers) was associated with prevalent severe CAC (defined as an Agatston score greater than the 90th age- and sex-specific percentile) in the Generation 3 cohort upon multivariable adjustment.[7] In our present analysis of a slightly larger sample (total n=2531) we observed a consistent association of premature parental CVD with any CAC (CAC score >0) as well as with CAC modeled as a continuous trait in multivariable-adjusted statistical models. A few studies also evaluated the association of a positive family history for CVD with CAC progression. In MESA, for example, a family history of premature CHD was associated with new-onset (incident) CAC,[22] but not a family history of late-onset (≥55 years of age in men and ≥65 years of age in women) CHD.[22] In Whites, a

Table 6. Association of Parental CVD at Any Age (Any Parental CVD) With Subclinical Disease Components in the Offspring

Exposure Variable	CAC Score (Continuous)			
	Estimate	95% CI	*P* Value	Decrease in CAC Score (95% CI) Per 5 y Increment of Parental CVD Age
Any parental CVD	1.225	0.500 to 1.950	0.001*	
Age of onset of parental CVD	−0.015	−0.026 to −0.004	0.006*	−0.075 (−0.129 to −0.022)
Exposure Variable	**Progression of CAC (Continuous)**			
	Estimate	**95% CI**	***P* Value**	**Decrease in CAC Progression (95% CI) Per 5 y Increment of Parental CVD Age**
Any parental CVD	0.339	−0.163 to 0.841	0.186	
Age of onset of parental CVD	−0.004	−0.012 to 0.003	0.262	−0.021 (−0.058 to 0.016)
Exposure Variable	**Carotid IMT (Continuous)**			
	Estimate	**95% CI**	***P* Value**	**Decrease in Carotid IMT (95% CI) Per 5 y Increment of Parental CVD Age**
Any parental CVD	0.392	0.086 to 0.699	0.012*	
Age of onset of parental CVD	−0.004	−0.009 to 0.000	0.049*	−0.021 (−0.043 to 0.001)
Exposure Variable	**ABI (Continuous)**			
	Estimate	**95% CI**	***P* Value**	**Increase in ABI (95% CI) Per 5 y Increment of Parental CVD Age**
Any parental CVD	−0.037	−0.076 to 0.001	0.059	
Age of onset of parental CVD	0.001	0.000 to 0.001	0.069	0.003 (−0.0004 to 0.005)

The subclinical disease components CAC, CAC progression, carotid IMT and ABI were modeled as continuous traits. We adjusted the multivariable model additionally for "age of onset of parental CVD" to get an effect estimate for parental age of CVD onset. The statistical model was adjusted for age, sex, body mass index, current smoking, diabetes mellitus, the total/high-density lipoprotein cholesterol ratio, systolic blood pressure, antihypertensive medication, and age of onset of parental CVD. ABI indicates ankle-brachial index; CAC, coronary artery calcification; CVD, cardiovascular disease; and IMT, intima media thickness.

*indicate $P<0.05$.

family history of premature CHD was also statistically significantly associated with progression of CAC in those participants with any CAC at baseline.[22] In our present analyses, parental CVD before age 65 years and before age 70 years, respectively, were associated with CAC progression upon multivariable adjustment, but only when CAC progression was modeled as a binary trait (Table 3). In MESA, it also was reported that the progression of prevalent CAC and new-onset (incident) CAC share many conventional risk factors, including, for example, advancing age, male sex, higher body mass index, diabetes mellitus, hypertension, and a positive family history of heart attack.[23]

Association of Premature Parental CVD With Carotid IMT in the Offspring

There is accumulating evidence from community-based and clinical samples suggesting that a family history of premature CVD is associated with subclinical atherosclerosis in the carotid arteries.[8,9] In the ARIC (Atherosclerosis Risk in Communities) cohort, a family risk score was positively associated with carotid IMT in Whites and in Black women, but not in Black men.[8]

In the CARDIA study, premature parental stroke or MI was associated with a higher prevalence of higher IMT (>90th percentile) in Whites but not in Black participants.[6] Also in a referral sample of patients with premature (age ≤60 years) acute stroke (total N=382), a positive family history for stroke was associated with increased IMT of the internal carotid artery in patients <45 years, but not in patients ≥45 years (effect modification by age).[24] In contrast, a positive family history for CHD in a sibling or parent at any age was not associated with carotid plaque or increased carotid IMT in a moderate-sized sample from Korea (n=662).[12]

In a prior analysis, FHS investigators reported that premature parental CHD (defined as CHD before the age of 60 years) was associated with higher mean IMT of the internal carotid artery.[9] We extend these prior analyses by demonstrating that the association between premature parental CVD and offspring IMT (modeled as continuous trait) was relatively consistent in strength as the age threshold for defining premature onset of CVD in the parents varied from ages 60 to 70 years (Table 4).

