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MAOA Genotype, Childhood Trauma and Subclinical Atherosclerosis: A Twin Study

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Abstract

Objective—A functional promoter polymorphism in the MAOA gene has been implicated in neuropsychiatric disorders and also moderates the association between early life stress and mental disorders, which often co-occur with cardiovascular disease. No study has examined the relationship between MAOA genotype, childhood trauma and subclinical atherosclerosis. The objective of this investigation was to examine whether childhood trauma moderates the association between MAOA genotype and subclinical atherosclerosis.

Methods—A sample including 289 middle-aged male twin pairs was studied. Subclinical atherosclerosis was assessed by brachial flow-mediated dilation (FMD) using ultrasound. Childhood trauma, before age 18, was measured with the Early Trauma Inventory and included physical, emotional, and sexual abuse as well as general trauma. Generalized estimating equation models were used to test the main and interactive effects of the MAOA genotype and each domain of childhood trauma on FMD, adjusting for known risk factors.

Results—General trauma was the most prevalent childhood trauma (28.4%), followed by physical abuse (25.0%), emotional abuse (19.4%) and sexual abuse (11.6%). MAOA genotype was not associated with any domain of childhood trauma ($\beta = 0.36$). There was no significant evidence for a main effect for the MAOA genotype ($\beta = 0.02$, $p = 0.82$) or childhood trauma ($0.005 < \beta < 0.10$, $p > 0.54$) on early atherosclerosis. However, a significant interaction was observed between MAOA genotype and physical ($\beta_{\text{interaction}} = 0.37$, $p = 0.026$) or emotional abuse ($\beta_{\text{interaction}} = 0.43$, $p = 0.025$) on subclinical atherosclerosis.

Conclusion—This study provides initial evidence that childhood trauma modulates the impact of MAOA variant on subclinical atherosclerosis, independent of traditional cardiovascular risk factors.

Disclosures: None

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Keywords

MAOA genotype; childhood trauma; gene $\times$ environment interaction; subclinical atherosclerosis; twin study

INTRODUCTION

Atherosclerosis is a multifactorial process resulting from the complex interplay between gene and environment (1). Early life stress (ELS) plays an important role in the development of atherosclerosis (2, 3). Exposure to childhood adversity directly increases the risk of atherosclerotic cardiovascular disease (CVD). For example, in a retrospective study, individuals who as children experienced adversity (childhood abuse, neglect and household dysfunction) exhibited a significantly higher risk of developing ischemic heart disease (1.3- to 1.7-fold) in adulthood compared to those without adversity (4). Another study demonstrated that childhood maltreatment (sexual abuse, physical abuse and neglect) was associated with an almost 9-fold increase in cardiovascular disorders as well as a significant increase in the odds of lifetime depressive disorders (2). Childhood traumatic events are also associated with cardiovascular risk factors such as smoking (5), obesity, (6) inflammation (7, 8), and depression (2, 9).

Monoamine oxidase A (MAOA) is a mitochondrial enzyme that selectively degrades neurotransmitters such as serotonin (5-HT), noradrenaline (NE) and dopamine (DA). These neurotransmitters play an important role in the regulation of hypothalamic-pituitary-adrenal (HPA) axis (10, 11), a mechanism implicated in CVD (12). The gene encoding MAOA enzyme is located on the short arm of the X chromosome (X11.23-11.4). A variation that has been mostly studied is a variable number tandem repeat (VNTR) in the promoter region of the MAOA gene (MAOA-uVNTR) (13, 14). This polymorphism, 30 base pair (bp) in length, demonstrates a transcriptional activity in gene reporter assays. The “high activity” alleles (mostly have 4 repeats of the 30 bp sequence) transcribed 2-10 times more efficient than the “low activity” alleles (mostly have 3 repeats of the 30 bp sequence) (13). Allelic variation in MAOA-uVNTR is associated with stress-related disorders such as impulsive (15) and mental disorders (16, 17). The MAOA-uVNTR polymorphism is also associated with coronary risk factors such as lipid levels (18), body mass index (BMI) (19), and smoking behavior (20).

