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## Decreased heritability and emergence of novel genetic effects on pulse wave velocity from youth to young adulthood

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Increased arterial stiffness measured by pulse wave velocity (PWV) is an important parameter in the assessment of cardiovascular risk. Our previous longitudinal study has demonstrated that carotid-distal PWV showed reasonable stability throughout youth and young adulthood. This stability might be driven by genetic factors that are expressed consistently over time. We aimed to illustrate the relative contributions of genetic and environmental factors to the stability of carotid-distal PWV from youth to young adulthood. We also examined potential ethnic differences. For this purpose, carotid-distal PWV was measured twice in 497 European American (EA) and African American (AA) twins, with an average interval time of 3 years. Twin modelling on PWV showed that heritability decreased over time (62–35%), with the nonshared environmental influences becoming larger. There was no correlation between the nonshared environmental factors on PWV measured at visit 1 and visit 2, with the phenotypic tracking correlation ( $r = 0.32$ ) completely explained by shared genetic factors over time. Novel genetic influences were identified accounting for a significant part of the variance (19%) at the second measurement occasion. There was no evidence for ethnic differences. In summary, novel genetic effects appear during development into young adulthood and account for a considerable part of the variation in PWV. Environmental influences become larger with age for PWV.

Increased arterial stiffness measured by pulse wave velocity (PWV) has been shown to be an important parameter in the assessment of cardiovascular (CV) risk. Previous longitudinal studies have confirmed the value of PWV measurements involving elastic arteries such as carotid-femoral and carotid-distal PWV in predicting cardiovascular events in patients with hypertension<sup>1</sup>, diabetes<sup>2</sup>, or end-stage renal disease<sup>3</sup> as well as in general populations<sup>4,5</sup>. Cross-sectional studies have shown that individual differences in PWV were influenced by demographic factors such as age, gender and ethnicity, as well as genetic factors. Family and twin studies have shown that up to 53% of the individual differences in PWV can be attributed to genetic factors<sup>6–8</sup>.

Previously, we demonstrated reasonable stability of carotid-femoral and carotid-distal PWVs from youth to young adulthood<sup>9</sup>. Part of this stability might be caused by genetic factors that are expressed steadily over time. There have been no studies reporting the relative contribution of genetic and environmental factors to PWV stability over time. Understanding the sources of PWV stability over time is of considerable interest for the design of studies aiming to identify its determinants at an early age. On the other hand, PWV is known to increase with age and has been used as an index of vascular aging<sup>10</sup>. The age-specific increase in PWV raises several interesting questions. First, do novel environmental and/or genetic influences on PWV become apparent during the course of development? Second, is the age-specific increase in PWV levels a heritable trait itself? That is, to what extent is the increase of PWV over age genetically determined. All these questions have not been addressed in previous studies. Built on the Georgia Cardiovascular Twin Cohort which has carotid-distal PWV measured twice in 497 European American (EA) and African American (AA) twins, with an intervening period of 3 years, we will address these questions using bivariate twin modeling. Furthermore, ethnicity and gender differences in PWV have been well demonstrated with AAs and males having higher PWV than EAs and females<sup>11,12</sup>. Our bi-ethnic

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cohort with both males and females will allow us to further test the ethnic and gender dependency of the relative contribution of genes and environment to the individual differences in PWV over time.

## Methods

**Subjects.** The present study comprised subjects from the Georgia Cardiovascular Twin Study which was established in 1996. It included roughly equal numbers of EAs and AAs (> 500 twin pairs) with the purpose to evaluate the change in relative influence of genetic and environmental factors on the development of cardiovascular risk factors. All twin pairs were reared together and zygosity was determined using five standard microsatellite markers in DNA collected with buccal swabs<sup>13</sup>. Subjects were recruited from the southeastern United States and were overtly healthy and free of any acute or chronic illness based on parental report. Study design, selection criteria and the criteria to classify subjects as EAs or AAs have been described previously<sup>8,13</sup>.