Association of (Premature) Parental CVD With ABI in the Offspring

In the San Diego Population Study, parental PAD (at any age) was associated with higher odds of prevalent PAD (defined as ABI ≤0.9 or leg revascularization)

Table 7. Association of Parental CVD at Any Age (Any Parental CVD) With Subclinical Disease Components in the Offspring

Exposure Variable	CAC (Binary)			
	Odds Ratio	95% CI	*P* Value	Odds Ratio (95% CI) Per 5 y Increment of Parental CVD Age
Any parental CVD	4.72	2.04–10.88	<0.001*	
Age of onset of parental CVD	0.98	0.97–1.00	0.007*	0.92 (0.86–0.98)
Exposure Variable	**CAC Progression (Binary)**			
	Odds Ratio	**95% CI**	***P* Value**	**Odds Ratio (95% CI) Per 5 y Increment of Parental CVD Age**
Any parental CVD	2.97	1.04–8.45	0.042*	
Age of onset of parental CVD	0.99	0.97–1.00	0.157	0.95 (0.88–1.02)
Exposure Variable	**Carotid IMT (Binary)**			
	Odds Ratio	**95% CI**	***P* Value**	**Odds Ratio (95% CI) Per 5 y Increment of Parental CVD Age**
Any parental CVD	3.65	1.14–11.72	0.029*	
Age of onset of parental CVD	0.98	0.97–1.00	0.058	0.93 (0.85–1.00)
Exposure Variable	**ABI (<0.9)**			
	Odds Ratio	**95% CI**	***P* Value**	**Odds Ratio (95% CI) Per 5 y Increment of Parental CVD Age**
Any parental CVD	9.19	1.82–46.28	0.007*	
Age of onset of parental CVD	0.97	0.95–0.99	0.011*	0.86 (0.76–0.97)

The subclinical disease components CAC, CAC progression, carotid IMT and ABI were modeled as binary traits. We adjusted the multivariable model additionally for "age of onset of parental CVD" to get an effect estimate for parental age of CVD onset. The statistical model was adjusted for age, sex, body mass index, current smoking, diabetes mellitus, the total/high-density lipoprotein cholesterol ratio, systolic blood pressure, antihypertensive medication, and age of onset of parental CVD. ABI indicates ankle-brachial index; CAC, coronary artery calcification; CVD, cardiovascular disease; and IMT, intima media thickness.

*indicate $P<0.05$.

or prevalent severe PAD (defined as ABI ≤0.7 or leg revascularization).[11] Likewise, in a large case-control study from the Mayo Clinic, parental history of PAD was associated with greater odds of prevalent PAD in the offspring.[10]

In our sample, we observed a consistent association of parental CVD with an ABI <0.9 in the offspring across different age cut points in age- and sex-adjusted models, but the associations were attenuated upon multivariable adjustment becoming statistically nonsignificant, except for the association of parental CVD before age 55 years with binary ABI (<0.90 versus ≥0.90). Valentine and colleagues examined relatives of patients with early onset PAD[25] and reported that the prevalence of premature CVD was higher in parents of patients with PAD as compared with parents of healthy controls. Additionally, ultrasonographic evidence of vascular disease was common (50%) in clinically asymptomatic siblings.[25]

Strengths and Limitations

We extend prior reports linking premature parental CVD and subclinical disease in offspring in several ways. First, most prior studies modeled premature parental CVD as a binary trait (parental CVD before a specific age threshold),[6,7,9] but did not evaluate whether there might be a graded relation depending on the age cut points used to define premature parental CVD. Such a gradient is conceivable since the contribution of genetic predisposition to disease might diminish with advancing age. Accordingly, we used 4 different age cut points to define premature parental CVD. However, for most subclinical disease traits in the offspring, the strength of association between parental CVD and offspring subclinical disease burden was relatively consistent, suggesting that a parental history of CVD per se may be more important than the specific age of CVD onset in the parent, a premise that warrants testing in larger samples.

