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Heritability of Vascular Structure and Function: A Parent–Child Study

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***Background*—**Understanding the heritable contribution of vascular measures, from parent to offspring, may aid in risk stratification and atherosclerosis prevention efforts. We hypothesized that measures of vascular structure and function would be heritable in this cohort of parents and their adolescent offspring.

***Methods and Results*—**High-resolution ultrasound scans of the brachial and carotid arteries were obtained in parents (n=558) and their offspring (n=369). Lumen diameter and flow-mediated dilation were measured in the brachial artery. Intima-media thickness, lumen diameter, incremental elastic modulus, diameter distensibility, and cross-sectional distensibility were measured, and carotid cross-sectional compliance was measured in the carotid artery. Carotid–radial pulse wave velocity was obtained using SphygmoCor®. Heritability analysis (h^2, expressed as %) using Sequential Oligogenic Linkage Analysis Routines was performed on the entire cohort and adjusted for age, sex, race, body–mass index, smoking, and mean arterial pressure. Data are presented as mean±SE. Measures of brachial artery diameter (h^2=25±9%, P=0.001), lumen diameter (h^2=55±9%, P<0.001), intima-media thickness (h^2=29±13%, P=0.014), diameter distensibility (h^2=28±7%, P<0.001), cross-sectional distensibility (h^2=27±7%, P<0.001), and pulse wave velocity (h^2=26±9%, P<0.001) were significantly heritable. Flow-mediated dilation and incremental elastic modulus were not significantly heritable. Similar associations were observed in analysis restricted to siblings and complete Trios (mother, father, and child).

***Conclusions*—**These data show that the majority of noninvasive measures of vascular structure and function are heritable, suggesting that measurement of these subclinical risk factors in parents may be helpful in assessing childhood risk for future cardiovascular disease. **(*J Am Heart Assoc*. 2017;6:e004757. DOI: 10.1161/JAHA.116.004757.)**

Key Words: carotid artery • carotid intima-media thickness • heritability • vascular endothelial function • vascular imaging

Risk factors for cardiovascular disease, including insulin sensitivity,[1] blood pressure,[2] lipids, cholesterol,[3,4] anthropometric measures, and obesity[3,5] have been shown to have significant heritability.[1] However, the heritability of measures of subclinical atherosclerosis have not been well studied.

Noninvasive measures of vascular structure and function are used as surrogate measures of subclinical atherosclerosis.[6] These include measures of arterial stiffness, flow-mediated dilation (FMD), and carotid intima-media thickness (cIMT), which all have been shown to be predictive of cardiovascular morbidity and mortality in adulthood.[7–9] Age, sex, blood pressure, and obesity are well-described modifiers of these noninvasive measures of subclinical atherosclerosis.[10–14] From a cardiovascular disease prevention perspective, understanding the multitude of factors and their corresponding level of contribution to adverse subclinical atherosclerotic risk may aid in risk stratification for individuals early in life.

Genetics[15] has been shown to play a role in modification of the vascular system and twin studies have demonstrated a genetic or heritable association to cardiovascular disease risk,[16–18] including noninvasive measures of subclinical atherosclerosis.[19] However, twin studies provide an upper limit estimate of heritability and may not be applicable to nontwin populations. Moreover, few studies have examined vascular measures among nontwins or among parents and offspring,[20–22] and to our knowledge no studies have examined parent–child relationships while the offspring were measured exclusively during childhood.

The purpose of this study was to examine the heritable relationships of multiple noninvasive measures of vascular

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structure and function among parents and their offspring during childhood, while accounting for other risk factors. In addition to the general heritability analyses, specific analyses were conducted among nontwin siblings, fathers and their offspring, mothers and their offspring, and complete trios (where mother, father, and child are present) in order to better clarify these associations.

Methods

Participants

The original cohort for this study (N=10 423) underwent blood pressure screening in first to third grade in the Minneapolis Public Schools during the 1977–1978 school year. Following this screening, participants were selected for long-term evaluation of cardiovascular risk factors; the longitudinal cohort was composed of all children from the top and bottom 5 percentiles of the normal systolic blood pressure distribution, 50% of the remaining black children, and 1 out of 9 of the remaining white children.[23] These children have been followed since the initial screening and are the parents for the present analysis.

