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Observational and Genetic Associations of Resting Heart Rate with Aortic Valve Calcium

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Abstract

It is unknown if lifelong exposure to increased hemodynamic stress from an elevated resting heart rate may contribute to aortic valve calcium (AVC). We performed multivariate regression analyses using data from 1,266 Framingham Heart Study (FHS) Offspring cohort participants and 6,764

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Multi-Ethnic Study of Atherosclerosis (MESA) participants. We constructed a genetic risk score (GRS) for HR using summary-level data in the CHARGE AVC Consortium to investigate if there was evidence in favor of a causal relation. AVC was present in 39% of FHS Offspring participants and 13% of MESA participants. In multivariate adjusted models, participants in the highest resting HR quartiles had significantly greater prevalence of AVC, with a prevalence ratio (PR) of 1.19 (95% CI 0.99–1.44) for the FHS Offspring and 1.32 (95% CI 1.12–1.63) for MESA, compared to those in the lowest quartile. There was a similar increase in the prevalence of AVC per standard deviation increase in resting HR in both FHS Offspring (PR 1.08 ,95% CI 1.01–1.15) and MESA (1.10, 95% CI 1.03–1.17). In contrast to these observational findings, a HR associated GRS was not significantly associated with AVC. While our observational analysis indicates that a higher resting HR is associated with AVC, our genetic results do not support a causal relation. Unmeasured environmental and/or lifestyle factors associated with both increased resting HR and AVC that are not fully explained by covariates in our observational models may account for the association between resting HR and AVC.

Keywords

Aortic valve calcium; resting HR; epidemiology; genetics; risk factors; computed tomography (CT); cardiovascular disease; epidemiology; epigenetics

Aortic valve calcium (AVC) is a precursor of aortic stenosis (AS), the most common reason for aortic valve replacement in older individuals.[1] Observational studies have shown that traditional cardiovascular risk factors including dyslipidemia are associated with AVC.[2,3] While randomized trials investigating statin therapy have not prevented the progression of AVC in persons with AS,[4,5] data are lacking on the primary or primordial prevention of AS. A greater resting heart rate (HR) is associated with an increased rate of progression of AS and increased cardiovascular death among individuals with asymptomatic AS.[6] A greater resting HR may contribute to AVC due to increased mechanical strain of the cusps, which contributes to aortic valve fibrosis and calcification.[7] Exercise and greater fitness, key determinants of resting HR, can prevent AVC in mice.[8] We investigated whether higher resting HR is associated with AVC, because if HR is causal in the genesis of AVC then HR reducing therapies may prevent AVC. To further understand if there is a causal link, we utilized genetic risk scores (GRS) that predispose to higher resting HR, to establish whether genetically increased resting HR is associated with AVC.

Methods

The primary analyses were performed using observational data from the Framingham Heart Study (FHS) Offspring cohort and the Multi-Ethnic Study of Atherosclerosis (MESA), both of which have been described in detail elsewhere.[9,10] We also performed a secondary genetic analyses in order to evaluate if there is a causal relation between resting HR and AVC using a previously described genetic risk score for HR derived from summary level genome-wide association data in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) AVC consortium (n = 6,942 participants).[11]

In MESA, all participants at Examination 1 (2000–2002) underwent cardiac computed tomography scanning and participants were excluded if they were missing resting HR (n=48) or AVC (n=2), for a final total of 6,764 participants. We used HR, covariates, and AVC data from MESA Examination 1 in order to examine the cross-sectional relation between resting HR and AVC.

In order to provide a prospective analysis complementary to the cross-sectional analysis conducted in MESA, we examined the relation between resting HR, including a long-term average resting HR, and AVC. In the FHS Offspring cohort, 1,418 participants underwent multi-detector computed tomography (MDCT) at Examination 7 (2002–2005), of which 1,394 participants had images suitable for AVC analysis.[12] Data were obtained from the FHS Offspring Examination 3 (1983–1987) (which is the earliest FHS Offspring Examination with all covariates of interest available for this analysis) through 7 (2002–2005). Participants in FHS Offspring were excluded if they did not attend Examination 7 (1998–2001), had missing covariate data from Examination 7, missing risk factors at three or more examinations, or had a permanent pacemaker (n=152) for a total of 1,266 participants included in these analyses.