Another important difference is that we used validated parental occurrence of CVD (as opposed to self-reported family history), given the transgenerational nature of the FHS, where parents were followed systematically for occurrence of CVD. Use of validated CVD information obtained from longitudinal surveillance of parents renders potential misclassification of parental CVD status less likely. Others have noted limited accuracy of history of parental CVD

obtained via self-report.[26] Finally, we related premature parental CVD to a panel of subclinical CVD traits spanning different vascular beds and evaluated CAC progression.

The following limitations merit consideration. We performed multiple comparisons, analyzing 4 different age cut points for onset of parental CVD in relation to 4 different subclinical traits, each trait being modeled both as a continuous and as a binary trait. Even though these comparisons are not entirely independent of each other, the statistically significant observations should be interpreted with caution, given the extent of multiple testing, and some of them might be attributable to chance. Thus, additional replication in larger samples is warranted. Also, the observational (nonrandomized) nature of our investigation is a limitation, which could lead to residual confounding by unmeasured (or omitted) variables. Our sample consists almost exclusively of White individuals of European ancestry. The applicability of our observations to other ethnicities is unclear. Carotid IMT was available only in Generation 2, limiting the sample size for analyses of this trait.

CONCLUSIONS

In our community-based sample, we observed that premature parental CVD was associated with increased prevalence of subclinical disease in multiple vascular territories in the offspring, and that the strength of this association was relatively consistent across different age cut points used to define premature parental CVD. Whether systematic screening for subclinical CVD components is warranted in offspring of parents with premature CVD should be evaluated in future studies. Given that the subclinical disease burden increases with age, it is likely that the efficiency of such screening for subclinical disease may vary with the age of the population to be screened.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Tables S1–S6

REFERENCES

1. Lloyd-Jones DM, Nam BH, D'Agostino RB Sr, Levy D, Murabito JM, Wang TJ, Wilson PW, O'Donnell CJ. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA*. 2004;291:2204–2211.
2. Seshadri S, Beiser A, Pikula A, Himali JJ, Kelly-Hayes M, Debette S, DeStefano AL, Romero JR, Kase CS, Wolf PA. Parental occurrence of stroke and risk of stroke in their children: the Framingham Study. *Circulation*. 2010;121:1304–1312.
3. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012;308:788–795.
4. Philips B, de Lemos JA, Patel MJ, McGuire DK, Khera A. Relation of family history of myocardial infarction and the presence of coronary arterial calcium in various age and risk factor groups. *Am J Cardiol*. 2007;99:825–829.
5. Nasir K, Budoff MJ, Wong ND, Scheuner M, Herrington D, Arnett DK, Szklo M, Greenland P, Blumenthal RS. Family history of premature coronary heart disease and coronary artery calcification: Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2007;116:619–626.
6. Wilkins JT, Gidding S, Liu K, Ning H, Polak JF, Lloyd-Jones DM. Associations between a parental history of premature cardiovascular disease and coronary artery calcium and carotid intima-media thickness: the coronary artery risk development in young adults (CARDIA) study. *Eur J Prev Cardiol*. 2014;21:601–607.
7. Parikh NI, Hwang SJ, Larson MG, Cupples LA, Fox CS, Manders ES, Murabito JM, Massaro JM, Hoffmann U, O'Donnell CJ. Parental occurrence of premature cardiovascular disease predicts increased coronary artery and abdominal aortic calcification in the Framingham Offspring and Third Generation cohorts. *Circulation*. 2007;116:1473–1481.
8. Bensen JT, Li R, Hutchinson RG, Province MA, Tyroler HA. Family history of coronary heart disease and pre-clinical carotid artery atherosclerosis in African-Americans and whites: the ARIC study: Atherosclerosis Risk in Communities. *Genet Epidemiol*. 1999;16:165–178.
9. Wang TJ, Nam BH, D'Agostino RB, Wolf PA, Lloyd-Jones DM, MacRae CA, Wilson PW, Polak JF, O'Donnell CJ. Carotid intima-media thickness is associated with premature parental coronary heart disease: the Framingham Heart Study. *Circulation*. 2003;108:572–576.
10. Khaleghi M, Isseh IN, Bailey KR, Kullo IJ. Family history as a risk factor for peripheral arterial disease. *Am J Cardiol*. 2014;114:928–932.
11. Wassel CL, Loomba R, Ix JH, Allison MA, Denenberg JO, Criqui MH. Family history of peripheral artery disease is associated with prevalence and severity of peripheral artery disease: the San Diego population study. *J Am Coll Cardiol*. 2011;58:1386–1392.
12. Suh B, Shin DW, Lee SP, Lee H, Lee H, Park EA, Cho B. Family history of coronary heart disease is more strongly associated with coronary than with carotid atherosclerosis in healthy asymptomatic adults. *Atherosclerosis*. 2014;233:584–589.
13. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J III. Factors of risk in the development of coronary heart disease—six year follow-up experience. The Framingham Study. *Ann Intern Med*. 1961;55:33–50.
14. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. the Framingham Offspring Study. *Am J Epidemiol*. 1979;110:281–290.
15. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, D'Agostino RB Sr, Fox CS, Larson MG, Murabito JM, et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *Am J Epidemiol*. 2007;165:1328–1335.

