International Journal of Cardiology Hypertension 6 (2020) 100043

Contents lists available at ScienceDirect

International Journal of Cardiology Hypertension

journal homepage: www.journals.elsevier.com/international-journal-of-cardiology-hypertension/

Research Paper

Carotid intima-media thickness and metabolic syndrome in a rural population: Results from the Baependi Heart Study

Glaucylara Reis Geovanini [a,b,*], Iguaracy Pinheiro de Sousa [a], Samantha Kuwada Teixeira [a], Miguel José Francisco Neto [c,d], Luz Marina Gómez Gómez [a], Guilherme Ciconelli Del Guerra [c], Alexandre Costa Pereira [a], Jose Eduardo Krieger [a]

[a] Genetics and Molecular Cardiology Laboratory at InCor-Heart Institute, Medical School, University of São Paulo-USP, São Paulo, SP, Brazil
[b] HCor Research Institute-Hospital do Coracão (HCor), São Paulo, SP, Brazil
[c] Department of Imaging of Hospital Israelita Albert Einstein – HIAE, São Paulo, Brazil
[d] Institute of Radiology – InRad, Medical School, University of São Paulo – USP, São Paulo, Brazil

ARTICLE INFO

Keywords:
Carotid intima-media thickness
cIMT
Carotid ultrasound
Subclinical atherosclerosis
Baependi Heart Study
MetS

ABSTRACT

Background and aims: Carotid intima-media thickness (cIMT) is a strong predictor of cardiovascular events and associated with metabolic syndrome (MetS). MetS is a cluster of cardiovascular risk factors, but the association structure between specific factors and disease development is not well-established in rural populations. We described the association structure between MetS factors and cIMT in a sample from rural Brazil.
Methods: We studied 1937 participants from the Baependi Heart Study who underwent carotid ultrasound exam. We used ATP–III–2001 for MetS definition and linear mixed-effects models, adjusting by the family structure, to assess independent associations between the cardiovascular risk factors which define MetS and cIMT.
Results: The sample's mean age was 46 ± 16y, 61% female, 73% white, mean body-mass-index 26±5 kg/m^2, mean cIMT 0.53 ± 0.16 mm, with 35% of the sample classified with MetS. As expected, cIMT demonstrated a linear relationship with increasing age, and cIMT higher values were observed for MetS (0.58 ± 0.16 mm) compared to non-MetS (0.49 ± 0.14 mm). Considering models for cIMT with MetS and all of its factors, we found that blood pressure, glucose and obesity were independently associated with cIMT, but not HDL or triglycerides.
Conclusions: cIMT showed a linear relationship with increasing age. Blood pressure, obesity, and glucose were independently associated with cIMT, but not HDL-cholesterol or triglycerides. In a rural population, hypertension, diabetes and obesity play a more important role than lipids in determining cIMT interindividual variability.

1. Introduction

Carotid intima-media thickness (cIMT) is a traditional marker of atherosclerosis and it is a strong predictor of future cardiovascular events, especially acute myocardial infarction and stroke [1–5]. It is measured by a non-invasive ultrasound imaging method, easy to apply in epidemiological studies [4]. In addition, cIMT has been used as an early surrogate marker for atherosclerosis [3]. Indeed, a recently published systematic review showed that cIMT was higher in subjects with cardiovascular disease (CVD) compared to individuals free of CVD [6]. However, there is still a challenge of cIMT and risk association based on a non-linear relationship with vascular events in young individuals [1]. Furthermore, it has been shown that cIMT did not improve cardiovascular risk prediction in patients with elevated blood pressure [7].

In this context of uncertainty of the role of cIMT in CVD risk prediction [7,8], there is increased awareness of the context-dependent association of cardiovascular risk factors and markers of subclinical atherosclerosis, like cIMT. Recently, it has been shown that body-mass-index (BMI), a measure of obesity, is increasing faster in rural areas than in cities, contrary to the knowledge that urbanization is the most important driver of the global obesity epidemic in adults [9]. As a result, these trends pointed to a reversal of the gap in BMI between urban

* Corresponding author. Genetics and Molecular Cardiology Laboratory at InCor-Heart Institute, Medical School, University of São Paulo-USP, Av Dr Eneas de Carvalho Aguiar, nº44, bloco 2, 10th floor, Cerqueira Cesar, São Paulo, SP, 05403-000, Brazil.
E-mail addresses: gal.geovanini@gmail.com (G.R. Geovanini), iguaracy.sousa@usp.br (I. Pinheiro de Sousa), samantha.teixeira@incor.usp.br (S.K. Teixeira), miguel.jneto@einstein.br (M.J. Francisco Neto), lgomez928@gmail.com (L.M. Gómez Gómez), guilhermeciconelli@gmail.com (G.C. Del Guerra), alexandre.pereira@incor.usp.br (A.C. Pereira), krieger@incor.usp.br (J.E. Krieger).