Each participant in the FHS Offspring cohort underwent 2 scans with a prospectively gated sequential scan protocol using an 8-slice MDCT scanner as previously described.[12] Calcium measurements were performed by an experienced reader (TeraRecon, San Matteo, California). AVC measurement, scan validation, and inter-observer characteristics have been previously reported for the FHS Offspring cohort.[2] MESA participants underwent electronic beam computed tomography at the Chicago, Los Angeles, and New York field centers and MDCT at the Baltimore, Forsyth County, and St. Paul field centers.[13] The MESA scans were standardized across field centers using calcium phantoms scanned alongside participants and scans were read at the Harbor-University of California, Los Angeles Research and Education Institute.[14] AVC was measured using the Agatston method with a threshold criteria of an area of ≥3 connected pixels with an attenuation of ≥130 Hounsfield units. AVC was categorized as present (AVC >0 Agastston units) or absent for this analysis.

Resting 12 lead electrocardiograms were used to record resting HR in both cohorts. In MESA, we used resting HR measured at Examination 1. In FHS Offspring, we used resting HR obtained at Examination 3, as well as a long-term resting HR calculated as the mean value of the resting HRs collected at FHS Offspring Examination 3 through Examination 7. Long-term resting HR could not calculated for the MESA participants due to the cross-sectional nature of the analysis in MESA.

Covariates were obtained from the FHS Offspring cohort Examination 3 and MESA Exam 1 study visits and AVC scan data was obtained from FHS Offspring cohort Examination 7 and MESA Exam 1 (Figure 1). Blood pressure and lipids were measured using standard protocols as previously described.[9,15] Diabetes was defined as a fasting blood glucose ≥126 mg/dL or use of a blood glucose lowering medication. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Smoking status was defined as never, former, and current. Physical activity was measured in MESA using the Typical Week Physical Activity Survey and in the FHS Offspring cohort using the

Minnesota Leisure Time Physical Activity questionnaire, which assessed the frequency and time spent engaging in various physical activities.[16,17] Time spent in each activity was multiplied by the metabolic equivalent level to obtain MET-hours/week. AV nodal blocking medications were defined as beta-blockers, non-dihydropyridine calcium channel blocking agents, and/or digoxin. We did not adjust for lipoprotein (a) (Lp (a)) in our analyses as there is no plausible biological mechanism to account for an increased Lp (a) level leading to an increased resting HR. We also confirmed the absence of an association between resting HR and Lp (a) levels in MESA (Supplemental Table 1).

In order to complement our observational analyses and examine if evidence supports a causal link between resting HR and AVC, we conducted genetic analyses using the principle of Mendelian randomization with data from the CHARGE AVC consortium, which has been described in detail in prior publications.[11,18,19] In brief, it includes 6,942 participants from 3 cohorts (MESA, FHS and AGES-RS) with AVC measurement by CT and genome-wide genotyping.

Over 550,000 SNPs were available from the Affymetrix platform (Affymetrix, Santa Clara, California) with imputation to 2.5 million HapMap SNPs, as previously described.[20] In addition to 21 SNPs known to be associated with HR at the genome-wide level of significance, we included all SNPs that were associated with HR at $p<0.01$, from a previously published GWAS of HR, for a total of 42,858 SNPs.[21] After pruning for linkage disequilibrium 9,166 SNPs remained for analysis (included SNPs must have been available in each 3 cohorts in CHARGE in order to be included).