While childhood adversity has profound impact on human health into adulthood, interindividual variability in stress resiliency varies significantly. Some individuals exposed to childhood abuse develop disease while others do not. Therefore, the interaction of gene polymorphisms with adverse childhood experiences is believed to play a substantial role in influencing an individual's susceptibility to disease risk. Recent findings indicate that MAOA gene moderates an individual's response to stress or stress-induced disorders (16, 21-24). Caspi *et al* (21) first reported that individuals with low activity MAOA alleles (MAOA-L) who were maltreated as children were more likely to develop violent and antisocial behaviors as adults than individuals with high-activity MAOA alleles who were maltreated as children. This gene $\times$ environment interaction effect on behavioral disorders, however, has not been consistently replicated, with some studies reporting replication (16, 25, 26), but others finding no (27, 28) or even opposite direction (29). Though results are mixed (27, 30, 31), these findings suggest a potential critical role of interactions between the MAOA-uVNTR genotype and childhood adversity on the vulnerability of behavioral and/or neuropsychiatric disorders, which often co-occur with cardiovascular disease (32, 33).

This study aims to examine whether the MAOA-uVNTR genotype is associated with subclinical atherosclerosis, and whether childhood traumatic experiences moderate this association in a well-characterized twin sample. To our best knowledge, this is the first study to investigate the potential relationship between MAOA genotype, childhood trauma and subclinical atherosclerosis using a well-matched co-twin control design.

SUBJECTS AND METHODS

Study population

The Emory Twins Study (ETS) is an investigation of psychological, behavioral and biological risk factors for subclinical cardiovascular disease in twins, and the methods were previously described (34). In brief, the study includes samples recruited in two companion studies: the Twins Heart Study (THS) and the Stress and Vascular Evaluation in Twins (SAVEIT). Both projects recruited middle-aged male monozygotic (MZ) and dizygotic (DZ) twin pairs from the Vietnam Era Twin Registry, one of the largest twin registries in the United States (35). Both studies followed identical procedures, measurements, and protocols. THS enrolled 180 twin pairs (102 MZ pairs, 78 DZ pairs) between 2002 and 2006, and SAVEIT included 124 twin pairs (83 MZ pairs, 41 DZ pairs) enrolled between 2005 and 2010. All twins were born between 1946 and 1956 and were free of symptomatic cardiovascular disease at baseline based on preexisting survey data (36). In addition, a sample of twin pairs discordant for major depressive disorder (MDD) was included in THS, and a sample of twin pairs discordant for posttraumatic stress disorder (PTSD) was included in SAVEIT. Twins were examined together at the Emory University General Clinical Research Center, where their medical history was updated. The study protocol was approved by the Institutional Review board at Emory University, and informed consent was obtained from all twins. Because over 95% of the twin participants are white, to avoid population stratification, the present analyses only include 289 white twin pairs (175 MZ pairs, 114 DZ pairs, 169 pairs from THS and 120 pairs from SAVEIT). Zygosity information was determined by DNA analysis using methods described previously (37).

Risk factor measurements

All measurements were performed in the morning after an overnight fast, and both twins in a pair were tested at the same time. A medical history and a physical exam were obtained from all twins. Weight and height were used to calculate body mass index (BMI) as weight in kilograms divided by height in meters squared. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by mercury sphygmomanometer on the right arm with the participant in sitting position after 10 minutes of rest. Cigarette smoking was classified into current smoker (any number of cigarettes) versus never or past smoker. Physical activity was assessed by means of a modified version of the Baecke Questionnaire of Habitual Physical Activity (38) a 16-question instrument documenting level of physical activity at work, during sports and non-sports activities. The total physical activity score was used in the analysis. Information on alcohol consumption was collected by asking about the number of alcoholic drinks (beer, wine or liquor) consumed in a typical week. The total amount of alcohol consumption (in grams) per week was estimated based on the following algorithms: 4 oz of wine contains 10.8 g, 12 oz of beer contains 13.2 g, and 1.5 oz of liquor contains 15.1 g of ethanol. Total triglycerides and cholesterol were determined by enzymatic methods (Beckman Coulter Diagnostics, Fullerton, CA). Direct high-density lipoprotein (HDL) and direct low-density lipoprotein (LDL) cholesterol were obtained using homogeneous assays (Equal Diagnostics, Exton, PA). Glucose levels were measured on the Beckman CX7 chemistry autoanalyzer.