16. Romero JR, Preis SR, Beiser A, DeCarli C, D'Agostino RB, Wolf PA, Vasan RS, Polak JF, Seshadri S. Carotid atherosclerosis and cerebral microbleeds: the Framingham Heart Study. *J Am Heart Assoc*. 2016;5:e002377. DOI: 10.1161/JAHA.115.002377.
17. Hwang SJ, Onuma O, Massaro JM, Zhang X, Fu YP, Hoffmann U, Fox CS, O'Donnell CJ. Maintenance of ideal cardiovascular health and coronary artery calcium progression in low-risk men and women in the Framingham Heart Study. *Circ Cardiovasc Imaging*. 2018;11:e006209. DOI: https://doi.org/10.1161/CIRCIMAGING.117.006209.
18. Maas R, Xanthakis V, Polak JF, Schwedhelm E, Sullivan LM, Benndorf R, Schulze F, Vasan RS, Wolf PA, Boger RH, et al. Association of the endogenous nitric oxide synthase inhibitor ADMA with carotid artery intimal media thickness in the Framingham Heart Study offspring cohort. *Stroke*. 2009;40:2715–2719.
19. Haring R, Travison TG, Bhasin S, Vasan RS, Wallaschofski H, Davda MN, Coviello A, Murabito JM. Relation between sex hormone concentrations, peripheral arterial disease, and change in ankle-brachial index: findings from the Framingham Heart Study. *J Clin Endocrinol Metab*. 2011;96:3724–3732.
20. Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PW. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. *Arch Intern Med*. 2003;163:1939–1942.
21. Fornage M, Lopez DS, Roseman JM, Siscovick DS, Wong ND, Boerwinkle E. Parental history of stroke and myocardial infarction predicts coronary artery calcification: the coronary artery risk development in young adults (CARDIA) study. *Eur J Cardiovasc Prev Rehabil*. 2004;11:421–426.
22. Pandey AK, Blaha MJ, Sharma K, Rivera J, Budoff MJ, Blankstein R, Al-Mallah M, Wong ND, Shaw L, Carr J, et al. Family history of coronary heart disease and the incidence and progression of coronary artery calcification: Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2014;232:369–376.
23. Kronmal RA, McClelland RL, Detrano R, Shea S, Lima JA, Cushman M, Bild DE, Burke GL. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2007;115:2722–2730.
24. Oygarden H, Fromm A, Sand KM, Kvistad CE, Eide GE, Thomassen L, Naess H, Waje-Andreassen U. A family history of stroke is associated with increased intima-media thickness in young ischemic stroke—the Norwegian stroke in the young study (NOR-SYS). *PLoS One*. 2016;11:e0159811.
25. Valentine RJ, Verstraete R, Clagett GP, Cohen JC. Premature cardiovascular disease is common in relatives of patients with premature peripheral atherosclerosis. *Arch Intern Med*. 2000;160:1343–1348.
26. Murabito JM, Nam BH, D'Agostino RB Sr, Lloyd-Jones DM, O'Donnell CJ, Wilson PW. Accuracy of offspring reports of parental cardiovascular disease history: the Framingham Offspring Study. *Ann Intern Med*. 2004;140:434–440.

Supplemental Material

Table S1. Baseline characteristics of the sample, stratified by men and women.