Differences in baseline characteristics between participants with and without AVC were compared using the Wilcoxon rank sum test, chi-squared, or Fisher's exact test, as appropriate. Resting HR quartiles were calculated independently for the FHS Offspring and MESA participants. HR quartiles were used instead of clinical cutpoints in order to maximize statistical power, consistent with other prior published reports.[22,23] Prevalence of AVC (AVC >0 Agastston units) per quartile of resting HR were calculated as crude values and adjusted for the age, gender, and race of the MESA and FHS Offspring cohorts respectively. Results from MESA and FHS are presented using prevalence ratios. We constructed logistic regression models for (i) continuous resting HR expressed per standard deviation, as well as (ii) comparing 4th versus 1st quartile of resting HR. Models were progressively adjusted for (1) age, race and sex; (2) age, race, sex, BMI, systolic blood pressure, diastolic blood pressure, anti-hypertensive medication use, smoking, LDL-C, HDL-C, triglycerides, diabetes, lipid-lowering medication use, physical activity level, AV nodal blocker use. Results of these models are interpreted as the prevalence ratio of having AVC per 1 standard deviation increase in resting HR or the prevalence ratio of AVC in comparison to the lowest resting HR quartile. Progressively adjusted multivariate regression models were constructed with AVC as the outcome. We also performed sub-group sensitivity analyses modeling the prevalence ratio of AVC per standard deviation change in resting HR.

To test the hypothesis of a causal association between resting HR and AVC, we used age and sex-adjusted GWAS summary level data from the CHARGE AVC consortium to estimate the association between the resting HR GRS and AVC using the Genetics ToolboX (gtx) R

package version 0.08 (http://cran.r-project.org/web/packages/gtx/index.html). To confirm the utility of the GRS in predicting resting HR, we first examined the mean resting HR per GRS quartile in Framingham Offspring. We then generated GRS effect sizes (β_{GRS}), which we expressed as odds ratios ($OR_{GRS} = e^{\beta GRS}$) with 95% confidence intervals for the presence of AVC. We also performed sensitivity analyses using Egger regression, a novel method to correct for possible pleiotropic effects [24].

Results

AVC was present in 38.6% of FHS Offspring participants and 13.4% of MESA participants. Within each cohort, participants with AVC were older and more likely to be men, with higher systolic blood pressure, less favorable lipid profiles, and greater use of a prescribed AV-nodal blocking medication (Table 1). Absolute differences in baseline risk factors between cohorts are in accordance with the approximately 20-year age difference between the cohorts at the time of covariate collection, as well as different recruitment strategies (MESA excluded individuals with baseline clinical cardiovascular disease whereas FHS did not). The mean ages at the time of cardiac CT scan acquisition were similar at 62 years for MESA participants and 64 years for FHS Offspring cohort participants. The mean resting HR within each of the resting HR quartiles was similar between cohorts (Supplemental Table 2).

In general, the prevalence of AVC increased by quartile of resting HR, and the highest resting HR quartile had the highest prevalence of AVC for both MESA (15.1%) and the FHS Offspring cohort (44.4%) (Figure 2). In multivariate adjusted models the participants in the highest resting HR quartiles had a significantly greater risk of AVC compared to those in the lowest resting HR quartile with a PR for AVC of 1.32 (95% CI 1.10–1.58) for MESA and 1.19 (95% 0.99–1.44) for the FHS Offspring cohort (Table 2 and Figure 3). Increasing resting HR quartile was also significantly associated with a greater prevalence of AVC in both MESA (p-value for trend = 0.002) and FHS Offspring cohort (p-value for trend = 0.029). In multivariate adjusted models, the prevalence of AVC per SD increase in resting HR was significantly increased, with a PR of 1.10 (95% CI 1.03–1.17) for MESA and 1.08 (95% CI 1.01–1.15) for the FHS Offspring cohort. When we examined the long-term average of resting HR in FHS Offspring, the PR per SD increase in long-term resting HR for AVC was 2.17 (95% CI 1.16–4.08).

Sub-group analyses showed no significant differences between sub-groups of age, physical activity, or AV nodal blocker medications use and no significant change in results after including hsCRP as a covariate (Supplemental Table 3 and Supplemental Table 4). There was also no significant change in the observational results when the analysis was performed using clinical HR cutpoints or in only White participants (Supplemental Tables 5 and 6).

The GRS explained 2% of variance ($R^2 = 0.021$) of HR and there was a significant increase in resting HR by GRS quartile ($p<0.001$) (Supplemental Table 7). In CHARGE participants, there was no significant association between the resting HR GRS and AVC (1.00 (0.999, 1.01) p=0.13). Furthermore, there was no correlation between β_{HR} with β_{AVC} across all SNPs associated with a higher resting HR (r=0.009, 95% CI −0.012–0.029, p=0.40). In

sensitivity analysis, we found evidence of pleiotropy using Egger regression (MR-Egger test for the intercept p-value of 0.0082). However, MR-egger effect estimates, after adjustment for the contribution of pleiotropy remained non-significant (p=0.13).

