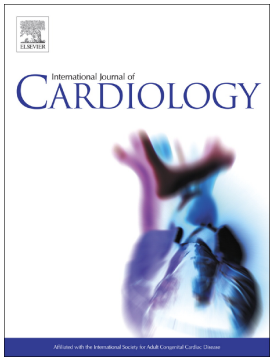

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PII: S0167-5273(20)30478-2

DOI: https://doi.org/10.1016/j.ijcard.2020.05.034

Reference: IJCA 28612

To appear in: *International Journal of Cardiology*

Received date: 31 January 2020

Revised date: 30 April 2020

Accepted date: 13 May 2020

Please cite this article as: E. Medda, C. Fagnani, G. Alessandri, et al., Association between personality profile and subclinical atherosclerosis: The role of genes and environment, *International Journal of Cardiology* (2020), https://doi.org/10.1016/j.ijcard.2020.05.034

Association between personality profile and subclinical atherosclerosis: the role of genes and environment

Emanuela Medda, MSc[a*], Corrado Fagnani, MSc[a*], Guido Alessandri, PhD[b*], Claudio Baracchini, MD, PhD[c*], Anita Hernyes, MD[d*], Pierleone Lucatelli, MD[e*], Giacomo Pucci, MD[f*], Adam D. Tarnoki, MD, PhD[d*], David L. Tarnoki, MD, PhD[d*], Maria Antonietta Stazi, MSc[a*]

a. Centre for Behavioural Sciences and Mental Health, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy; emanuela.medda@iss.it; corrado.fagnani@iss.it; stazi@iss.it

b. Department of Psychology, University of Rome "Sapienza", Via dei Marsi 78, 00185 Rome, Italy; guido.alessandri@uniroma1.it

c. Department of Neuroscience, University of Padua School of Medicine, Via Giustiniani 5, 35128 Padua, Italy; claudiobaracchini@gmail.com

d. Medical Imaging Centre, Semmelweis University, Üllői út 26, H-1085 Budapest, Hungary; tarnoki2@gmail.com; anitahernyes@hotmail.com

e. Department of Radiological Oncological and Anatomo-Pathological Sciences, University of Rome "Sapienza", Viale del Policlinico 155, 00161 Rome, Italy; pierleone.lucatelli@gmail.com

f. Department of Medicine, University of Perugia, Piazzale Tristano di Joannuccio, 1 Terni, Italy; giacomo.pucci@gmail.com

*This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Corresponding author:

Emanuela Medda

Centre for Behavioural Sciences and Mental Health

Istituto Superiore di Sanità

Viale Regina Elena,299

00161 Rome, Italy

Tel: +390649904153

E-mail: emanuela.medda@iss.it

Cover title: Personality profile and atherosclerosis

Word Count: 1500 first version (revised version 2186)

Tables: 2

Author statement

Emanuela Medda: Conceptualization, Formal analysis, Writing - Review & Editing

Corrado Fagnani: Formal analysis, Data Curation, Writing - Review & Editing

Guido Alessandri: Methodology, Writing - Review & Editing

Claudio Baracchini: Investigation, Writing - Review & Editing

Anita Hernyes: Visualization, Writing - Review & Editing

Pierleone Lucatelli: Investigation, Writing - Review & Editing

Giacomo Pucci: Investigation, Writing - Review & Editing

Adam D. Tarnoki: Investigation, Writing - Review & Editing

David L. Tarnoki: Investigation, Writing - Review & Editing

Maria Antonietta Stazi: Supervision, Writing- Reviewing and Editing,

Association between personality profile and subclinical atherosclerosis: the role of genes and environment

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Abstract

Background. The mechanism underlying the association between personality profile and subclinical atherosclerosis is poorly understood. This study explores the association between personality, carotid atherosclerosis and arterial stiffness, and the contribution of genes and environment to this association.

Methods. Early atherosclerotic traits, including carotid intima-media thickness (CCA-IMT), aortic pulse wave velocity (PWVao) and heart rate, were assessed in 318 adult twins, who also completed a Big Five personality questionnaire. Using the co-twin control approach, the association between intra-pair differences in clinical and personality scores was assessed in dizygotic (DZ) and monozygotic (MZ) twins separately.

Results. An association between CCA-IMT and extroverted personality, as well as between PWVao and openness to experience was detected. The inverse association between CCA-IMT and extraversion was persistent in DZ and disappeared in MZ twins, suggesting genetic confounding. In contrast, the association between PWVao and openness to experience was of the same magnitude in DZ and MZ twins, thus surviving the adjustment for genetic and shared environmental factors.