https://doi.org/10.1016/j.ijchy.2020.100043
Received 27 March 2020; Received in revised form 6 June 2020; Accepted 17 July 2020
Available online 22 July 2020

and rural areas, especially in low- and middle-income countries (LMIC) and for women [9].

Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors. It is characterized by a combination of elevated blood pressure, hyperglycemia, high-density lipoprotein (HDL) cholesterol levels, elevated triglycerides, and abdominal obesity [10–12], but the association structure between its specific factors and cardiovascular disease is unclear for it varies depending of other situational variables. In fact, there is growing concern on how the combined effects of traditional cardiovascular risk factors (such as those part of MetS), which have been associated with carotid atherosclerosis in the general population [10,13], modulate cardiovascular risk in different populations.

Whether the association between the different cardiovascular risk factors part of MetS and established vascular disease is different in rural populations from LMIC is unknown. Therefore, in the presence of controversies about the specific role of the cIMT in atherosclerosis disease development, and based on the strong association between cIMT and MetS [10,13], the aim of the current study is to evaluate the shape of the relationship between cIMT and age in subjects from a rural family-based population, and also to explore the independent association between cIMT and traditional cardiovascular risk factors part of the MetS definition. Here we describe the association structure between MetS factors and cIMT in a representative sample from rural Brazil.

2. Material and Methods

2.1. Study population

The Baependi Heart Study is an epidemiological study in Baependi, a city in a rural area (752 Km^2, 18,307 inhabitants at the 2010 census) located in Minas Gerais State, Brazil (21.95 S, 44.88 W). The overarching goal of this cohort is to evaluate genetic and environmental influences on cardiovascular risk factors. The initial data collection phase occurred between December 2005/January 2006, and one hundred and nine families were selected, corresponding to 1627 individuals of both genders. Probands for each family were identified from the community at large in several stages. First, eleven census districts (from a total of twelve) were selected for study. Second, residential addresses within each district were randomly selected (first by randomly selecting a street, second a household). Finally, eligibility criteria (any individual living in the selected household who was 18 years old or above) within each household were established. Then, in 2010 during the first follow-up visit, 2239 individuals from the same families participated in the protocol. Details on the methodology of the original study have been previously published [14,15]. This current study is a cross-sectional analysis of data collected at the second evaluation visit (from 2010 to 2015) on subjects that underwent carotid ultrasonography. Individuals that presented angina, infarct, cardiac insufficiency and revascularization were removed from our analysis. We considered only individuals with complete data for all variables used in our analysis (n = 1937 subjects).

The study protocol was approved by the ethics committee of the *Hospital das Clínicas* (SDC: 3485/10/074), University of São Paulo (USP), Brazil, and each subject provided informed written consent before participation.

2.2. Covariates

Demographics and anthropometrics were assessed through questionnaires and following a standard protocol by trained technicians, respectively. Height was measured in centimeters and weight in kilograms using a calibrated digital balance and BMI was calculated as body weight (Kg) divided by height squared (m^2). Waist circumference was measured at the mean point between the lowest rib margin and the iliac crest with the subject standing [14,16]. Blood pressure (BP) was measured using a digital sphygmomanometer (OMRON, Brazil) on the left arm after 5 min rest, in the sitting position. Systolic BP (SBP) and diastolic BP (DBP) were calculated as an average of three readings [16]. After calculation of blood pressure values, we adjusted for medication usage by adding 15 and 10 mmHg to SBP and DBP, respectively, for individuals reported to be taking anti-hypertensive drugs [17]. Blood samples, after 12 h fasting, were collected and analyzed for lipid and glucose profiles. For lipid profile, we assessed total cholesterol, low-density lipoprotein (LDL) cholesterol, HDL cholesterol associated and triglycerides.