Discussion

Our results show a significant observational association between greater resting HR and AVC in both the MESA and FHS Offspring cohorts in multivariate adjusted models. The findings were consistent across sub-groups and the estimated effect sizes were similar, although somewhat higher in the FHS Offspring cohort. However, in the CHARGE consortium, a resting HR GRS was not significantly associated with AVC, which does not support a causal link between greater resting HR and AVC.

Despite the lack of evidence in favor of causality, the observational association between resting HR and AVC is novel and noteworthy. To date, there are few established risk factors for AVC and the mechanisms for the development of AVC are unclear. Our results suggest that an elevated resting HR, a known marker of poor physical fitness, may be an important acquired risk factor for the development of AVC in humans or alternatively a marker of a high risk AVC phenotype. Indeed, exercise has been shown to prevent aortic valve sclerosis in mice through several mechanisms[8]. Accordingly, the prevention of AVC, and possibly subsequent AS, may represent an added benefit of an active lifestyle. In FHS Offspring, adjustment for physical activity and other markers of metabolic health partially attenuated the association between resting HR and AVC suggesting that cardiometabolic health may mediate, at least in part, this association. Although this was not observed in MESA, this may be due to known differences in the prevalence of cardiometabolic risk factors across these cohorts. Nonetheless, despite adjustment for several possible confounders, a relation persisted between resting HR and AVC in both cohorts suggesting additional pathways between resting HR and AVC, which will require further study.

Biomechanical studies demonstrate that the perimeter of the aortic valve annulus deforms by up to 15% during each cardiac cycle with accompanying fluctuations in circumferential and radial strain and an increase in HR of only 1 beat per minute equates to an exposure of 5.3 million additional cardiac cycles per decade..[25] Tension and mechanical strain on aortic valve interstitial cells also contribute to valve fibrosis and calcification.[7] However, while these mechanisms are plausible, using data from the CHARGE consortium, we did not demonstrate a significant relation between a resting HR GRS and AVC, which argues against a direct causal role for resting HR in the development of AVC. Given our sample size and the relatively low variance explained by the GRS (i.e. ~2%), we calculate that within the CHARGE Consortium, which is the largest available genetic cohort with AVC data, we had sufficient power (>80%) to exclude a strong association (OR ≥ 1.59 per standard deviation) between genetically increased resting HR and AVC, but only low to modest power to detect a weaker association. We also did not detect any correlation between β coefficients for resting HR and for AVC across all SNPs included in the GRS, a highly sensitive approach that provides further evidence against a direct causal link. Accordingly, our results exclude a possible large direct causal contribution of resting HR in the development of AVC.

Environmental and/or lifestyle factors leading to an increased resting HR may be the predominant contributor to the observational association between resting HR and AVC and the covariates in our observational models may incompletely capture the potential confounding. In particular, cardiovascular fitness was not directly measured in either the MESA or FHS Offspring cohorts and the participant survey estimates likely incompletely describe the participants' true fitness. A direct measurement of exercise capacity such as treadmill or cardiopulmonary exercise testing might clarify the association between resting HR and AVC. Other unmeasured confounders associated with increased inflammation may also be implicated, such as the presence of a chronic disease, poor diet, and specific inflammatory mediators such as leukotriene B4, which is also implicated in increased HR and AVC.[26,27] However, our supplemental analysis that included hsCRP did not significantly impact the results. Additionally, resting HR and AVC are both established predictors of cardiovascular events and all-cause mortality and may function as risk markers for overall poor cardiovascular health.[23,28] Further work to identify additional possible mediators for the observed association could yield novel insights into the development of AVC.

Our genetic results do not provide supportive evidence for the pharmacological lowering of resting HR to prevent the incidence of AVC. This is in agreement with the Losartan Intervention for End Point Reduction in Hypertension (LIFE) trial, in which individuals randomized to atenolol did not have slowed progression of aortic sclerosis.[29] Findings from the Effect of Bisoprolol on Progression of Aortic Stenosis (BLAST) trial (clinicaltrials.gov identifier NCT01579058) as well as future studies utilizing ivabradine may provide further insight as to the efficacy of therapeutic HR lowering on AVC.