For the current study, data were available from 289 EA twins (46 monozygotic [MZ] vs. 75 dizygotic [DZ] pairs and 47 singletons; 52.2% females; aged  $17.4 \pm 3.4$  at baseline) and 208 AA twins (25 MZ pairs vs. 59 DZ pairs and 40 singletons; 58.7% females; age  $17.1 \pm 3.5$  at baseline) who had carotid-distal PWV measured at two visits with an average intervening time period of 3.7 years. The Institutional Review Board at the Augusta University had given approval for this study. Written informed consent was obtained from all subjects (and parents if subjects were < 18 years).

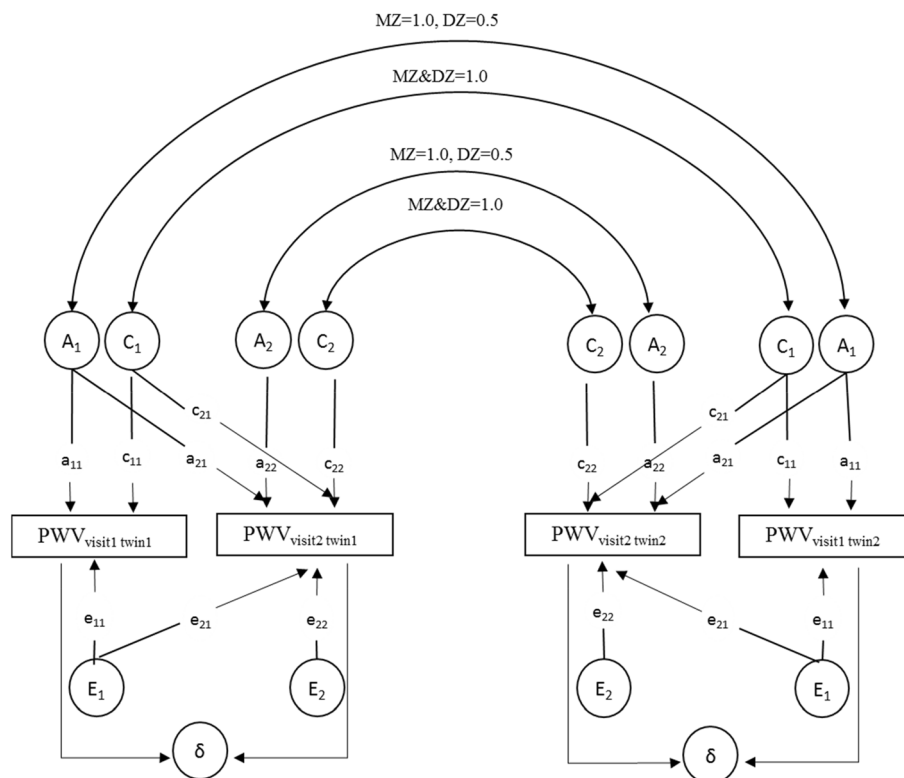
**Measurements.** Carotid-distal PWV was measured noninvasively with applanation tonometry (Millar Instruments) and the SphygmoCor CPV analysis software (SphygmoCor, AtCor Medical, Sydney, Australia). Pressure waves were recorded at the common carotid and dorsalis-pedis arteries for the carotid-distal PWV. The SphygmoCor system calculated PWV from measurements of pulse transit time and the distance traveled by the pulse between the two recording sites:  $PWV = \text{Distance (meters)}/\text{Transit Time (seconds)}$ . The carotid-distal rather than carotid-femoral was used due to its ease of access. Carotid-distal PWV measures arterial stiffness in both elastic and muscular artery and studies from our own and others<sup>9,14,15</sup> have demonstrated that it not only showed reasonable stability over time but also was comparable to carotid-femoral PWV regarding to its correlations with other CVD risk factors as well as its predictive value of CVD morbidity and mortality.

Systolic BP (SBP), diastolic BP (DBP) and mean arterial BP (MAP) (Dinamap 1864 SX; Criticon Incorporated, Tampa, FL) were taken at 11, 13 and 15 min, during a 15-min supine relaxation period. The average was used to represent resting SBP, DBP and MAP. Anthropometrics and body composition assessment were obtained during the examination. Height and weight were measured by standard methods using a wall-mounted stadiometer and a digital scale, respectively. Body mass index (BMI) was calculated as  $\text{weight}/\text{height}^2$  ( $\text{kg}/\text{m}^2$ )<sup>13</sup>.