Conclusions. This study highlights that the association between some psychological factors and cardiovascular traits may be partly explained by genetic factors. This result may provide support for the feasibility of prevention programs based on assessing familiarity for personality disorders to detect genetic risk for subclinical cardiovascular disease.

Key words: personality, twin, atherosclerosis

1. Introduction

In the last decade, increasing attention has been paid to the influences of psychological factors on the development and progression of cardiovascular diseases. Different pathophysiological pathways, involving endocrine, metabolic and inflammatory altered responses, have been proposed as possible mechanisms through which personality could affect atherosclerosis risk [1]. In particular, studies using the Big Five factor model as the reference framework [2] have repeatedly attested a link of heart rate variability (HRV), the marker of increased autonomic activity and sympathetic activity, which is a major determinant of cardiovascular autonomic control. Reduced HRV is an independent risk factor for the development of heart disease [3-6]. Although higher neuroticism or lower conscientiousness have been linked to cardiovascular death, studies demonstrated that life-style behaviors might mediate this association [7-8]. Narita et al. recently published a study showing that life-style behaviors in relation to personality traits, especially smoking, partially mediate the association between psychoticism and cardiovascular mortality [9].However, as few studies have gone beyond the reporting of mere correlations, a full understanding of the pathways linking individual personality to its underlying psychophysiological bases is still far to come. Moreover, studies investigating the possible role of personality on subclinical cardiovascular disease is still lacking.

Twins represent a powerful approach for dealing with confounding factors in observational studies. In particular, the "co-twin control" design, based on monozygotic (MZ) and dizygotic (DZ) intra-pair comparisons, allows one to elucidate the true nature of an observed within-individual association between exposure and outcome, thanks to the strong matching in non-measurable confounders such as genetic and early life environmental factors.

The aim of this study is twofold: i) to verify the within-individual association between subclinical cardiovascular disease or early traits of atherosclerosis and five major dimensions

of personality; ii) to define the role of genetics and environment in this association, exploiting the twin nature of the sample.

2. Methods

2.1 Participants

Subjects for this study are general population twins previously enrolled in the Italian Twin Registry [10,11]. Out of 348 invited twins, 320 twins (92%) gave their consent to be visited and to fill in the questionnaires, and 318 twins (mean age 52.07, SD 15.33 years) were considered for the analyses after exclusion criteria were applied.

Twin zygosity was determined by a standardized questionnaire on physical similarity [12].

The protocol of this study conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Moreover, it was under the general framework of the Italian Twin Registry research activities, approved by the Ethics Committee of the Istituto Superiore di Sanità. All twins provided written informed consent to participate in the study.

2.2 Measures

Participants completed a brief questionnaire on socio-demographic and clinical characteristics, as well as a well-validated adjectives checklist [13] to assess the Big Five factors of personality (extraversion, stability, openness to experience, agreeableness, conscientiousness). This latter questionnaire included a list of 25 adjectives describing personality traits, with participants rating the degree to which each adjective described themselves. Exploratory factor analysis was performed and supported the five-factor solution. Factor scores were estimated using a regression method and were used in all subsequent

analyses. Reliability computed with Cronbach's alpha was adequate, ranging from 0.71 (openness to experience) to 0.81 (stability), with a mean of 0.75 (DS = 0.08).

During clinical evaluation, body mass index (BMI), systolic and diastolic blood pressure (SBP, DBP), heart rate (HR), arterial stiffness, characterized by pulse wave velocity (PWVao) and common carotid artery intima-media thickness (CCA-IMT) were measured.

Brachial systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR) were measured after 10 min of rest, while mean arterial pressure (MAP) was calculated as (SBP+DBP)/3. IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface and measured with calipers. All twins underwent ultrasound examination of common carotid artery intima-media thickness (CCA-IMT) on left and right side 2 to 3 cm proximal from carotid bifurcation on dorsal wall (Esaote MyLab70, Genova, Italy in Rome; Sonoscape S8 in Perugia; Toshiba Aplio XG in Padua; Esaote MyLab60 in Terni, 12 MHz linear probes), and the average value was used in the analysis.

At least 3 IMT measurements were performed and were averaged. In case of plaque, IMT value was measured in the adjacent plaque-free segment.

Vascular stiffness was measured by aortic pulse wave velocity (PWVao) using a non-invasive and validated oscillometric device (Arteriograph, Medexpert Ltd., Budapest, Hungary) [14].

2.3 Statistical analysis

Subjects were analysed both as individuals and as twins belonging to pairs. Individual analyses included descriptives, both for the total sample and by zygosity, and the analysis of the associations between vascular profile (HR, CCA-IMT, PWVao) and the five dimensions of personality; this latter analysis was performed by multiple regression models. All the

studied variables were compared between MZ and DZ twins in order to identify any differences between the two groups.