The present sectional study was conducted in 558 of the originally recruited group of parents, current mean (SD) age 39.2 (2.1) years and 369 of their offspring, current mean (SD) age 12.4 (4.6) years. Parents and children were included if they had undergone vascular data collection at the University of Minnesota—Clinical Translational Science Institute and were paired with a sibling, or a parent, or a child participating in the same study. All participants were examined by the same study personnel and followed the same protocols. The study protocol(s) were approved by the University of Minnesota Institutional Review Board, and consent/assent was obtained from parents/children.

Anthropometrics, Blood Pressure, and Smoking Status

All testing was performed in the morning after the participants had been fasting (including no caffeine consumption) for a minimum of 8 hours. Height and weight were determined using a wall-mounted stadiometer and an electronic scale, respectively. Body-mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. BMI percentiles were determined using age- and sex-based Center for Disease Control definitions.[24]

Blood pressure was measured twice on the right arm with a random-zero sphygmomanometer with subjects in the seated position. The averages of the 2 measurements (systolic and fifth phase Korotkoff diastolic) were used in the analyses for systolic and diastolic blood pressure. Smoking status was determined by self-report.

Measurement of Endothelial Function, Vascular Structure, and Arterial Stiffness

Endothelial function was expressed by brachial artery FMD. FMD was measured via standard ultrasound using an 8 to 15 MHz linear array transducer to obtain B-mode images (Sequoia 512; Siemens, New York, NY) following current guidelines.[25] An electronic wall-tracking software program (Medical Imaging Applications, Coralville, IA) was used for the measurement of brachial artery diameter and blood flow. Following baseline measurements, a blood pressure cuff was placed on the forearm (distal to the imaged area) and inflated to a suprasystolic level (>200 mm Hg) for 5 minutes. After 5 minutes, cuff occlusion was released and B-mode ultrasound images were captured for ≈3 minutes after release. The maximum diameter recorded following reactive hyperemia was reported relative to baseline vessel diameter (FMD% =peak diameter−baseline diameter/baseline diameter). The same group of sonographers conducted the measurements under the supervision of the same laboratory director throughout. Our laboratory has previously documented satisfactory FMD reproducibility.[26]

Vascular structure was expressed by carotid intima-medial thickness (cIMT). Images for determining cIMT were obtained at end-diastole (gated by R wave on ECG) using B-mode images of the far wall of the left common carotid artery. Measurements were obtained at the distal 10 mm of the common carotid artery as recommended by pediatric guidelines.[27] An electronic wall-tracking software program was used for the analysis of cIMT. Our laboratory has previously documented satisfactory cIMT reproducibility.[28]

Carotid arteries also were imaged to capture the left common carotid artery lumen diastolic and systolic diameters to determine carotid incremental elastic modulus (cIEM, mm Hg), carotid diameter distensibility (cDD, %), carotid cross-sectional distensibility (cCSD, %), carotid diameter compliance (mm/mm Hg), and carotid cross-sectional compliance (cCSC, mm^2/mm Hg). Systolic and diastolic blood pressures were recorded with an automated blood pressure sphygmomanometer (Colin Medical Instruments Corp, San Antonio, TX) during the 10-s measurements. The ultrasound scanning system was interfaced with a standard computer, with images collected at 20 frames/s for 10 s (200 frames) to ensure the capture of full arterial diameter change during a cardiac cycle and calculated using a standard formula.[29] Arterial stiffness was also measured by carotid-radial pulse wave velocity (PWV) (SphygmoCor® system; AtCor Medical, Sydney, Australia).

PWV was calculated as distance (m)/transit time (s). The distance was measured between the carotid and radial sites and the sternal notch.