Our analysis has several limitations. First, although office-based resting HR correlates well with 24-hour ambulatory HR measures, a single resting HR measurement may not provide an accurate estimation of mean HR over the course of a day or longer term. Second, our primary analyses in MESA and FHS Offspring are based on observational data that does not allow for causal inferences, although we saw similar associations when risk factors were measured at the time of the AVC scan in MESA and when risk factors were measured approximately 18 years earlier in FHS Offspring. Third, the cross-sectional design of the MESA analysis may result in selection and/or temporal biases. Fourth, there were different measurement protocols of some covariates between the cohorts such as reagents for lab tests or wording of questionnaires, although these small differences and are unlikely to significantly impact the results. Fifth, we were unable to examine AVC as a continuous variable due to insufficient power. Finally, although we used the largest genetic cohort with AVC data, our genetic analysis provides evidence only to exclude a large causal effect between resting HR and AVC. The identification of rare variants with large effect sizes and/or creation of larger AVC cohorts, may facilitate further Mendelian randomization studies with greater statistical power.

In conclusion, our primary observational data analysis shows a consistent and significant association of increased resting HR with AVC. However, genetic analyses using the CHARGE Consortium exclude a strong causal association between resting HR and AVC. Overall, our results suggest that that lifestyle and/or environmental factors not fully captured by the covariates in our models may be the predominant contributor for the observational

association between resting HR and AVC. Future studies to further evaluate additional mediators linking resting HR and AVC are warranted and could provide new insight into the prevention of AVC and AS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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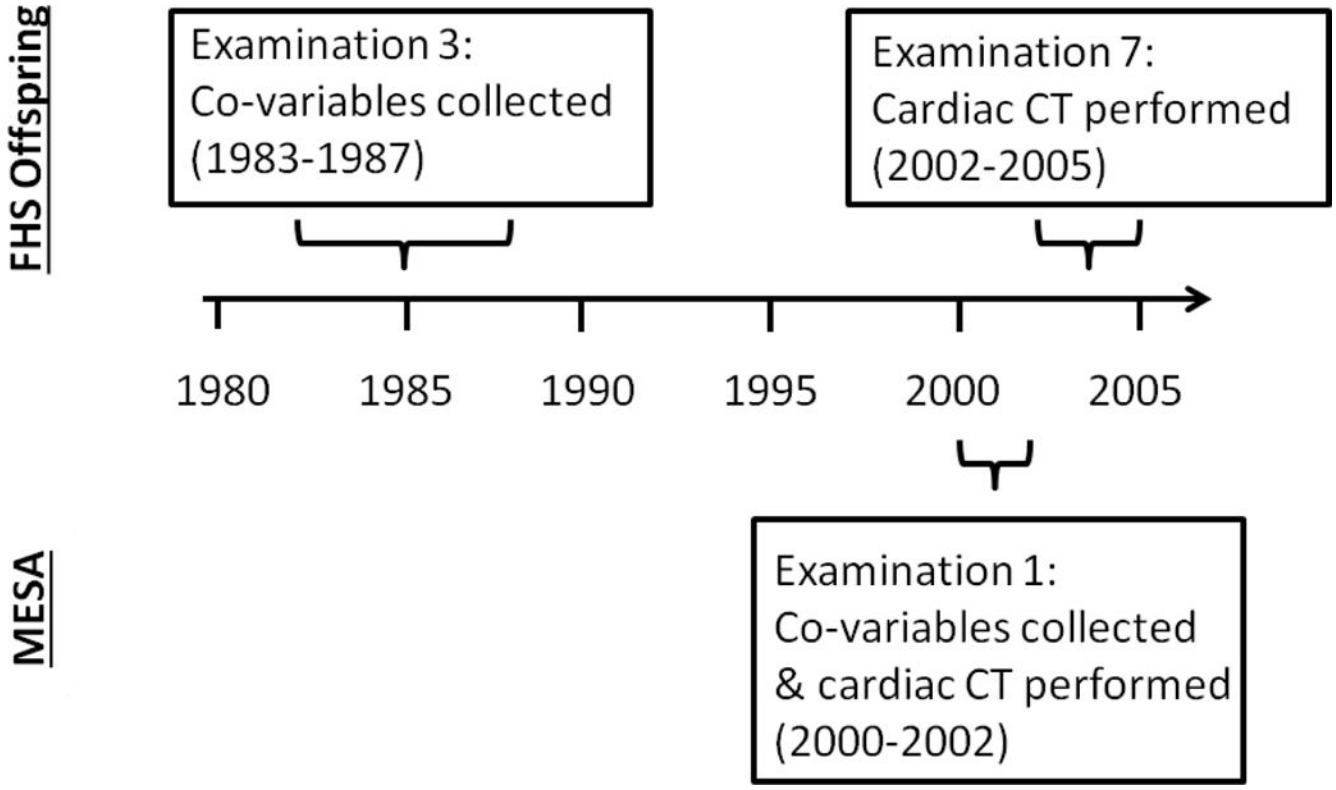