Based on the fact that we would like to explore the association of the cIMT and the presence or absence of MetS, we classified our analytical sample according to the MetS definition following experts classification from the National and Cholesterol Education Program—Third Adult Treatment Panel (NCEP ATP III) [18], which is the recommended classification by the Brazilian Society Guideline [19]. The ATP III 2001 suggests any three out of five features: abdominal obesity by waist circumference (>102 cm for male and >88 cm for female); triglycerides (>150 mg/dL); HDL cholesterol (<40 mgdl for male and <50 mg/dL for female); fasting blood glucose level (>110 mg/dL); systolic BP (≥130 mmHg) and diastolic BP (≥85 mmHg) [18].

Smoking status was collected by a questionnaire using the following question: "Did you already smoke cigarettes?" (1) Yes, in the past, but not currently; (2) Yes, and I still smoke; (3) I do not smoke. The three choices were then characterized as (1) former, (2) current, and (3) non-smokers, respectively, as previously published [20].

2.3. cIMT ultrasound imaging

The technique used to measure and calculate cIMT was to measure a double line with the definition of the light-intima and media-adventitia interfaces of the vessel. The distance between the two acoustic interfaces was considered the cIMT measure [21,22]. Measurements with reference to the light-intima and media-adventitia interfaces of the vessel were standardized using the Philips Envisor HD7 ultrasound equipment with a linear 7.5 MHz transducer.

Three measurements of the cIMT were performed on each side, starting 1.0 cm below the upper limit of the image (1.0 cm below the carotid bifurcation), using the posterior (distal) wall of the common carotid artery, with a 5 mm spacing between them. For each side, we performed the arithmetic mean of the measurements [23,24]. cIMT was calculated by the mean of the three measurements performed on the walls of the distal carotid, using Osirix ™ software. In addition, carotid bifurcation was studied at 4.0 cm for plaques. Images of common carotids acquired and documented in a 4.0 cm length starting at the carotid bifurcation. When plaques occurred that did not allow the measurement, 1.0 cm below the upper limit of the image, the measurement was performed immediately after the plaque. The atheromatous plaque was defined as a focal structure that extends at least 0.5 mm to the vessel lumen or measures more than 50% of the adjacent cIMT measurement value or a measurement greater than 1.5 mm [23,24].

2.4. Statistical analysis

Descriptive data on demographics, lipid and glucose blood profiles, anthropometric measures and blood pressure are shown as mean and standard deviation for continuous variables and percentage for categorical ones. Significant differences in descriptive data between males and females were assessed using a linear mixed-effects model (LMM), adjusting by the family structure, for continuous variables and a mixed logistic regression for categorical variables assuming a p-value < 0.05.

Initially, we explored the correlation of cIMT with the well-known cardiovascular risk factors, such as age, BMI, and smoking status, as well as the MetS components separately, each one at a time. A LMM was subsequently used to analyze the association between each risk factor and cIMT taking into account family structure in the random part of the model.

Table 1
Characteristics of the study sample and testing differences by sex groups.

	All (n = 1937)	Female (n = 1178)	Male (n = 759)	*p*-value
Age, yo	46 ± 16	46 ± 16	46 ± 16	0.556
Male sex, %	41	–	100	-
Race, %				
White	73	74	72	ref
Black	6	6	6	0.736
Brown	20	19	21	0.319
Others	1	1	1	0.948
Smoking status, %				
Never	66	73	55	ref
Former	22	16	30	**<0.001**
Current	12	11	15	**<0.001**
BMI, kg/m^2	26 ± 5	27 ± 5	25 ± 4	**<0.001**
Waist circumference, cm	92 ± 13	92 ± 13	92 ± 12	0.760
Systolic BP, mmHg	129 ± 20	127 ± 20	133 ± 19	**<0.001**
Diastolic BP, mmHg	79 ± 12	79 ± 12	80 ± 12	**0.0136**
cIMT, mm	0.53 ± 0.16	0.53 ± 0.15	0.53 ± 0.16	0.987
Total cholesterol, mg/dL	200 ± 41	202 ± 40	197 ± 42	**0.011**
HDL cholesterol, mg/dL	48 ± 12	50 ± 12	44 ± 10	**<0.001**
LDL cholesterol, mg/dL	124 ± 36	125 ± 35	124 ± 36	0.481
Triglycerides, mg/dL	138 ± 83	135 ± 76	144 ± 93	**0.017**
Glucose, mg/dL	93 ± 22	93 ± 22	93 ± 18	0.548
HbA1c, %	5.7 ± 1.5	5.6 ± 0.9	5.7 ± 2.1	0.312
Metabolic Syndrome, %	35	39	28	**<0.001**
Medication, %				
Statin	8	11	5	**<0.001**
Antihypertensive	28	32	22	**<0.001**
Hypoglycemic	6	7	4	0.017