Statistical Analysis

All heritability analysis (h^2, expressed as %) was performed using the variance components approach as implemented in the software package Sequential Oligogenic Linkage Analysis Routines (SOLAR).[30] The heritability of a given phenotype was determined using the variance components technique (SOLAR), and a likelihood ratio test was used to test whether the heritability of a given phenotype was significantly (P<0.05) greater than zero. Covariates of age, sex, race, BMI, smoking, and mean arterial pressure were controlled for in analysis. Subanalyses were conducted to examine heritability among complete trios (mother, father, and offspring), mother and their offspring, and father and their offspring. Associations between nontwin siblings or between a single parent and their offspring were conducted using partial Pearson correlations adjusted for age, sex, and race. Descriptive data are presented as mean (SE).

Results

Descriptive and vascular characteristics of parents and their offspring are displayed in Table 1. Along with main analysis conducted on the entire cohort (n=927), subanalyses were conducted on nontwin siblings (n=338), a single adult parent and their offspring (n=447), complete trios (eg, mother and father and child), (n=136), mothers and their offspring (n=291), and fathers and their offspring (n=186).

Table 2 shows results from SOLAR analysis generating h^2 estimates for vascular structure and function on the entire cohort. Model 1 adjusts for age, sex, and race; Model 2 adjusts for all factors included in Model 1 plus BMI; and Model 3 further adjusts for mean arterial pressure and smoking status. In the fully adjusted model (Model 3), brachial artery diameter (h^2=24.6±8.5%; P=0.001), carotid lumen diameter (cLD) (h^2=55.4±8.8; P<0.001), cIMT (h^2=29.4±12.6; P=0.012), cDD (h^2=27.6±7.0; P<0.001), cCSD (h^2=26.5±6.9; P<0.001), cCSC (h^2=26.9±8.5, P<0.001), and PWV (h^2=26.3±8.9; P<0.001) had statistically significant heritabilities. FMD, cIEM, and carotid diameter compliance were not significantly heritable. Adjusting for lipid values did not appreciably alter the results and was not included in the final models.

We examined the associations of measures of vascular structure and function among nontwin siblings as well as single parents and their offspring (Table 3). Partial person correlations were adjusted for age, sex, and race. Among siblings, brachial artery diameter (r=0.14, P=0.012), cLD (r=0.31, P<0.001), cIEM (r=0.16, P=0.002), cDD (r=0.15, P=0.005), cCSD (r=0.15, P=0.005), cCSC (r=0.21, P<0.001), and PWV (r=0.24, P<0.001) were significantly correlated. Among single parents and their offspring, brachial artery diameter (r=0.11, P=0.021), cLD (r=0.22, P<0.001), cDD (r=0.19, P<0.001), cCSD (r=0.19, P=0.003), cCSC (r=0.14, P=0.015), and PWV (r=0.14, P=0.018) all were significantly correlated.

Table 4 shows heritability among complete trios (father, mother, and a child), between mothers and their offspring, and between fathers and their offspring. All models were adjusted for age, sex, race, BMI, mean arterial pressure, and smoking status.

Table 1. Descriptive Characteristics and Measures of Vascular Structure and Function of Parents and Their Offspring

Overall n=927	Parents n=558	Children (Offspring) n=369
Age, y	39.20±2.05	12.37±4.59
Sex, n (%)	270 M/288 F 48.4% M/51.6% F	199 M/170 F 53.9% M/46.1% F
Race, n (%)		
White	371 (66.5%)	231 (62.6%)
Black	139 (24.9%)	110 (29.8%)
Other races	48 (8.6%)	28 (7.6%)
Height, cm	171.51±10.42	151.67±19.80
Weight, kg	86.43±22.86	52.42±26.12
BMI, kg/m^2	29.43±7.28	21.51±6.52
BMI—percentile, %	…	63.47±30.19
SBP, mm Hg	115.01±14.15	103.82±10.32
DBP, mm Hg	73.36±11.51	58.21±8.03
BF, %	35.36±10.98	25.87±12.02
Brachial artery diameter, mm	3.84±0.72	3.18±0.60
FMD, %	6.44±3.80	7.81±3.70
cIMT, mm	0.52±0.08	0.45±0.04
cLD, mm	6.31±0.75	6.03±0.59
cIEM, mm Hg	1851.14±751.16	982.62±440.80
cDD, %	7.86±2.17	14.64±3.84
cCSD, %	16.36±4.68	31.57±8.88
cDC, mm/mm Hg	10.01±0.44	15.48±0.52
cCSC, mm^2/mm Hg	11.00±4.33	16.31±5.27
PWV, m/s	7.95±1.31	6.97±1.23