Characteristics	Men (n=1681)*	Women (n=1906)*
Age, years	52.2 ± 12.8	52.6 ± 134
Body Mass Index, kg/m²	28.4 ± 4.5	26.8 ± 6.1
Systolic blood pressure, mm Hg	123 ± 15	120 ± 17
Total/HDL Cholesterol ratio	4.2 ± 1.3	3.2 ± 1.0
Total Cholesterol, mg/dL	188 ± 36	192 ± 35
Triglycerides, mg/dL	106 (74, 158)	88 (64, 127)
Hypertension treatment, n (%)	442 (26%)	425 (22%)
Lipid-modifying treatment, n (%)	450 (27%)	327 (17%)
Current smoking, n (%)	194 (12%)	221 (12%)
Diabetes mellitus, n (%)	146 (8.7%)	99 (5.2%)
Coronary artery calcium score, Agatston units	1.0 (0, 84)	0.0 (0, 6.0)
Coronary artery calcium score (>0)	632 (53%)	353 (32%)
Ankle-brachial index ratio†	1.20 (0.20)	1.14 (0.14)
Ankle-brachial index ratio (< 0.9) †	28 (1.7%)	48 (2.5%)
Carotid IMT, ‡ mm	1.53 (1.11, 2.02)	1.27 (0.93, 1.69)
Increased carotid IMT,‡ n (%)	117 (20%)	133 (20%)
Proportion of offspring with both parents with premature (parental age <70 years) CVD; n (%)	51 (3.0%)	52 (2.7%)
Proportion of offspring with one parent with premature CVD, n (%)	299 (18%)	323 (17%)
Proportion of offspring with one or more parents with CVD at any age, n (%)	928 (55%)	1041 (55%)

* For the characteristics displayed in Table S1, we used the largest sub-sample (the ABI sample) of the "base sample" of participants with at least one subclinical disease measurement.

Data are presented as mean±SD or median (Q1, Q3), unless otherwise noted.

HDL indicates high-density lipoprotein; IMT, intima media thickness; SD, standard deviation

† Ankle-brachial index ratio in Generation 3 was measured at examination cycle 2

‡ Carotid IMT was measured in the Generation 2 cohort only (total N=660 for women and total N=578 for men)

Table S2. Comparison of the cardiovascular risk profile and subclinical disease components in offspring in our sample (the largest subclinical disease sample, with both parents in the Framingham Heart Study [FHS] and information on ABI available) as compared to offspring who were excluded because they had only one or no parents in the FHS cohorts.

	Offspring with both parents in FHS	Offspring excluded from our sample (those with one or no parents in FHS)	P-Value*
	n=3587	n=1935	
Age, years	56 ± 11	67 ± 9	<0.001
Women, n (%)	1906 (53)	1064 (55)	0.188
Body Mass Index, kg/m²	28.2 ± 5.6	28.2 ± 5.3	0.002
Systolic blood pressure, mm Hg	121 ± 16	129 ± 18	<0.001
Total/HDL Cholesterol ratio	3.4 ± 1.2	3.5 ± 1.1	<0.001
Total Cholesterol, mg/dL	189 ± 36	186 ± 38	0.065
Triglycerides, mg/dL	116 ± 75	119 ± 71	0.004
Hypertension treatment, n (%)	1081 (30)	967 (50)	<0.001
Lipid-modifying treatment, n (%)	1000 (28)	845 (44)	<0.001
Current smoking, n (%)	348 (9.7)	169 (8.8)	0.243
Diabetes mellitus, n (%)	300 (8)	276 (14)	<0.001
Coronary artery calcium score, Agatston units	0 (0, 31)	1.2 (0, 121)	<0.001
Coronary artery calcium score (>0)	1052 (42)	468 (53)	<0.001
Ankle-brachial index ratio	1.17 ± 0.17	1.13 ± 0.17	0.033
Ankle-brachial index ratio (< 0.9)	76 (2.1)	84 (4.3)	<0.001
Carotid IMT, mm	1.38 (1.01, 1.87)	1.46 (1.03, 1.94)	0.082
Carotid IMT (≥1mm or >80th percentile), n (%)	250 (20)	276 (24)	0.017

HDL indicates high-density lipoprotein; IMT, intima media thickness

*P-Values were not adjusted for the age difference between the two groups

Table S3. **Association of parental CVD at different ages with offspring coronary artery calcification (CAC), modeled as a continuous and as a binary trait. Parental CVD age categories are mutually exclusive.**