By considering the twin pairs, intra-pair differences (Twin1 minus Twin2) were calculated for each variable after random assignment of the twin and the co-twin to Twin1 and Twin2. First, backward stepwise multiple regression analysis was used to assess the association between intra-pair differences in clinical (dependent variable) and personality scores (independent variable). In these models, mean arterial pressure (MAP), HR, BMI and SBP were included as covariates when necessary. The estimated beta coefficients indicate the effect of personality differences on clinical differences between the two members of the same pair, over and above the overall influence of factors common to both twins, such as genetic and family background. As a second step, when a significant association was detected, two multiple regression models were fitted for DZ and MZ pairs separately. These models allow for total (i.e. 100% in MZ pairs) or partial (50% in DZ pairs) control of genetic effects. Furthermore, in both models, environmental factors shared by the twins within the family are controlled for. In this scenario, if the within-individual association between exposure and outcome weakens in DZ pairs and disappears in MZ pairs, this indicates genetic confounding; if, instead, the association is persistent and with a similar strength in individual and within-pair analyses, this provides evidence against genetic and shared environmental confounding. Therefore, the "co-twin control" approach makes it possible to draw causal inferences from observational, cross-sectional data [15].

3. Results

Three-hundred and eighteen Caucasian twins (84 MZ, 75 DZ pairs), aged 20-78 years (mean 52.1), were enrolled in the study. Cardio-circulatory characteristics, anthropometric data and

personality profile are shown in Table 1. No significant differences were observed between MZ and DZ twins in any of the considered variables.

Individual-based regression models showed that HR was significantly associated to stability (beta: -1.45, 95% confidence interval, 95%CI, -2.57; -0.35) and openness to experience (beta: 1.61, 95%CI: 0.30; 2.93). These associations disappeared in within-pair analysis, suggesting total familial confounding (HR with stability: p=0.70; HR with openness to experience: p=0.76).

Similarly, arterial stiffness (PWVao) was associated with three personality traits: stability (beta: -0.26, 95%CI: -0.44; -0.08), openness to experience (beta: 0.25, 95%CI: 0.03; 0.48) and extraversion (beta: -0.25, 95%CI: -0.48; -0.02) (Table 2). In within-pair analysis, the association was confirmed only for openness to experience (beta: 0.30, 95%CI: 0.03; 0.56); the estimated coefficients were similar in MZ (beta: 0.35, 95%CI: -0.02; 0.71) and DZ twins (beta: 0.31, 95%CI: -0.07; 0.70), consistent with no genetic or shared environmental confounding. An association between carotid intima-media thickness and extroverted personality was detected both in individual-based (beta: -0.02, 95%CI: -0.05; -0.003) and in within-pair analysis (beta: -0.03, 95%CI: -0.05; -0.01). This association, as well as that observed between CCA-IMT and openness to experience was persistent in DZ twins and disappeared in MZ twins, consistent with genetic confounding. As regards the association between CCA-IMT and openness to experience, "negative" genetic confounding may come into play because the association only emerged in the within-pair (i.e. adjusted) analysis. A similar pattern was observed for stability and agreeableness. Conscientiousness did not show any association with HR, PWVao or CCA-IMT.

4. Discussion

This study aimed to explore the influences of personality on vascular stiffness and structure of arteries using a well-characterized twin sample. Results suggest that subclinical atherosclerotic processes and personality profiles may be only weakly inter-connected, as shown by a generally inconsistent and unsystematic pattern of within-twin pair associations. With this premise in mind, some atherosclerotic traits may be related, at least in part, to specific personality traits. We found that arterial stiffness, as measured by PWVao and HR, is associated with stability and openness to experience, suggesting that a secure and confident behaviour might reduce atherosclerotic-related arterial stiffening, while in curious and inventive subjects these processes might be accelerated. This result is in line with previous studies attesting to neuroticism as the personality trait most associated with HR and risk of cardiac disease [3,4], and also brings further proofs that openness to experience is associated with heart rate parameters.

In addition, the study highlights that extraversion is inversely associated with CCA-IMT, a well-recognized predictor of cardiovascular diseases. Our results are consistent with those obtained by Rosenstrom and colleagues on a sample of young adults [16]. They show that increased IMT values are associated with a disorganized character configuration, antisocial temperament and tendency to be persistent despite intermittent reinforcement as measured by the TCI, and conclude that psychological well-being may have positive effects in reducing preclinical atherosclerosis.