**Statistical analysis.** The aim of this study was to determine the relative contributions of genetic and environmental factors to the development of PWV from age 17 and 20 years and to what extent they depend on gender and ethnicity. Prior to all analyses, PWV was log transformed. Structural equation modeling (Fig. 1) was used to compare the variance–covariance matrices in MZ and DZ twins. The observed phenotypic variance of PWV at each visit was decomposed into additive genetic components (A), common environmental component shared by a twin pair (C), and unique environmental component specific to individuals (E). Dominance genetic effects (D) were not considered based on inspection of the twin correlations. The heritability ( $h^2$ ) was defined as the proportion of the total variance attributable to the additive genetic variation. A bivariate twin model was used for the current study (see Fig. 1). With the so-called Cholesky decomposition model, we can not only estimate the heritability of PWV at the first visit ( $h^2_{\text{visit } 1} = a_{11}^2/(a_{11}^2 + c_{11}^2 + e_{11}^2)$ ) and PWV at the second visit ( $h^2_{\text{visit } 2} = (a_{21}^2 + a_{22}^2)/(a_{21}^2 + a_{22}^2 + c_{21}^2 + c_{22}^2 + e_{21}^2 + e_{22}^2)$ ), but also can test whether the magnitude of the genetic influence differs between the 1st and 2nd visit (i.e.  $h^2_{\text{visit } 1} = h^2_{\text{visit } 2}$ ). By constraining certain path coefficients to zero (Fig. 1) we can further test whether the genes influencing PWV at the second visit are the same (i.e.,  $a_{22} = 0$ ?), partly the same (i.e.,  $a_{21} \neq 0$  and  $a_{22} \neq 0$ ?), or entirely different (i.e.,  $a_{21} = 0$ ?) from the genes influencing PWV at the first visit. If they were partly the same, this bivariate model allows further determination of the amount of overlap between genes influencing PWV measured at both visits by calculating the genetic correlation (i.e. genetic tracking coefficient) between the 2 PWV measurements. Shared and unique environmental correlations can be calculated in a similar fashion. Within the best fitting bivariate model of the PWV, we also calculated the heritability of PWV change between visit 1 and 2. The heritability of the difference score (i.e., PWV visit 2–PWV visit 1) can simply be derived from the parameter estimates of the phenotype levels in the bivariate model (Fig. 1). Significance of all of these models was tested by likelihood ratio tests. The model has been described in our previous study<sup>16</sup>.

The ethnic and gender differences were examined by comparing a full model in which the parameter estimates were allowed to differ among the four ethnic and gender groups (i.e. EA males, EA females, AA males and AA females), with a reduced model in which the parameter estimates were constrained to be equal across the groups. Significance of all of these models was tested by likelihood ratio tests.

Because BP is an important determinant of PWV and might explain part of its familial aggregation, we performed all model-fitting analyses before and after adjustment for MAP. All quantitative genetic modeling was carried out using OpenMx, version 1.2, an open source R-based package for analysis of twin data<sup>17,18</sup>. All parameter estimates in the twin analyses were obtained from full maximum-likelihood estimates in OpenMx, which enables handling of missing data and the inclusion of singletons.



**Figure 1.** Bivariate structural equation model. The  $A_1$  and  $A_2$  are additive genetic factors. The  $E_1$  and  $E_2$  are unique environment factors. The  $C_1$  and  $C_2$  are shared environment factors. The paths of genetic factors are  $a_{11}$  through  $a_{22}$ . The paths of unique environment factor are  $e_{11}$  through  $e_{22}$ . The paths of shared environment factor are  $c_{11}$  through  $c_{22}$ . Subtracting the level of measured PWV at visit 2 from visit 1 is established by setting the path coefficients of  $\delta$  originating from visit 1 and visit 2 to  $-1$  to  $1$ , respectively.