Figure 1.
Timeline of data collection for heart rate and aortic valve calcium measurements in the FHS Offspring and MESA studies

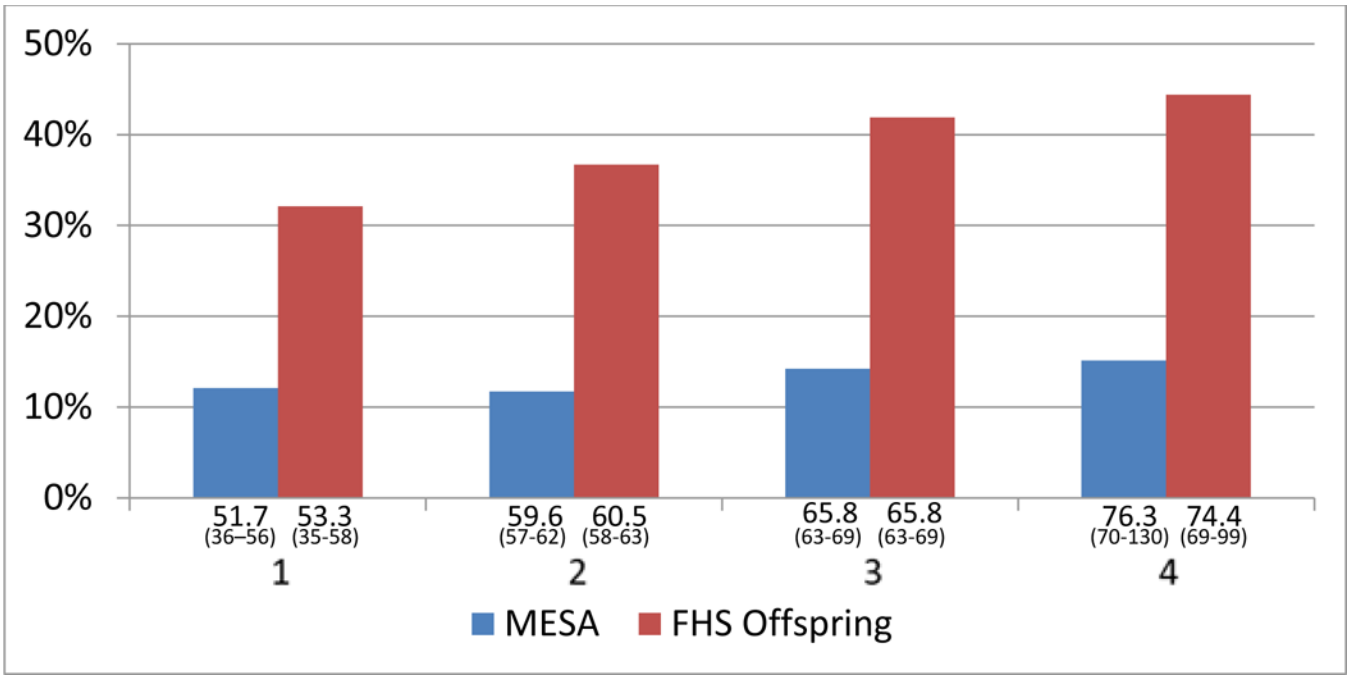

Figure 2 -

Prevalence of aortic valve calcium by resting heart rate quartiles

*Mean heart rate value and range listed below the respective bar.