Brachial artery flow-mediated dilatation (FMD) assessment

Endothelium-dependent brachial artery flow-mediated dilatation (FMD), an index of subclinical atherosclerosis (39), was determined using bi-mode ultrasound according to standardized procedures, as described previously (40). In brief, images were obtained with an Acuson 10 mHz linear array transducer and ultrasound system (Mountain View, CA). We performed imaging with the participant resting supine for at least 10 minutes on a hospital bed in a quiet setting. Optimal brachial artery images were obtained between 2 and 10 cm above the antecubital crease. After baseline measurements a blood pressure cuff was inflated to 200 mm Hg over the proximal portion of the right forearm for 5 minutes. Endothelium-dependent function was determined during the first two minutes of release of the cuff (41). After a 15-minute period to reestablish baseline conditions, endothelium-independent dilation was assessed with similar procedures before and 3 minutes after administration of 0.4 mg of sublingual nitroglycerin. Images were digitized online, and arterial diameters were measured with edge-detection software (Medical Imaging Applications, Inc, Iowa) by an individual blinded to other data about the participant. Arterial diameter was measured in mm from the leading edge of the intima-lumen interface of the near wall (echo zone 3) to the leading edge of the lumen-intima interface of the far wall (echo zone 5), coincident with the R-wave on the electrocardiogram (i.e., end-diastole). The brachial artery vasodilator response was quantified as percent change in vessel diameter from baseline. In order to minimize error, the same technician did FMD measurements throughout the study, and the same equipment and analytic software was used to measure FMD for all the twin participants. In our lab, the mean difference in FMD (%) between 2 consecutive assessments performed in 11 participants an average of 8 days apart was 1.26 (± 0.76) %, with a Pearson correlation of 0.75. The mean difference in the FMD (%) between 2 readings of the same 11 measurements was 0.82 (± 0.48)%, with a Pearson correlation of 0.97.

Assessment of childhood trauma

We assessed a history of childhood trauma experiences using the short form self-reported version of the Early Trauma Inventory (ETI-SR) (42). The ETI-SR contains 27 “true” or “false” items designed to assess whether someone was exposed to potential traumatic experiences before the age of 18 years. The inventory is divided into four scales measuring: general trauma (11 items), physical trauma (5 items), emotional abuse (5 items) and sexual abuse (6 items). Scores on each scale represent the number of items that were endorsed. The ETI-SR is a valid instrument for the measurement of childhood physical, emotional, and sexual abuse, as well as general trauma, and has a high level of internal consistency within the individual domains (42). For descriptive purpose, history of childhood traumatic experiences for each domain was categorized using mean plus one standard deviation as cutoffs based on the data for healthy individuals (lack of depression or PTSD) reported by Bremner et al (42). Individuals with a traumatic score of greater than the cutoff were treated as having early trauma and those less than the cutoff as not having early trauma.

Genotyping of the MAOA-uVNTR variant—Genomic DNA was extracted using standard method. Genotyping of the MAOA-uVNTR variant was performed according to using previously published protocols (31). Briefly, DNA was amplified with forward primer 5'-ACAGCCTGACCGTGGAGAAG-3' (fluorescently labeled with FAM) and reverse primer 5'-GAACGGACGCTCCATTCGGA-3', with PCR thermal cycling conditions of 10-min denaturation at 95 °C, then 35 cycles of 95 °C for 30 sec, 60 °C for 30 sec and 72 °C for 1 min. This was followed by 5-min extension at 72 °C. Amplified PCR products were visualized on a capillary-based ABI3100 Genetic Analyzer along with GeneScan 500 ROX as sizing standard. Data collection and allele scoring was performed using GeneScan 3.7 and Genotyper 3.7 (Applied Biosystems).

Statistical analyses—We first examined the main effects of MAOA genotype and each domain of childhood trauma (0/1) on interindividual variability in FMD, adjusting for known coronary risk factors. We then tested for interaction between the MAOA genotype (high vs. low activity alleles) and exposure to each domain of childhood trauma (0/1) on FMD variability by assessing the statistical significance of the interaction term in generalized estimating equation (GEE) models. GEE was used here to account for the lack of independence of twins with pairs. In order to obtain effects that are independent of traditional cardiovascular risk factors, all analyses accounted for covariates including age, smoking, BMI, history of diabetes, history of hypertension, LDL, HDL, alcohol consumption (gram/week), and physical activity level as well as zygosity. As described before, our study included a random sample of twins with major depression or PTSD. To examine whether depression or PTSD potentially confounds the results, we conducted sensitivity analyses by further adjusting for depressive symptoms (as measured by Beck Depressive Inventory II scores) or PTSD ($n = 79$). To examine the potential impact of education level and socio-economic status (SES) on our results, we performed analyses by further adjusting for these two variables in the statistical models. Moreover, we conducted analysis to examine whether inclusion of twins from two studies (THS or SAVEIT) influences our results by including a study affiliation variable in the GEE model.