Data are mean±SD. BF indicates body fat; BMI, body-mass index; cCSC, carotid cross-sectional compliance; cCSD, carotid cross-sectional distensibility; cDC, carotid diameter compliance; cDD, carotid diameter distensibility; cIEM, carotid incremental elastic modulus; cIMT, carotid intima media thickness; cLD, carotid lumen diameter; DBP, diastolic blood pressure; FMD, flow-mediated dilation; PWV, pulse wave velocity; SBP, systolic blood pressure.

Table 2. Familial Relationships of Measures of Vascular Structure and Function for Entire Cohort (n=927)

	Model 1		Model 2		Model 3	
	Age, Sex, and Race		Model 1+BMI		Model 2+MAP+Smoking	
Measure	h^2 (SE)	*P* Value	h^2 (SE)	*P* Value	h^2 (SE)	*P* Value
Brachial artery diameter, mm	27.2 (8.2)	<0.001	22.3 (8.5)	0.003	24.6 (8.5)	0.001
FMD (%)*	7.3 (8.3)	0.19	4.3 (8.4)	0.31	3.5 (8.4)	0.34
cLD, mm	60.2 (8.5)	<0.001	54.7 (8.9)	<0.001	55.4 (8.8)	<0.001
cIMT, mm	26.1 (13.4)	0.027	26.8 (12.9)	0.02	29.4 (12.6)	0.012
cIEM, mm Hg	18.7 (9.9)	0.027	13.4 (9.4)	0.071	11.9 (9.3)	0.09
cDD (%)	28.6 (7.0)	<0.001	28.6 (7.0)	<0.001	27.6 (7.0)	<0.001
cCSD (%)	27.4 (6.9)	<0.001	27.4 (6.9)	<0.001	26.5 (6.9)	<0.001
cDC, mm/mm Hg	8.0 (9.7)	0.20	7.0 (9.6)	0.22	3.4 (9.3)	0.35
cCSC, mm^2/mm Hg	28.6 (8.5)	<0.001	28.6 (8.5)	<0.001	26.9 (8.5)	<0.001
PWV, m/s	22.9 (8.9)	0.003	23.3 (8.9)	0.003	26.3 (8.9)	<0.001

Model 1 is adjusted for age, sex, and race of both parents and offspring; Model 2 further adjusts Model 1 for BMI of both parent and offspring; Model 3 further adjusts Model 2 for MAP and smoking status of both parent and offspring. BMI indicates body-mass index; cCSC, carotid cross-sectional compliance; cCSD, carotid cross-sectional distensibility; cDC, carotid diameter compliance; cDD, carotid diameter distensibility; cIEM, carotid incremental elastic modulus; cIMT, carotid intima media thickness; cLD, carotid lumen diameter; FMD, flow-mediated dilation; h^2, heritability analysis; MAP, mean arterial pressure; PWV, pulse wave velocity.
*Denotes all models further adjusted for brachial artery diameter.

Estimates of cIMT, FMD for father-offspring, and carotid diameter compliance for mother-offspring could not be reliably performed even after data transformations were attempted. Among complete trios, brachial artery diameter (h^2=21.4±12.3%; *P*=0.035), cLD (h^2=58.3±10.3; *P*<0.001), cIEM (h^2=30.2±11.8; *P*=0.005), cDD (h^2=33.2±9.9; *P*<0.001), cCSD (h^2=30.6±9.8; *P*<0.001), cCSC (h^2=23.5±10.7, *P*=0.012), and PWV (h^2=29.4±12.2; *P*=0.006) all had significant heritability estimates. Among mothers and their offspring, brachial artery diameter (h^2=37.5±10.2%; *P*<0.001), cLD (h^2=49.2±10.6; *P*<0.001), cDD (h^2=23.4±9.8; *P*=0.006), cCSD (h^2=22.9±9.7; *P*=0.007), cCSC (h^2=19.4±9.9, *P*=0.02), and PWV (h^2=33.3±11.0; *P*<0.001) all had significant heritability estimates. Among fathers and their offspring, cLD (h^2=74.1±12.8; *P*<0.001), cIEM (h^2=42.7±12.7; *P*<0.001), cDD (h^2=41.5±10.7; *P*<0.001), cCSD (h^2=40.5±10.7; *P*<0.001), cCSC (h^2=51.0±12.8, *P*<0.001), and PWV (h^2=23.1±13.0; *P*=0.032) all had significant heritability estimates.