	Offspring CAC (continuous); MV-adjusted model			Offspring CAC (binary); MV-adjusted model		
	Estimate*	**95% CI**	**P-Value**	**Odds Ratio**	**95% CI**	**P-Value**
No parental CVD (943/2095)	Ref.			Ref.		
First parental CVD prior to age 55 years (142/2095)	0.436	(0.066 0.805)	0.021	1.66	(1.09, 2.52)	0.019
First parental CVD between age 55 and <60 years (154/2095)	0.444	(0.011, 0.878)	0.044	1.77	(1.12, 2.79)	0.014
First parental CVD between age 60 and <65 years (144/2095)	0.252	(-0.167, 0.671)	0.238	1.80	(1.08, 3.01)	0.024
First parental CVD between age 65 and <70 years (196/2095)	0.065	(-0.267, 0.396)	0.701	1.11	(0.75, 1.65)	0.605
First parental CVD age ≥70 years (516/2095)	0.075	(-0.180, 0.330)	0.563	1.25	(0.91, 1.72)	0.162
Parental CVD, modeled as an ordinal variable	-0.092	(-0.153, -0.031)	0.003	0.89	(0.83, 0.95)	0.001

Offspring with both parents with any CVD were only counted once using the earlier parental CVD age.

*The effect estimate indicates the change in the dependent variable (CAC score) for the selected parental CVD age category as compared to the referent category of “No parental CVD”.

Multivariable-adjusted (MV) model included age, sex, body mass index, current smoking, diabetes, the total/HDL cholesterol ratio, systolic blood pressure and antihypertensive medication. CI indicates confidence interval; CVD, cardiovascular disease.

The ordinal parental CVD variable was coded as: “1” = parental CVD before age 55 years in at least one parent; “2” = parental CVD between age 55 and <60 years in at least one parent; “3” = parental CVD between age 60 and <65 years in at least one parent; “4” = parental CVD between age 65 and <70 years in at least one parent; “5” = parental CVD age 70 years and older in at least one parent; "6" = no parental CVD.

Table S4. **Association of parental CVD at different ages with offspring CAC progression, modeled as a continuous and a binary trait. Parental CVD age categories are mutually exclusive.**

	Offspring CAC progression (continuous); MV-adjusted model			Offspring CAC progression (binary); MV-adjusted model		
	Estimate*	95% CI	P-Value	Odds Ratio	95% CI	P-Value
No parental CVD (576/1263)	Ref.			Ref.		
First parental CVD prior to age 55 years (85/1263)	0.151	(-0.107, 0.410)	0.251	1.77	(1.06, 2.95)	0.029
First parental CVD between age 55 and <60 years (84/1263)	0.157	(-0.124, 0.437)	0.274	1.40	(0.76, 2.59)	0.280
First parental CVD between age 60 and <65 years (79/1263)	0.203	(-0.057, 0.462)	0.126	1.85	(1.05, 3.28)	0.034
First parental CVD between age 65 and <70 years (127/1263)	-0.094	(-0.303, 0.116)	0.381	1.10	(0.65, 1.88)	0.719
First parental CVD age ≥70 years (312/1263)	-0.006	(-0.165, 0.154)	0.943	1.24	(0.85, 1.79)	0.261
Parental CVD, modeled as an ordinal variable	-0.035	(-0.076, 0.007)	0.100	0.90	(0.82, 0.98)	0.013

Offspring with both parents with any CVD were only counted once using the earlier parental CVD age.

*The effect estimate indicates the change in the dependent variable (ln_CAC second CAC assessment - ln_CAC first CAC assessment) for the selected parental CVD age category as compared to the referent category of “No parental CVD”.

Multivariable-adjusted (MV) model included age, sex, body mass index, current smoking, diabetes, the total/HDL cholesterol ratio, systolic blood pressure and antihypertensive medication. CAC indicates coronary artery calcification; CI, confidence interval; CVD, cardiovascular disease.

The ordinal parental CVD variable was coded as: “1” = parental CVD before age 55 years in at least one parent; “2” = parental CVD between age 55 and <60 years in at least one parent; “3” = parental CVD between age 60 and <65 years in at least one parent; “4” = parental CVD between age 65 and <70 years in at least one parent; “5” = parental CVD age 70 years and older in at least one parent; "6" = no parental CVD.