RESULTS

The age of the twins ranged from 46 to 65 years with a mean of 55. There was no significant difference between monozygotic (MZ) and dizygotic (DZ) twins in any of the risk factors examined. **Table 1** presents the demographic characteristics of the twin participants.

MAOA allele frequencies

Genotypes in the twin sample consisted of three variants of the 30-bp repeat sequence: 3R (34.2%), 3.5R (0.4%) and 4R (65.4%). These allele frequencies are similar to the frequencies reported in other samples of white participants (13, 16). Chi-square analysis revealed no evidence for deviation from Hardy-Weinberg Equilibrium. On the basis of different transcription efficiency of these alleles (13), twins carrying the 3 repeat allele were assigned to the low activity group, and those carrying the 3.5 or 4 repeat alleles were assigned to the high activity group. The frequencies of low and high activity alleles were 65.8% and 34.2%, respectively. Dropping the rare 3.5R allele did not alter the pattern of our findings nor their significance.

Exposure to childhood trauma

General trauma was the most prevalent childhood traumatic experiences in our study sample (28.4%), followed by physical abuse (25.0%), emotional abuse (19.4%) and sexual abuse (11.6%). The mean number of the four traumatic events was 2.6, 1.7, 1.4 and 0.21, respectively. The four domains of childhood trauma are highly correlated with each other (correlation ranging from 0.2 to 0.5, all p 's < 0.0001). There was no statistical difference in the number of reported traumatic events between high and low activity MAOA alleles.

Main genetic effect and MAOA $\times$ trauma interaction on subclinical atherosclerosis

We did not find evidence for a main effect of the MAOA genotype or childhood trauma on FMD. However, MAOA genotype significantly modulated the effect of physical abuse (interaction $p = 0.026$) and emotional abuse (interaction $p = 0.025$) on FMD variability. Among twins carrying the high activity alleles, exposures to early traumatic experience (physical abuse or emotional abuse) has no effect on FMD. However, among twins carrying the low activity allele, those exposed to physical abuse exhibited significant smaller FMD compared to those not exposed (4.69% vs. 6.22%, $p=0.01$). The similar pattern was also

observed for emotional abuse (4.87% vs. 6.21%, $p=0.045$), suggesting an unfavorable effect of the low activity allele on subclinical atherosclerosis in the presence of childhood traumatic experiences. Statistical analysis stratified by the MAOA genotype (low vs. high activity alleles) also demonstrated that, among twins unexposed to physical abuse, the low activity allele carriers did not exhibit a significantly higher FMD level than the high activity allele carriers (6.22% vs. 5.10%, $p=0.10$). Similar pattern was also observed for emotional abuse (5.26% vs. 4.69%, $p=0.11$). These results suggest that the observed interaction effect may be mostly likely due to higher FMD level in unexposed, rather than lower FMD level in exposed twins carrying the low activity allele. The interaction of MAOA genotype with childhood trauma (physical or emotional abuse) remained statistically significant after accounting for known risk factors. **Table 2** shows the results of multivariate GEE for the interaction between MAOA genotype and childhood trauma on FMD. **Figures 1 and 2** schematically illustrate the interactions of MAOA genotype with childhood physical or emotional abuse, respectively, on FMD. We did not observe main or interactive effect of sexual abuse or general trauma on FMD. Sensitivity analyses indicated that the observed interactive effect of MAOA genotype with physical or emotional abuse was not affected by depression or PTSD. Further adjustments for education level and socio-economic status (SES) did not change our results. Additional control for study affiliation had no effect on the $G \times E$ interactions.

DISCUSSION

Our results suggest that childhood physical or emotional abuse modulates the association between MAOA genotype and subclinical atherosclerosis. The observed $MAOA \times$ childhood trauma interactions remain unchanged after correction for multiple risk factors, implying novel biological pathways that are independent of traditional cardiovascular risk factors.