	European American				African American			
	Visit 1		Visit 2		Visit 1		Visit 2	
	Male	Female	Male	Female	Male	Female	Male	Female
N	138	151	138	151	86	122	86	122
Age (years)	17.2 (3.6)	17.5 (3.1)	20.6 (4.2)	21.4 (4.0)	16.7 (3.1)	17.3 (3.8)	20.2 (4.3)	21.3 (4.4)
Height (cm)	171.1 (11.4)	161.3 (7.8)	175.6 (7.8)	162.4 (6.7)	172.0 (10.6)	162.6 (5.6)	175.9 (7.8)	163.5 (5.8)
Weight (kg)	69.0 (21.7)	59.7 (14.6)	77.90 (21.5)	64.2 (16.0)	73.0 (24.4)	68.8 (18.3)	81.5 (21.4)	76.7 (21.9)
BMI (kg/m <sup>2</sup> )	23.6 (5.9)	22.9 (4.8)	25.3 (6.5)	24.3 (5.6)	24.7 (6.0)	26.0 (6.5)	26.4 (6.1)	28.7 (7.8)
Waist (cm)	81.9 (15.11)	76.5 (12.3)	86.7 (15.6)	81.1 (14.0)	79.6 (14.9)	80.5 (13.2)	84.5 (15.4)	88.2 (18.3)
SBP (mmHg)	114.2 (10.6)	107.4 (8.3)	114.6 (10.8)	107.5 (9.6)	118.2 (10.6)	120.6 (10.9)	110.9 (10.6)	113.2 (11.9)
DBP (mmHg)	57.2 (6.9)	59.9 (6.8)	59.1 (7.7)	61.7 (6.6)	60.0 (6.7)	62.1 (8.2)	61.9 (7.5)	65.3 (8.7)
PWV (m/s)	7.08 (0.88)	6.99 (0.89)	7.60 (0.97)	7.24 (0.90)	6.98 (0.73)	7.21 (1.02)	7.73 (0.97)	7.82 (0.96)

**Table 1.** General characteristics of study participants by visit, ethnicity and gender. Data were present as mean (SD). All variables showed significant increase from visit 1 to visit 2 with  $p < 0.001$ .

### Results

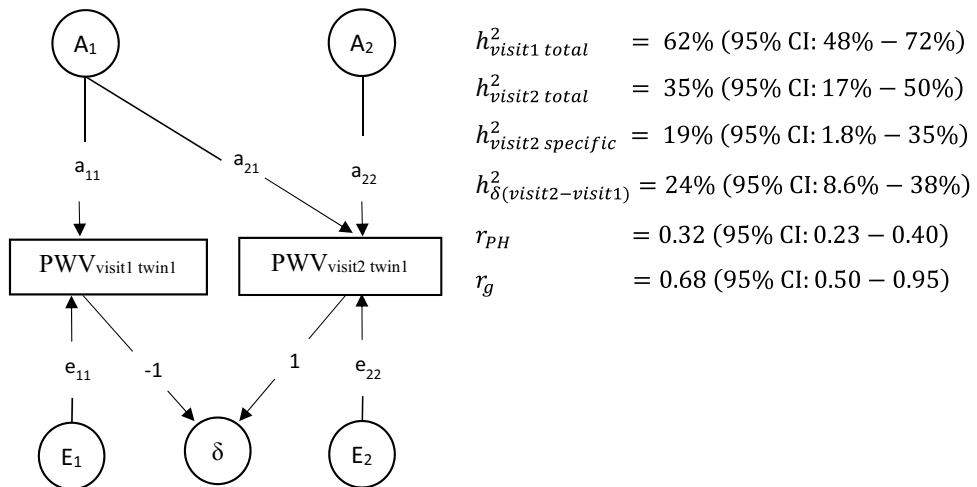
The general characteristics of the participants by visit, ethnicity and gender were presented in Table 1. The mean age was 17 for the first visit and 20 for the second visit. Overall, PWV increased with age ( $p < 0.01$ ) and AAs had higher PWV than EAs ( $p < 0.01$ ). A significant 3 way interaction among ethnicity, gender and visit was observed. In the stratified analysis by ethnicity, EA males had higher PWV levels ( $p < 0.01$ ) and faster increase over time ( $p = 0.02$ ) than EA females, while no differences in PWV levels and rate of increase were observed between AA males and females.