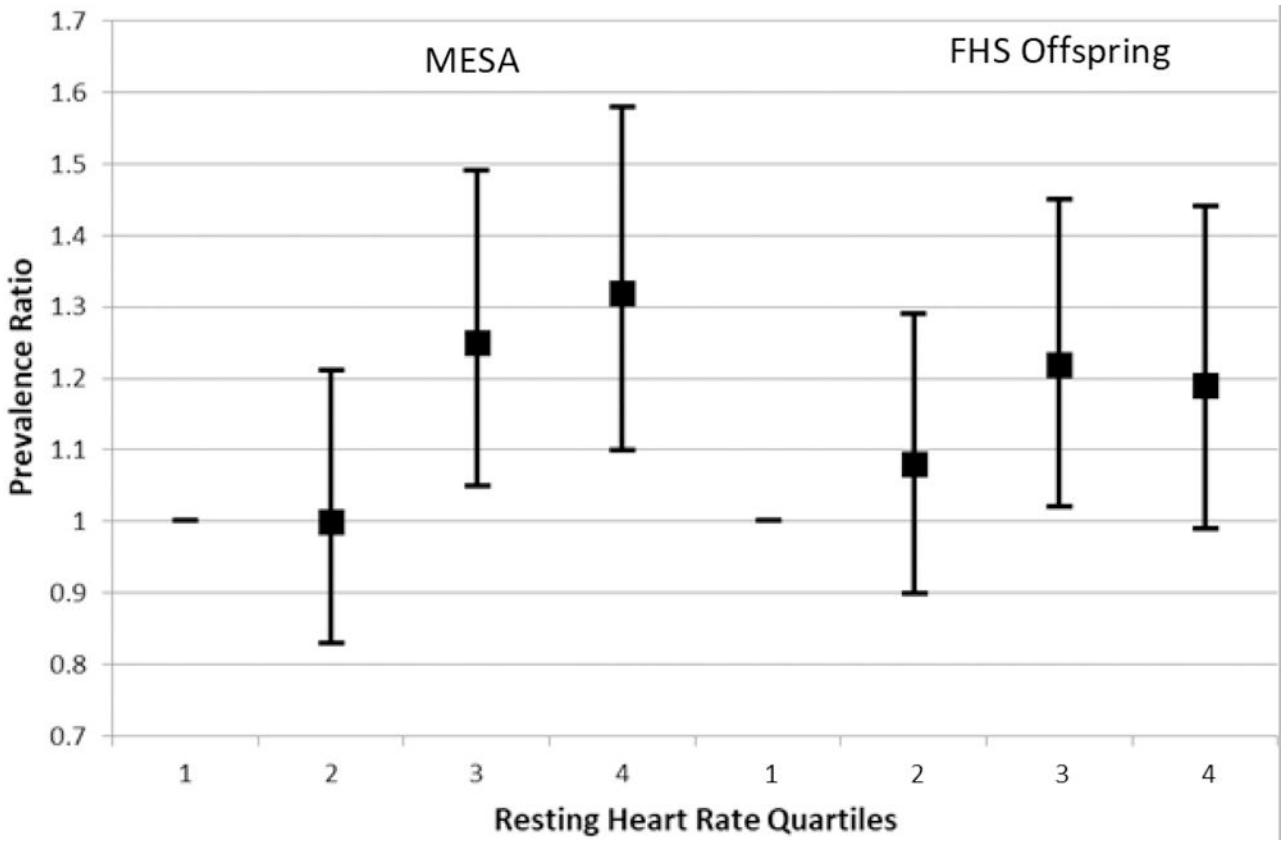

Figure 3 -

Prevalence ratio of aortic valve calcium stratified by resting heart rate quartiles

* Prevalence Ratio and 95% Confidence Intervals

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Table 1.

Baseline participant characteristics stratified by presence or absence of aortic valve calcium for MESA Examination 1 and FHS Offspring cohort Examination 3.