The biological mechanisms linking *MAOA* variant, early life abuse and atherosclerosis are unknown. According to results shown in **Figures 1 and 2**, among twins who were exposed to early trauma, there was no significant difference in FMD between participants carrying the low activity allele and those carrying the high activity allele; whereas among twins who were unexposed to childhood trauma, carrying the low activity allele resulted in a larger FMD compared to carrying the high activity allele. This observation appears to support a protective role of the low activity allele against subclinical atherosclerosis in the absence of early trauma. Alternatively, physical or emotional abuse in early life may induce hypersensitivity of the hypothalamic-pituitary-adrenal (HPA) axis (43), which has been implicated in the pathogenesis of atherosclerotic cardiovascular disease (12, 44). There is evidence that the effect of MAOA on the hippocampus may underlie the interaction between *MAOA* and childhood trauma (24). For example, in a large sample of healthy volunteers, carriers of the low activity allele at *MAOA-uVNTR* locus was associated with hyperactivity of the hippocampus and amygdale during emotional arousal, compared with carriers of the high activity allele (45). A third possibility is that childhood trauma or *MAOA* variant could influence the vulnerability of atherogenesis through increasing inflammatory responses in the vascular system, the underlying mechanism of atherosclerosis. For instance, childhood trauma has been shown to influence long-term inflammatory process (7, 8, 46). Recent research suggests that early life adversity may also influence cardiovascular risk through modifying the epigenome (47, 48).

Atherosclerosis begins early in life and develops inconspicuously for many decades before manifestation of clinical cardiovascular disease (49). It develops as a consequence of interactions between the “initial” conditions, coded in the genotype, and exposures to environmental agents (1). Genetic effects on cardiovascular risk may be observed only under

certain environmental contexts or in conjunction with environmental exposures, or conversely, an exposure may only relate to cardiovascular outcomes among individuals with specific genetic background. In this study, neither the single MAOA-uVNTR genotype nor childhood physical or emotional abuse is associated with FMD variability when they were analyzed separately, however, their interaction significantly influences susceptibility to subclinical atherosclerosis.

In this study, we only detected a significant interaction between MAOA genotype and childhood physical or emotional abuse on the susceptibility to subclinical atherosclerosis. There was no evidence for an interaction of MAOA genotype with other domains of childhood traumatic experiences (i. e., sexual abuse and general trauma). This is probably because that different domain of childhood trauma reflects different aspects of the childhood traumatic experiences (42). It is also possible that cardiovascular system responses differently to stress induced by different types of trauma.

Depression and PTSD are risk factors for cardiovascular risk (50). However, the observed interactive effect of MAOA genotype $\times$ childhood trauma on preclinical CVD is unlikely to be mediated by depression or PTSD because MAOA genotype was not associated with either depressive symptoms or PTSD. Moreover, further adjustments for these two neuropsychiatric conditions did not attenuate the interaction between MAOA genotype and physical or emotional trauma.

Our results should be understood in the context of some limitations. First, our sample was derived from a twin registry of male military veterans; therefore, the generalizability to other populations is not known. In addition, our results were derived from healthy middle-aged twins, and therefore may not extend to younger people or populations with clinically manifest cardiovascular disease. Second, our sample size is relatively small. Studies relating genetic polymorphisms to complex disease typically need larger samples, in particular for testing $G \times E$ interactions. Thus, the present results should be interpreted with caution until these findings have been replicated in larger samples. However, our study may gain power by using subclinical measure of atherosclerosis because it is genetically closer to the pathogenic genotype than the complex clinical endpoint such as CVD. Nonetheless, the significant $G \times E$ interaction found in the present study is remarkable considering the relatively smaller sample size. Third, we used a retrospective measure to assess the occurrence of childhood traumatic experiences. It may be subject to information bias, even though the instrument used in assessing childhood trauma has been shown to be valid and sensitive (42). In addition, due to the cross-sectional assessment of subclinical CVD, our findings could not explore the temporal order linking childhood emotional abuse, genetic variants and atherosclerosis. Finally, because of the sensitive nature of questions about childhood traumatic experiences, the responses probably represent an underreporting of their actual occurrence.