In both ethnic groups, twin correlations of MZ pairs were larger than those of DZ pairs, indicating genetic influences. Overall, the correlations of the second visit were smaller than the first visit for all groups (Table 2).

Results from bivariate testing, using the model depicted in Fig. 1, are shown in Fig. 2. The overall best fit to the data for PWV at both visits is the model including an additive genetic and unique environmental component

	European American		African American	
	Monozygotic	Dizygotic	Monozygotic	Dizygotic
N of pairs	46	75	25	59
Visit 1 PWV	0.66	0.54	0.70	0.54
Visit 2 PWV	0.41	0.27	0.64	0.37

**Table 2.** Twin correlations of visit 1 and visit 2 by ethnicity and zygosity.



**Figure 2.** Path diagram for best fitting bivariate structural equation model (Cholesky model). The best fitting model was model composed of additive genetic factor (A), unique environment factor (E). The path of genetic factors between two visits is  $a_{21}$ . The path of unique environmental factors between the phenotypes of the two visits is  $e_{21}$ . The pathway  $a_{21}$  and  $a_{22}$  cannot be set to 0 while pathway  $e_{21}$  can be set to 0.  $r_{PH}$  is the phenotypic correlation for PWV between visit 1 and visit 2.  $r_g$  is the genetic correlation for PWV between visit 1 and visit 2.  $r_g = \text{COV}_A(1\text{st visit}, 2\text{nd visit}) / \sqrt{(V_A\ 1\text{st visit} * V_A\ 2\text{nd visit})}$ , with  $\text{COV}_A$  represents covariance and  $V_A$  represents variance.

(ACE vs. AE  $\chi^2_3 = 1.29, p = 0.73$ , ACE vs. CE  $\chi^2_3 = 7.65, p = 0.05$ , AE vs. E  $\chi^2_3 = 51.43, p < 0.001$ ). Furthermore, for both time points, no significant differences in the estimates of genetic and environmental variance components between males and females or between AAs and EAs were identified by the structural equation modelling, indicating the relative contribution of genetic and environmental factors to the variances of PWV over time does not depend on gender and ethnicity.

As shown in Fig. 2, significant heritability was found for PWV at both visits. However, there was a large decrease in heritability of PWV (from 0.62 to 0.35,  $p < 0.01$ ) in visit 2. The path  $e_{21}$  can be set to zero ( $e_{21} \neq 0$  vs.  $e_{21} = 0, \chi^2_1 = 0.46, p = 0.50$ ) while  $a_{21}$  cannot be set to zero ( $a_{21} \neq 0$  vs.  $a_{21} = 0, \chi^2_1 = 17.61, p < 0.001$ ), indicating that the tracking of PWV over time (i.e. phenotypic correlation  $r_{ph} = 0.32$ ) can be completely accounted by shared genetic factors overtime. Furthermore,  $a_{22}$  cannot be set to 0 ( $a_{22} \neq 0$  vs.  $a_{22} = 0, \chi^2_1 = 5.15, p = 0.02$ ), indicating that there are new genetic influences emerging at the second visit. The specific heritability due to novel genetic effects emerging in visit 2 was 19% (95% CI: 1.8–25%). We also observed that the increase of PWV over time (i.e. delta in Fig. 1) was influenced by genetic factors with a heritability of 24% (95% CI: 8.6–37.9%).

The results from the twin modeling were identical after adjustment for MAP, indicating that the findings on PWV are independent of BP.

## Discussion

The important findings in this study are that independent of ethnicity and gender, the overall genetic influences on PWV decrease over time (from 62 to 35%), with emergence of novel genetic influences on PWV at visit 2. Furthermore, genetic factors are the major contributors to the tracking stability of PWV, with the phenotypic tracking coefficient completely explained by shared genetic factors over time, and the age specific increase in PWV is a heritable trait itself with a heritability of 24%.