	MESA			FHS Offspring		
Variable	**No AVC (n=5,858)**	**AVC (n=906)**	**p-value**	**No AVC (n=777)**	**AVC (n=489)**	**p-value**
Age (years)	60.9 ± 9.9	70.5 ± 8.1	<0.001	42.6 ± 8.4	51.3 ± 7.6	<0.001
Heart rate (beats/minute)	63.1 ± 9.6	63.5 ± 10.1	0.12	63.6 ± 10.2	64.8 ± 10.3	0.047
Men	45.2 %	60.0 %	<0.001	40.3 %	57.5 %	<0.001
White	37.2 %	45.0 %	<0.001	100.0 %	100.0 %	n/a
Black	28.2 %	25.6 %	0.10	n/a	n/a	n/a
Chinese	12.6 %	7.4 %	<0.001	n/a	n/a	n/a
Hispanic	22.0 %	22.1 %	0.99	n/a	n/a	n/a
Systolic blood pressure (mmHg)	125.3 ± 21.1	134.9 ± 22.1	<0.001	117.7 ± 14.4	123.5 ± 15.6	<0.001
Diastolic blood pressure (mmHg)	71.9 ± 10.3	72.2 ± 10.0	0.41	76.7 ± 9.2	79.7 ± 8.9	<0.001
LDL cholesterol (mg/dL)	117.0 ± 31.0	118.8 ± 34.4	0.34	122.0 ± 33.2	145.7 ± 34.4	<0.001
HDL cholesterol (mg/dL)	51.3 ± 14.9	49.0 ± 14.2	<0.001	53.5 ± 14.1	48.7 ± 13.3	<0.001
Triglycerides (mg/dL) *	110 ± 77, 159	121 ± 83, 172	<0.001	77 ± 55,112	106 ± 73,159	<0.001
Total cholesterol (mg/dL)	194.0 ± 35.3	195.1 ± 38.1	0.84	194.2 ± 35.9	219.2 ± 36.3	<0.001
Body mass index (kg/m^2)	28.3 ± 5.6	28.5 ± 5.0	0.07	25.2 ± 4.5	26.8 ± 4.2	<0.001
Diabetes mellitus	11.5 %	19.8 %	<0.001	1.1 %	2.0 %	0.223
Current smoker	13.4 %	10.6 %	0.02	23.0 %	24.5 %	0.561
Hypertensive medication use	34.4 %	55.2 %	<0.001	7.6 %	16.1 %	<0.001
Lipid lowering medication use	14.6 %	25.5 %	<0.001	0.4 %	0.4 %	1.0
Atrioventricular node blocker use	11.8 %	18.7 %	<0.001	4.0 %	10.5 %	<0.001
Moderate and vigorous physical activity †	97.6	83.2	<0.001	118.8 ± 107.9	117.2 ± 107.2	0.804

*median value and interquartile range

†Physical Activity: MET-hours/week

Table 2.

Prevalence ratio of aortic valve calcium stratified by resting heart rate quartile

	MESA			FHS Offspring		
Quartile	**Mean heart rate (min – max)**	**Model 1**	**Model 2**	**Mean heart rate (min – max)**	**Model 1**	**Model 2**
1	51.7 (36–56)	Reference	Reference	53.3 (34.8, 57.6)	Reference	Reference
2	59.6 (57–62)	0.91 (0.76–1.10)	1.00 (0.83–1.21)	60.5 (57.8, 63.2)	1.14 (0.96 – 1.37)	1.08 (0.90 – 1.29)
3	65.8 (63–69)	1.16 (0.99–1.37)	1.25 (1.05–1.49)	65.8 (63.3, 68.8)	1.30 (1.09 – 1.54)	1.22 (1.02 – 1.45)
4	76.3 (70–130)	1.23 (1.05–1.44)	1.32 (1.10–1.58)	74.4 (69.0, 98.5)	1.40 (1.18 – 1.67)	1.19 (0.99 – 1.44)
p for trend		0.002	0.002		<0.001	0.029

Model 1 – age, sex, race

Model 2 – Model 1 + body mass index, systolic blood pressure, diastolic blood pressure, anti-hypertensive medication use, smoking, LDL-C, HDL-C, triglycerides, diabetes, lipid-lowering use, physical activity level, AV nodal blocker use