In summary, this study provides evidence that a functional polymorphism in the MAOA-uVNTR gene moderates the impact of childhood physical or emotional trauma on subclinical atherosclerosis in a sample of male twins.

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Figure 1.
MAOA genotype $\times$ childhood physical abuse on FMD.

Figure 2.
MAOA genotype $\times$ childhood emotional abuse on FMD.

Table 1

Demographic, clinical and laboratory characteristics of twins

Characteristic	MZ (n=175 pairs)	DZ (n=114 pairs)	P [*]
	Mean ± SD or %	Mean ± SD or %	
Age (years)	54.9±3.3	55.2±3.2	0.10
Race, white (% , N)	94.6% (n=331)	95.8 (n=218)	0.73
Current smoking (% , N)	19.6 (n=69)	20.5 (n=46)	0.76
BMI (kg/m ²)	29.4±4.6	29.8±5.2	0.33
SBP (mmHg)	130.8±16.2	129.5±15.9	0.48
DBP(mmHg)	81.6±10.6	80.4±10.1	0.31
HDL (mg/dL)	38.7±11.3	39.7±10.5	0.28
LDL (mg/dL)	124.3±36.6	117.2±31.3	0.06
Total cholesterol (mg/dL)	186.3±39.2	184.6±37.1	0.72
Total triglyceride (mg/dL)	177.8±90.1	182.7±99.8	0.70
Blood glucose (mg/dL)	102.5±24.0	103.7±19.0	0.73
Alcohol consumption (gram/week)	13.9±36.3	18.9±40.4	0.14
Physical activity level	7.3±1.8	7.2±1.8	0.70
Physical abuse score	1.8±1.1	1.6±1.1	0.17
Emotional abuse score	1.4±1.4	1.3±1.4	0.17
Sexual abuse score	0.2±0.7	0.2±0.6	0.52
General trauma score	2.7±2.1	2.4±2.0	0.12
Type 2 diabetes (%)	11.5 (n=40)	10.1 (n=23)	0.62
Hypertension (%)	36.9 (n=129)	37.7 (n=86)	0.86
Brachial artery FMD (% change)	5.29±3.16	4.91±3.28	0.28

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high density lipoprotein; LDL = low density lipoprotein; FMD = flow-mediated dilation

* P values were obtained with generalized estimating equations (GEE) taking into account intra-pair correlations.

Table 2

Interaction between MAOA genotype and childhood trauma on FMD by multivariate GEE *

Variable	Physical abuse		Emotional abuse	
	β	P	β	P
MAOA genotype	0.26	0.42	0.33	0.24
Physical abuse	-0.08	0.20	-	-
MAOA $\times$ physical abuse	-0.37	0.026	-	-
Emotional abuse	-	-	-0.13	0.32
MAOA $\times$ emotional abuse	-	-	-0.43	0.025
Age	-0.02	0.07	-0.02	0.10
Current smoking	-0.05	0.55	-0.04	0.57
Body mass index	-0.0001	0.99	-0.001	0.89
Diabetes	-0.08	0.57	-0.09	0.52
Hypertension	-0.03	0.68	-0.04	0.61
Low-density lipoprotein	-0.0005	0.60	-0.0009	0.37
High-density lipoprotein	0.0008	0.56	0.0004	0.74
Alcohol consumption	-0.0006	0.52	-0.0005	0.57
Physical activity	0.03	0.21	0.02	0.23
Zygosity	-0.07	0.35	-0.07	0.37

P values are multivariate-adjusted. Additionally adjusted for depressive symptoms or PTSD did not attenuate the results. Similarly, further adjustments for study affiliation, education and SES did not change the results.

* FMD was log-transformed.

Table 3

Distributions of FMD and childhood trauma characteristics by the MAOA genotype

Characteristic	Low activity allele	High activity allele	P [*]
	mean ± SD	mean ± SD	
Brachial artery FMD (% change)	5.09±3.16	5.22±3.31	0.95
Physical activity score	1.67±1.12	1.70±1.10	0.84
Emotional abuse score	1.427±1.34	1.39±1.38	0.42
Sexual abuse score	0.24±0.73	0.20±0.64	0.47
General trauma score	2.67±1.88	2.55±2.12	0.71

^{*} P values adjusted for within twin pair correlations by GEE