Only limited studies are available which could help to understand how arterial stiffness would be influenced by personality, with extraversion having a protective role. It is known that affective temperaments may play a role in the development of hypertension and arterial stiffening, and may thus represent markers of cardiovascular risk [17]. A recently published Swiss study is in contrast to our findings, and showed that extraversion was associated to chronic low-grade inflammation as measured by IL-6 levels, while higher conscientiousness

was protective against cardiovascular risk. However, neuroticism showed no significant association with any inflammatory biomarker, and no direct association with arterial stiffness or carotid IMT was studied [18]. In contrast, an Italian study reported that high neuroticism and low conscientiousness are both associated with higher levels of IL-6 and C-reactive protein, markers of chronic inflammation [19]. Further, smoking and weight partially mediated the association between impulsivity-related traits and higher IL-6 levels. Our findings might be in agreement with those of Roh et al., who showed that extraversion was associated with low levels of triglyceride, which is a pro-atherosclerotic factor [20]. Individuals who are impulsive and lack discipline (low conscientiousness) have been shown to have leptin resistance, a factor that contributes to obesity [21]. Due to the insufficient data on the possible underlying pathomechanism, future studies should be stimulated to identify biomarkers associated with personality, thus elucidating the physiological mechanisms responsible for the observed connections between personality traits and subclinical atherosclerosis.

An important novelty of the present study is the attempt to establish if the detected associations, though generally weak, can be due to genetic or environmental confounding. First, we identified an association between openness to experience and early stages of arterial stiffness as measured by PWVao. This association was of the same magnitude at the individual level as well as within DZ and MZ pairs; this result represents evidence against genetic or environmental confounding, and is thus consistent with a possibly direct, yet still weak, relationship.

It is important to highlight that these findings could be biased by suggestive pathways, since personality can affect atherosclerosis through different mechanisms such as health behavior. Some life-style behaviors in relation to personality traits, especially smoking, but also alcohol consumption, unhealthy dietary habits, decreased physical activity, increased body mass

index (central adiposity) partially mediate the association between psychoticism and CVD mortality [9].

The second main result of this study is the inverse association between extraverted personality and CCA-IMT. The association was of the same magnitude at the individual level and within DZ pairs, while it disappeared in MZ pairs; this suggests possible confounding by genetic factors that may be positively associated with extraversion and negatively associated with CCA-IMT (or vice versa).

This study suffers from some limitations. First, a relatively small sample size, which may have affected within-pair association analysis in MZ and DZ pairs separately. Second, the self-reported psychological information. Third, the cross-sectional design. Forth, a broad age range of participants, which may have masked some associations in specific sub-groups, especially in older ages where atherosclerotic risk is higher; this would have required the investigation of age interaction effects, which was not robustly feasible in this under-powered sample. Also, future studies on larger samples are needed not only to better explore the genetic and environmental overlap between atherosclerotic and personality traits, for example by applying multivariate genetic twin models, but also to investigate the possible mediating role of life-style behaviors (e.g. smoking, alcohol consumption, unhealthy dietary habits, decreased physical activity, increased body mass index) in the association between personality and atherosclerosis.

Within all the above limitations and with the caution required by sparse and modest-strength associations, our study draws attention on the possible relationship between personality profiles and development or progression of atherosclerosis, and may thus contribute to generating speculations on the feasibility of innovative psychologically-based prevention strategies aimed to reduce cardiovascular disease mortality and morbidity.

Sources of Funding

Medexpert Ltd and Ministry of Foreign Affairs of Republic of Italy has provided financial support for this study.

Disclosures

AD and DL Tarnoki received travel reimbursement from Medexpert Ltd.

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Table 1. Descriptive statistics for the total sample and by zygosity

	ALL TWINS		MONOZYGOTIC - MZ		DIZYGOTIC - DZ	
	N	Mean ± SD or %	N	Mean ± SD or %	N	Mean ± SD or %
Total	318		168		150	
Sex, male	128	40.25%	73	43.45%	55	36.67%
Zygosity,						
MZ	168	52.83%	168	52.83%	-	-
DZ	150	47.17%	-	-	150	47.17%
Age, years	318	52.07 ± 15.33	168	52.65 ± 15.24	150	51.43 ± 15.47
Body mass index (BMI)	318	25.47 ± 4.25	168	25.29 ± 4.10	150	25.67 ± 4.42
Systolic Blood Pressure, mmHg	317	124.72 ± 18.12	168	124.86 ± 18.33	149	124.56 ± 17.93
Diastolic Blood Pressure, mmHg	315	74.11 ± 11.42	168	74.07 ± 10.94	149	74.16 ± 11.96
Heart Rate, beats per minute	315	66.80 ± 9.87	166	67.46 ± 9.66	149	66.07 ± 10.07
PWVao, m/sec	310	8.84 ± 2.21	164	8.96 ± 2.26	146	8.71 ± 2.14
Common carotid artery IMT, mm	317	0.70 ± 0.20	167	0.68 ± 0.19	150	0.71 ± 0.20
Extraversion*	317	3.37 ± 0.63	168	3.375 ± 0.61	149	3.36 ± 0.66

