Nutrition, Metabolism & Cardiovascular Diseases (2014) **24**, 511–517

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Heritability of arterial stiffness and carotid intima-media thickness: An Italian twin study☆

E. Medda [a,2], C. Fagnani [a,*,2], G. Schillaci [b], A.D. Tarnoki [c], D.L. Tarnoki [c], C. Baracchini [d], G. Meneghetti [d], F. Fanelli [e], A. Alaeddin [b], G. Pucci [b], S. Alviti [a], R. Cotichini [a,1], S. Brescianini [a], E. Boatta [e], P. Lucatelli [e], L. Nisticò [a], L. Penna [a], M. Salemi [a], V. Toccaceli [a], C. Zini [e], Z. Garami [f], M.A. Stazi [a]

[a] *Istituto Superiore di Sanità, National Centre for Epidemiology, Surveillance and Health Promotion, Genetic Epidemiology Unit, Viale Regina Elena 299, 00161 Rome, Italy*
[b] *University of Perugia, Department of Medicine and Unit of Internal Medicine, Terni University Hospital, Terni, Italy*
[c] *Department of Radiology and Oncotherapy, Semmelweis University, Budapest, Hungary*
[d] *Department of Neurosciences, School of Medicine, University of Padua, Padua, Italy*
[e] *Department of Radiological Sciences, La Sapienza University of Rome, Rome, Italy*
[f] *The Methodist Hospital DeBakey Heart and Vascular Center, Houston, TX, USA*

Received 22 July 2013; received in revised form 17 October 2013; accepted 22 October 2013
Available online 4 December 2013

KEYWORDS
Augmentation index;
Pulse wave velocity;
Carotid thickness;
Twin study

Summary *Background and aims:* Carotid intima-media thickness (IMT) and arterial stiffness parameters, including aortic augmentation index (AIx) and pulse wave velocity (PWV), are independent predictors of stroke and cardiovascular disease. Genetic effects on these traits were never explored in a Mediterranean country. The present study aims to quantify the contribution of genes, environment and age to carotid IMT and aortic Aix and PWV.
Methods and results: The twin design was used. A total of 348 adult twins from the Italian Twin Register underwent measurements of carotid IMT and aortic PWV and AIx in three university hospitals located in Rome, Padua and Perugia. Carotid IMT was measured by B-mode ultrasound, aortic PWV and AIx by Arteriograph. Genetic modelling was performed to decompose total variance of traits into genetic, shared and unshared environmental and age components. For each phenotype, the best-fitting model included additive genetic, unshared environmental and age effects. For IMT, heritability was 0.32 (95% confidence interval (CI): 0.25–0.38), unshared environmental component was 0.25 (0.18–0.32) and age contribution was 0.44 (0.39–0.49). For AIx and PWV, heritabilities were 0.42 (0.29–0.55) and 0.49 (0.35–0.62), unshared environmental components were 0.31 (0.22–0.44) and 0.37 (0.26–0.51) and age contributions were 0.27 (0.16–0.39) and 0.14 (0.06–0.24), respectively.
Conclusion: This study shows substantial genetic and unshared environmental influences on carotid intima-media thickness and arterial stiffness and confirms the relevant role of age in the aetiology of these traits. Further support is provided for prevention and health promotion strategies based on modifiable factors.

Acronyms: IMT, carotid intima-media thickness; AIx, aortic augmentation index; PWV, pulse wave velocity; h^2, heritability; MAP, mean arterial pressure; SD, standard deviation; RSES, Rosenberg self-esteem scale; MZ, monozygotic twins; DZ, dizygotic twins; A, additive genetic effects; C, common environmental effects; E, unique environmental effects; AIC, Akaike Information Criterion.

☆ This article was presented during the International Congress on Twin Studies in Florence, April 2012.

* Corresponding author. Tel.: +39 06 4990 4174; fax: +39 06.4990 4151.
E-mail address: corrado.fagnani@iss.it (C. Fagnani).

[1] Present address: Institute of Clinical Physiology, CNR, Pisa, Italy.

[2] Each of the authors contributed equally to this article.

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http://dx.doi.org/10.1016/j.numecd.2013.10.031

Diseases of the heart and circulatory system represent the main cause of death in Europe, with large differences in mortality rates between countries [1]. In Italy, morbidity and mortality rates due to cardiovascular disease remain high despite a wide diffusion of a Mediterranean diet [2] and the adoption of major prevention strategies at the population level, such as campaigns against smoke and alcohol consumption, promotion of maintenance of healthy body weight and participation in physical activity.