Data are shown in mean ± SD for continuous and percentage for categorical variables. A linear mixed-effects model (LMM), adjusting by the family structure, for continuous variables and a mixed logistic regression for categorical variable assuming a *p*-value < 0.05. BMI = body mass index; BP = blood pressure; cIMT = carotid intima-media thickness; HDL = high-density lipoprotein; LDL = low-density lipoprotein; HbA1c = glycated hemoglobin. Metabolic syndrome was defined by any three out of five features: abdominal obesity by waist circumference (>102 cm for male and >88 cm for female); triglycerides (>150 mg/dL); HDL cholesterol (<40 mgdl for male and <50 mg/dL for female); fasting blood glucose level (>110 mg/dL); systolic BP (≥130 mmHg) and diastolic BP (≥85 mmHg). Values in bold highlights the results those are statistically significant.

Further, to test the independent association of cIMT with cardiovascular risk factors, we developed two different LMMs, one with MetS data (as a binary variable) and a second with its individual components.

Some risk factors that define MetS are highly correlated with each other and this can inflate the variances of the regression coefficients and impair the statistical power. To address this issue, we ran an exploratory factor analysis (EFA) model and a confirmatory factor analysis (CFA) model. The latent variables (factors) resulting from these analyses and the independent factors were used to fit the multiple LMM to study the independent association with cIMT. Models were corrected for age, sex, smoking status, and statin use, all well-known confounders in the context of atherosclerosis [4, 25]. To check factors and well-known confounders for multicollinearity, we assessed the variance inflation factor (VIF) in the LMM.

Univariate analysis was conducted to test the difference in means between cIMT and groups with MetS vs without MetS.

We used the kinship 2 package in R (version 3.5.2) to adjust models for family structure, dlookr for exploratory analysis, coxme for univariate and multiple linear regression, stats and psych packages for exploratory factorial analysis, lavaan to confirm factorial analysis using structural equations analysis and performance to VIF analysis. The alpha level of significance was set as <0.05.

3. Results

Table 1 displays results for the full analytical sample that underwent carotid ultrasound for cIMT measurement (n = 1937). In general, it is a young sample with mean age of 46 ± 16y, most female (61%), 73% white, 66% never-smoking, 8% on statin, 6% on oral hypoglycemic, and 28% on anti-hypertensive medication. Thirty five percent of the sample was classified with MetS (Supplemental Table 1S), following the ATP-III 2001 definition [18]. Table 1 also shows sex differences. Interestingly, despite several differences in the risk profile between males and females, cIMT values were quite similar between sex groups.

Considering Person's correlation, age was the strongest variable, among all covariates, correlated to cIMT with a coefficient of 0.57 ($p < 0.001$) (Supplemental Table 2S). The relationship between age and cIMT was linear as shown in Supplemental Fig. 1S. We also conducted a univariate analysis checking separately all covariates, including the MetS components, and its association with cIMT, but accounting for family structure in LMM. All covariates were significantly associated with cIMT, except for HDL-cholesterol (Supplemental Table 3S).

Since several covariates, including variables used to define MetS, are highly correlated (Supplemental Table 4S), we conducted an exploratory factorial analysis to determine how many factors explain most of the phenotypic variance associated with the tested cardiovascular risk factors. We derived four distinct factors: the first one represents waist circumference and BMI, the second total cholesterol and LDL cholesterol, the third SBP and DBP and the last one represents glucose and glycated hemoglobin. HDL cholesterol and triglycerides were not represented in any factor (Supplemental Fig. 2S). Following structural equation analysis, we observed that the factors fit as latent variables representing the cited covariates (*p*-value of chi-square test < 0.0001). Each of these factors, as well as HDL-cholesterol and triglycerides, was tested independently for their association with cIMT using a multiple LMM, adjusted by age, sex, smoking status, statin use and familial structure. Only factors 1, 3 and 4 were significantly associated with cIMT (Supplemental Table 5S).

Considering models for cIMT with MetS and all factors that determine MetS that were statistically significant in the analyses above, we found that all derived factors included in the model (factors 1, 3 and 4) were independently associated with cIMT, as well as MetS (Tables 2 and 3). Furthermore, results from VIF analysis demonstrated that there is a low collinearity among factors and covariates included in the models

Table 2
Linear mixed model analysis testing the independent association between cIMT (outcome) and traditional cardiovascular risk factors (exposures).