Table 3. Association Between Vascular Structure and Function Measures Among Siblings and Parent and Their Offspring

	Siblings (n=338)		Parent-Offspring (n=477)	
Measure	*r*	*P* Value	*R*	*P* Value
Brachial artery diameter, mm	0.14	0.012	0.11	0.021
FMD, %*	0.04	0.53	0.01	0.90
cLD, mm	0.31	<0.001	0.22	<0.001
cIMT, mm	0.11	0.052	0.08	0.073
cIEM, mm Hg	0.16	0.002	0.04	0.36
cDD, %	0.15	0.005	0.19	<0.001
cCSD, %	0.15	0.005	0.19	<0.001
cDC, mm/mm Hg	−0.03	0.58	0.03	0.46
cCSC, mm^2/mm Hg	0.21	<0.001	0.14	0.015
PWV, m/s	0.24	<0.001	0.14	0.018

Data are partial Pearson correlations adjusted for age, sex, race, BMI, MAP, and smoking of both participants. BMI indicates body-mass index; cCSC, carotid cross-sectional compliance; cCSD, carotid cross-sectional distensibility; cDC, carotid diameter compliance; cDD, carotid diameter distensibility; cIEM, carotid incremental elastic modulus; cIMT, carotid intima media thickness; cLD, carotid lumen diameter; FMD, flow-mediated dilation; MAP, mean arterial pressure; PWV, pulse wave velocity.
*Denotes further adjustment for brachial artery diameter.

Conclusion

The results from this study show that in a large, multiracial cohort of adults and their children, the majority of noninvasive measures of vascular structure and function have a significant heritable relationship. To our knowledge this is the first study conducted in parents and children prior to adulthood. Of the variables measured, cLD had the highest level of heritability. Most measures of arterial stiffness, cIMT, and brachial artery diameter showed only modest heritable relationships, and FMD was not found to be heritable in any of the analyses performed. Nontwin siblings demonstrated familial vascular measurement associations that were similar to the associations of parents and their offspring. Heritable relationships in

Table 4. Relationship of Mothers, Fathers, or Complete Trios (Both Mother and Father) With Their Offspring for Measures of Vascular Structure and Function

	Complete Trios (n=136)		Mother-Offspring (n=291)		Father-Offspring (n=186)	
Measure	h^2 (SE)	*P* Value	h^2 (SE)	*P* Value	h^2 (SE)	*P* Value
Brachial artery diameter, mm	21.4 (12.3)	0.035	37.5 (10.2)	<0.001	34.0 (11.6)	<0.001
FMD (%)*	2.2 (12.4)	0.43	18.6 (14.1)	0.08	N/A†	N/A†
cLD, mm	58.3 (10.3)	<0.001	49.2 (10.6)	<0.001	74.1 (12.8)	<0.001
cIMT, mm	N/A†	N/A†	N/A†	N/A†	N/A†	N/A†
cIEM, mm Hg	30.2 (11.8)	0.005	5.3 (10.9)	0.31	42.7 (12.7)	<0.001
cDD (%)	33.2 (9.9)	<0.001	23.4 (9.8)	0.006	41.5 (10.7)	<0.001
cCSD (%)	30.6 (9.8)	<0.001	22.9 (9.7)	0.007	40.5 (10.7)	<0.001
cDC, mm/mm Hg	8.6 (10.1)	0.19	N/A†	N/A†	6.2 (10.2)	0.27
cCSC, mm^2/mm Hg	23.5 (10.7)	0.012	19.4 (9.9)	0.02	51.0 (12.8)	<0.001
PWV, m/s	29.4 (12.2)	0.006	33.3 (11.0)	<0.001	23.1 (13.0)	0.032

Data are adjusted for age, sex, race, BMI, MAP, and smoking of both parents and offspring. BMI indicates body-mass index; cCSC, carotid cross-sectional compliance; cCSD, carotid cross-sectional distensibility; cDC, carotid diameter compliance; cDD, carotid diameter distensibility; cIEM, carotid incremental elastic modulus; cIMT, carotid intima media thickness; cLD, carotid lumen diameter; FMD, flow-mediated dilation; h^2, heritability analysis; MAP, mean arterial pressure; PWV, pulse wave velocity.