It is well established that PWV increases with age<sup>19,20</sup>. Our study on PWV trajectories also documented an increase of PWV with age from youth to young adulthood in both AAs and EAs as well as males and females<sup>21</sup>. The increase in PWV with age suggests that different genetic or environmental mechanisms may have their influence on PWV in different periods of life. Without available genome-wide association study (GWAS) data on different age categories this question can only be answered through longitudinal twin or family studies in which the same subjects are measured repeatedly, although comparing cross-sectional family and twin studies

conducted in different age groups may give us some clues. Our previous cross-sectional study on the Georgia Cardiovascular Twin Cohort observed a heritability of 53% for PWV at age  $17.7 \pm 3.3$  years<sup>8</sup>. Tarnoki et al<sup>22</sup> reported a heritability of 50% in healthy Hungarian and American Caucasian twins aged  $43 \pm 17$  years, Medda et al<sup>23</sup> reported a heritability of 49% in a middle age population ( $54.6 \pm 12.4$  years) from the Italian Twin Register, and the Twins UK study<sup>6</sup> reported a heritability of 38% in female twins aged  $58 \pm 10$  years. While a trend of small decrease in PWV heritability with aging might be detected, the large age range of these studies and the small differences in PWV heritabilities prevent us from drawing any solid conclusions. Recently, in a large family study in a Brazilian population, Alvim et al<sup>24</sup> reported a heritability of 30–35% for PWV in participants with age  $\leq 45$  and 13–20% in participants with age  $> 45$ , providing the first piece of evidence on the decreased heritability of PWV with age. Our longitudinal twin study not only confirmed this finding, but also observed the emergence of new genetic influence on PWV with age. These results have important implications for gene-finding studies. In current gene-finding efforts for complex traits, large sample sizes are required to reach sufficient statistical power, especially when a GWAS design is used. Our study calls caution in pooling data from different age groups. Since the current study only targeted the PWV development from age 17 to 20, further follow-up of our twin sample will enable us to determine at what age the genetic component stabilizes (i.e. at what age no further novel genetic effects are expressed).

Progression of arterial stiffness measured by PWV changes over time has been used as an index of vascular aging<sup>10</sup>. Recently, the Twins UK study<sup>25</sup> observed a heritability of 55% for the annual progression of PWV in female twins aged  $57.9 \pm 8.6$  years with a follow-up of 5 years. In this study, we showed that even in youth and young adult, the PWV change over 3 years was a heritable trait with a heritability of 24%. So far, few studies have explored the physiological determinants of accelerated progression of aortic stiffness. The identified factors included high BP, smoking and male gender<sup>19,25,26</sup>. The identified heritability of PWV changes over time in youth and young adults implicates that genes also play an important role in the accelerated progression of aortic stiffness.

Ethnic differences in PWV have been reported with AAs having higher values than EAs<sup>14,15,27</sup>. We documented the same difference in the current study. However, the twin modelling analysis showed that the difference in mean values did not convert to many differences in genetic and environmental variability within each ethnic group. However, the fact that a similar amount of variation is explained by genetic factors within EAs and AAs does not exclude the possibility that the actual genes or their number responsible for these effects may differ between these two ethnic groups.

This study has several limitations. First, the generalizability of the results from the current study, which is comprised of youth and young adults, to other adult or elderly populations remains to be determined. Second, our overall sample size was substantial for longitudinal PWV measurements but may not have enough power to detect ethnic or gender differences in the relative contributions of genetic and environmental factors to the variations of PWV. Future twin studies with large sample sizes and long-term follow-up involving multiethnic groups are warranted.

In summary, our study demonstrated that the heritability of PWV decreased with age and different genes may have their influence on PWV in different periods of life. The increase of PWV with age is itself a heritable trait. These findings have important implications for gene finding studies.

**Ethics approval and consent to participate.** This study was approved by the Institutional Review Board of Augusta University, and performed following the guidelines of the Declaration of Helsinki. Written informed consent was provided by all participants or by their parents if they were less than 18 years.

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## Author contributions

Y.H. conducted the analysis and drafted the manuscript; S.S. conducted the analysis and critically revised the manuscript; H.S. critically revised the manuscript; F.T. designed the original study and critically revised the manuscript; G.K. participated in the collection of the data. X.W. designed the study, participated in the draft of the manuscript and made critical revision of the manuscript.

## Competing interests

The authors declare no competing interests.

## Additional information

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