Table S5. **Association of parental CVD at different ages with offspring carotid intima media thickness (cIMT), modeled as a continuous and as a binary trait (higher cIMT).**

	Offspring cIMT (continuous); MV-adjusted model			Offspring cIMT (binary); MV-adjusted model		
	Estimate*	**95% CI**	**P-Value**	**Odds Ratio**	**95% CI**	**P-Value**
No parental CVD (279/1238)	Ref.			Ref.		
First parental CVD prior to age 55 years (112/1238)	0.091	(-0.040, 0.221)	0.175	1.26	(0.67, 2.36)	0.471
First parental CVD between age 55 and <60 years (121/1238)	0.185	(0.035, 0.334)	0.016	1.82	(1.02, 3.27)	0.044
First parental CVD between age 60 and <65 years (95/328)	0.121	(-0.013, 0.255)	0.077	1.54	(0.83, 2.85)	0.168
First parental CVD between age 65 and < 70 years (146/1238)	0.085	(-0.024, 0.195)	0.128	1.26	(0.70, 2.26)	0.441
First parental CVD age ≥70 years (485/1238)	0.053	(-0.033, 0.139)	0.224	1.06	(0.68, 1.66)	0.799
Parental CVD, modeled as an ordinal variable	-0.028	(-0.050, -0.005)	0.015	0.90	(0.82, 1.00)	0.047

Parental CVD age categories are mutually exclusive. Offspring with both parents with any CVD were only counted once using the earlier parental CVD age.

*The effect estimate indicates the change in the dependent variable (cIMT in mm) for the selected parental CVD age category as compared to the referent category of “No parental CVD”.

Multivariable-adjusted (MV) model included age, sex, body mass index, current smoking, diabetes, the total/HDL cholesterol ratio, systolic blood pressure and antihypertensive medication. CI indicates confidence interval; CVD, cardiovascular disease.

The ordinal parental CVD variable was coded as: “1” = parental CVD before age 55 years in at least one parent; “2” = parental CVD between age 55 and <60 years in at least one parent; “3” = parental CVD between age 60 and <65 years in at least one parent; “4” = parental CVD between age 65 and <70 years in at least one parent; “5” = parental CVD age 70 years and older in at least one parent; "6" = no parental CVD.

Table S6. Association of parental CVD at different ages with offspring ankle-brachial index (ABI), modeled as a continuous and as a binary trait.

	Offspring ABI (continuous); MV-adjusted model			Offspring ABI (binary); MV-adjusted model		
	Estimate*	**95% CI**	**P-Value**	**Odds Ratio**	**95% CI**	**P-Value**
No parental CVD (1435/3360)	Ref.			Ref.		
First parental CVD prior to age 55 years (253/3360)	-0.015	(-0.036, 0.007)	0.186	2.21	(1.06, 4.61)	0.034
First parental CVD between age 55 and <60 years (242/3360)	-0.020	(-0.042, 0.003)	0.082	1.47	(0.62, 3.5)	0.385
First parental CVD between age 60 and <65 years (222/3360)	-0.014	(-0.037, 0.009)	0.237	2.05	(0.88, 4.8)	0.096
First parental CVD between age 65 and <70 years (285/3360)	0.007	(-0.013, 0.026)	0.502	0.54	(0.14, 2.05)	0.366
First parental CVD age ≥70 years (923/3360)	0.002	(-0.014, 0.017)	0.821	0.80	(0.40, 1.63)	0.544
Parental CVD, modeled as an ordinal variable	0.004	(0.0001, 0.007)	0.045	0.82	(0.72, 0.94)	0.005

Parental CVD age categories are mutually exclusive. Offspring with both parents with any CVD were only counted once using the earlier parental CVD age.

*The effect estimate indicates the change in the dependent variable (ABI, a ratio) for the selected parental CVD age category as compared to the referent category of “No parental CVD”.

Multivariable-adjusted (MV) model included age, sex, body mass index, current smoking, diabetes, the total/HDL cholesterol ratio, systolic blood pressure and antihypertensive medication. CI indicates confidence interval; CVD, cardiovascular disease.

The ordinal parental CVD variable was coded as: “1” = parental CVD before age 55 years in at least one parent; “2” = parental CVD between age 55 and <60 years in at least one parent; “3” = parental CVD between age 60 and <65 years in at least one parent; “4” = parental CVD between age 65 and <70 years in at least one parent; “5” = parental CVD age 70 years and older in at least one parent; "6" = no parental CVD.