Since major cardiovascular risk factors and the deriving risk equations are able to predict a substantial but limited proportion of cardiovascular events, the assessment of early vascular changes has gained increasing popularity in both the prevention and clinical settings as a means to improve cardiovascular risk stratification over and beyond traditional risk factors [3]. Carotid intima–media thickness (IMT) and parameters of arterial function based on pulse wave analysis are independent predictors of stroke and cardiovascular disease [4–6]. The distance between lumen–intima and media–adventitia interfaces of the common carotid arteries can be easily measured by ultrasound and arterial stiffness parameters, including aortic augmentation index (AIx) and pulse wave velocity (PWV) can be assessed non-invasively [7]. All these parameters are widely used in the clinical setting, and their heritability has been investigated in some twin and family studies [8] using invasive measurements of arterial stiffness or samples of same-gender subjects.

Moderately high genetic influences on carotid IMT were detected in recent studies, with heritability (h^2) estimates ranging from 0.35 [9,10] to 0.65 [11]. Evidence from a twin study also suggests that unique environmental factors may contribute significantly to carotid IMT [12]. Few studies have been conducted on the genetic component of stiffness parameters. The carotid–femoral PWV was evaluated in 1480 participants representing 817 pedigrees in the Framingham Study Offspring cohort and heritability estimates were moderate ($h^2 = 0.40$) [13]. Using 930 individuals connected in a single pedigree from an isolated population, heritability estimate of PWV, after adjustment for appropriate risk factors, was 0.26 [9]. Another study conducted on 496 women from the UK Adult Twin Registry found a similar heritability (0.34) [14]. Aortic AIx, a prognostically relevant measure of the impact of intensity and timing of pulse wave reflection from peripheral sites on central haemodynamics [6], has been only sporadically used to examine genetic and environmental influences on arterial stiffness. In a twin study on 819 white female twin pairs, Snieder et al. [15] concluded that most of the variance in this surrogate measure of arterial stiffness could be explained by genetic (37%) and unique environmental factors (44%). Other heritability estimates for AIx derive from family studies, such as the Strong Heart Family Study and the Framingham Study cohort, in which 18–21% of total variance was due to heritable factors [13,16].

In the present study, we sought to quantify the influence of genetic and environmental factors on carotid IMT, aortic PWV and aortic AIx in a sample of Italian twins. We were also interested in determining to what extent age contributes to individual differences of the investigated atherosclerotic phenotypes.

Methods

Study population

The present study is based on the classical twin design. Subjects were recruited as part of the International Twin Study 2009 project [17,18]. Twins previously enrolled in the Italian Twin Register [19] were contacted by mail and invited to participate. The study took place in three Italian cities, and twins attended a single visit at the local university hospitals. Subjects were selected from the Italian Twin Register if they were older than 18 years and both members of the pair were resident in Rome, Padua or Perugia. Pregnant women and twins affected by diseases possibly interfering with measurement of parameters were excluded. Zygosity of the same-gender twin pairs was assessed by genetic testing on DNA extracted from saliva. All subjects provided informed consent to participate in the study.

Measurements

The measurements of common carotid IMT were performed by B-mode ultrasound using commercially available high-resolution colour-coded duplex sonography scanners (Esaote Technos MPX, Biosound Esaote, Indianapolis, IN, USA; and Philips iU22), using high-frequency (5–10 MHz) linear probes and with a dedicated software that measures the IMT thickness automatically. The IMT of proximal and distal common carotid artery and of proximal internal carotid artery were measured bilaterally. In the presence of a carotid plaque, carotid IMT was measured in an adjacent plaque-free segment.

Brachial systolic and diastolic blood pressure was measured by oscillometric technique (TensioMed Arteriograph, Medexpert Ltd., Budapest, Hungary) on the dominant arm with the subject in supine position after 10 min of rest. Mean arterial pressure (MAP) was calculated as ((systolic blood pressure (SBP) + 2 × diastolic blood pressure)/3). Aortic PWV, AIx and central SBP were measured in supine position by two trained radiologists (ADT and DLT) using Arteriograph (Medexpert Ltd., Budapest, Hungary), a clinically validated oscillometric device which has been favourably compared with intra-arterial invasive measurements [7]. If the automatic quality control was appropriate at first (standard deviation (SD) of aortic PWV <1 m s^{-1}), only one measurement was performed. In case of SD of aortic PWV >1 m s^{-1}, the subjects underwent at least three measurements. At the first measurement, one twin was measured by ADT, whereas the other one by DLT at the same time. The subsequent tests were performed together by DLT and ADT. All subjects were asked not to smoke 3 h, not to eat for 1 h and not to drink alcohol and coffee 10 h prior to their visit.

Twins answered extended questionnaires regarding demographic and socioeconomic characteristics, medical