Stability	316	3.09 ± 0.66	166	3.12 ± 0.63	150	3.05 ± 0.68
Openness to experience	313	3.07 ± 0.71	163	3.12 ± 0.73	150	3.02 ± 0.70
Agreeableness	310	3.83 ± 0.54	163	3.82 ± 0.51	147	3.83 ± 0.56
Conscientiousness	315	3.70 ± 0.55	168	3.72 ± 0.56	147	3.68 ± 0.54

*Original items scores were considered in sample descriptives, but standardized factor scores were used in subsequent analyses; No significant differences were observed between MZ and DZ twins in any of the considered variables.

Extraversion (outgoing/energetic vs. solitary/reserved), Stability (sensitive/nervous vs. secure/confident), Openness to experience (inventive/curious vs. consistent/cautious), Agreeableness (friendly/compassionate vs. challenging/detached), Conscientiousness (efficient/organized vs. easy-going/careless). IMT: intima-media thickness, PWVao: aortic pulse wave velocity.

For the purposes of the analysis, the average IMT across right, left, proximal and distal measurements of the common carotid artery was considered

Table 2. Results of multiple regression analyses of atherosclerotic traits on personality dimensions.

		PWVao (m/sec)				CCA-IMT (mm)			
Big Five personality dimensions		Individual model*	Intrapair model†	Intrapair DZ†	Intrapair MZ†	Individual model	Intrapair model	Intrapair DZ	Intrapair MZ
Extraversion	*Beta (95% CI) p*	-0.25 (-0.48; -0.02) p=0.03	p=0.43	p=0.49	p=0.65	-0.02 (-0.05; -0.003) p=0.03	-0.03 (-0.05 ; -0.01) p=0.001	-0.04 (-0.07 ; -0.02) p=0.001	p=0.57
Stability	*Beta (95% CI) p*	-0.26 (-0.44; -0.08) p=0.004	p=0.56	p=0.40	p=0.68	-0.0004 (-0.02; 0.02) p=0.96	0.02 (-0.001 ; 0.04) p=0.06	0.02 (-0.003 ; 0.05) p=0.08	p=0.56
Openness to experience	*Beta (95% CI) p*	0.25 (0.03; 0.48) p=0.03	0.30 (0.03 ; 0.56) p=0.03	0.35 (-0.02 ; 0.71) p=0.06	0.31 (-0.07 ; 0.70) p=0.11	0.009 (-0.01; 0.03) p=0.36	0.02 (0.003 ; 0.04) p=0.02	0.03 (0.004 ; 0.05) p=0.02	p=0.62
Agreeableness	*Beta (95% CI) p*	0.18 (-0.07; 0.43) p=0.16	-0.22 (-0.50 ; 0.06) p=0.13	p=0.64	-0.24 (-0.60 ; 0.13) p=0.20	0.004 (-0.01; 0.02) p=0.67	-0.02 (-0.04 ; -0.002) p=0.03	-0.02 (-0.05 ; 0.001) p=0.07	p=0.62

Conscientiousness	*Beta (95 % CI) p*	0.18 (-0.02; 0.39) p=0.08	0.23 (-0.04 ; 0.51) p=0.10	p=0.21	p=0.28	-0.0006 (-0.02; 0.02) p=0.94	p=0.98	p=0.77	p=0.80

*Covariates in the regression models beyond the Big Five factors: PWVao model: age, gender, BMI, MAP; CCA-IMT model: age, gender, BMI, Systolic Blood Pressure.

† Covariates in the stepwise regression models beyond the Big Five factors: *PWVao model*: gender, ΔBMI, ΔMAP; *CCA-IMT model*: gender, ΔBMI, ΔSystolic Blood Pressure.

Beta Coefficient gives the expected change in the difference between Twin1 and Twin 2 on the outcome variable for each unit of change (Twin1-Twin2) on the exposure variable.

Beta:Beta coefficient; 95% CI: 95% confidence intervals. IMT: intima-media thickness, PWVao: aortic pulse wave velocity.

Highlights

- Personality profile and early traits of atherosclerosis are weakly associated
- Association of personality with atherosclerotic traits is mostly due to genetics
- Results draw attention on early detection of cardiovascular risk based on personality