*Denotes all models further adjusted for brachial artery diameter.

†N/A, estimates were unable to be reliably performed.

complete trios were similar to the whole cohort analyses. Examination of parent-offspring relationships showed greater heritability estimates for cLD and measures of arterial stiffness for father-offspring than mother-offspring. All of these relationships were independent of other factors such as age, sex, race, BMI, smoking, and mean arterial pressure.

To our knowledge, this is the first study to examine heritability for PWV, FMD, and measures of carotid compliance and dispensability (cDD, cCSD, CSC1, and carotid diameter compliance) in parents and their offspring. However, prior studies have measured heritability of other vascular measurements. Similar to this study, significant heritability estimates for cLD, cIMT, and cIEM were reported by North and colleagues from a multigenerational cohort of adult American Indians in the Strong Heart Family Study.[20] By contrast, our adjusted heritability estimates were higher for cLD (55.4% versus 44%), cIMT (28.1% versus 21%), and lower for cIEM or β (12.7% versus 23%), but the CIs overlap each other. These differences may be possibly attributable to differences in age (ie, our inclusion of adolescents) and racial/ethnic groups included in the 2 studies. For cIMT, our heritability estimates are similar to that of Xiang and colleagues,[31] who estimated heritability from parents to offspring in hypertensive Latino families (28.1% versus 34%) and Zannad et al, in a study of parents and their adolescent and young adult offspring (28.1% versus 30%).[32]

However, our findings are not in line with a small cohort study examining the relationship of brachial artery diameter and FMD among mono- and dizygotic twins (n=22). Hopkins and colleagues found a significant heritable relationship between twins for FMD but a nonsignificant relationship for brachial artery diameter.[19] The present study found the opposite: We report significant heritability for brachial artery diameter in the cohort as a whole, siblings, single parent and offspring, and complete trios, but no significant relationships for FMD. While it is not clear why these conflicting results occurred, it may simply be related to twin studies not being an ideal comparison as opposed to our familial study or the advantage of studying a substantially larger cohort. Of additional interest is our observation that father-offspring heritability estimates for measures of cLD and arterial stiffness were consistently higher than that of mother-offspring, despite similar levels of significance. To our knowledge, none of the previously published studies examined heritability of vascular measures by sex of parents, making comparisons challenging and representing a future direction for other studies to explore.

This study had some potential limitations. The sample size was small, possibly affecting subanalyses, and we were unable to examine racial differences. The cross-sectional nature, as opposed to longitudinal data, did not permit evaluation of the heritable measures relative to cardiovascular outcomes. Our use of carotid-radial PWV is not the standard measurement location of arterial stiffness for this measure (eg, carotid-femoral PWV is standard) and may have affected our findings for this metric. Additionally, the measurement of blood pressure did not comply with current guidelines, as these data were collected before measures in triplicate using

an automated cuff were standard. These limitations are offset by the study strengths, including the large sample of adults and offspring; examination of offspring prior to adulthood; equal sex distribution; racial diversity; an ability to control for several important covariates; and a broad-based measure of vascular structure and function.

In conclusion, we observed in a large cohort of parents and their child-adolescent offspring that the majority of noninvasive measures of vascular structure and function are heritable. Measures of structure showed stronger degrees of heritability than those related to functionality of vessels. Thus, adverse vascular phenotypes that develop early in the lifespan may contribute to increased lifetime burden of cardiovascular disease. These findings, when combined with other measures of cardiovascular risk, particularly in high-risk families, may be beneficial in counseling parents about their children's cardiovascular health.

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Disclosures

None.

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