	Beta coefficient	se	*p*-value	VIF
(Intercept)	0.29341	0.01005	**<0.0001**	
Factor 1	0.00765	0.00341	**0.0251**	1.35
Factor 3	0.00999	0.00329	**0.0024**	1.34
Factor 4	0.01040	0.00408	**0.0107**	1.34
Age, yo	0.00505	0.000203	**<0.0001**	1.20
Smoking status (factor = former)	0.00069	0.00733	0.9250	1.12
Smoking status (factor = current)	−0.00085	0.00893	0.9240	1.12
Statin (factor = yes)	−0.01690	0.01071	0.1147	1.08
Sex (factor = male)	−0.00625	0.00597	0.2954	1.06

Adjustments for traditional confounders in the context of the cIMT and cardiovascular diseases were forced in the model independent of results from the univariate analysis: age, sex (reference = female), smoking status (reference = never), and statin use. cIMT = carotid Intima-media thickness, se = standard error; LDL = low-density lipoprotein; BMI = body mass index. Factor 1 composed of waist circumference and BMI; Factor 3 composed of systolic blood pressure and diastolic blood pressure; Factor 4 composed of glucose and glycated hemoglobin. VIF - Variance Inflation Factor. Values in bold highlights the results those are statistically significant.

Table 3
Multiple linear mixed model analysis testing the independent association between cIMT (Outcome) and MetS.

	Beta coefficient	se	*p*-value	VIF
(Intercept)	0.26698	0.00881	**<0.0001**	
Age, yo	0.00547	0.02164	**<0.0001**	1.23
MetS (factor = yes)	0.02164	0.00642	**0.0008**	1.10
Smoking status (factor = former)	0.00042	0.00722	0.9534	1.11
Smoking status (factor = current)	−0.00279	0.00881	0.7514	1.11
Statin (factor = yes)	−0.01410	0.01048	0.1786	1.07
Sex (factor = male)	−0.00187	0.00588	0.7504	1.06

Adjustments for traditional confounders in the context of the cIMT and cardiovascular diseases were forced in the model independent of results from the univariate analysis: age, sex (reference = female), smoking status (reference = never), and statin use. Metabolic syndrome (MetS) was defined by any three out of five features: abdominal obesity by waist circumference (>102 cm for male and >88 cm for female); triglycerides (>150 mg/dL); HDL cholesterol (<40 mgdl for male and <50 mg/dL for female); fasting blood glucose level (>110 mg/dL); systolic blood pressure (≥130 mmHg) and diastolic blood pressure (≥85 mmHg). VIF - Variance Inflation Factor. Values in bold highlights the results those are statistically significant.

(Tables 2 and 3). Nonetheless, MetS classification as a binary variable (MetS present/MetS absent) showed the strongest effect size (Table 3). Then, we ran LMM to test cIMT by groups (age and MetS), due to the high correlation between cIMT and age, as well as the knowledge that MetS increases with age. Both, age and MetS, influence cIMT (p-value $\leq$ 0.0001 and 0.0008, respectively), and the interaction between both was almost significant (p-value = 0.051).

4. Discussion

Our findings contribute to a better understanding of MetS components and the role of each component in the association with cIMT in a rural sample from Brazil. In this family-based and relatively young population, we observed that 35% were classified with MetS and those with MetS had higher values of cIMT, independently of age. From MetS defining cardiovascular risk factors, we observed that only blood pressure, obesity and glycemia, three out of five, were independently associated with cIMT, even after adjusting for main confounders in the atherosclerosis context, such as age, sex, smoking status and statin. We also confirmed the linear relationship between age and cIMT.

Because MetS is a phenotype of clustering factors, growing in prevalence worldwide particularly among rural populations [10–13], the role of each factor should be explored separately not only for quantifying factor contribution but also for getting a more specific phenotypic characterization of disease development and targeting specific therapies. In this context of phenotypic characterization, cardiovascular risk factors, such as BMI, systolic BP, hypertension, and diabetes mellitus, have been previously associated with increased cIMT [7,26], as well as sex [27,28]. However, those associations have been controversial, since studies did not assess the same risk factors and usually did not consider the correlation between them. Mannami et al. demonstrated that men present more risk factors associated with cIMT than women in a Japanese population [29], while Loboz-Rudnicka et al. showed the opposite [28]. In contrast to what has been previously described, we didn't find any evidence of sex differences in cIMT in our population, even though a previous study in Brazil using a higher number of individuals demonstrated that cIMT is higher in men [21].

Furthermore, HDL-cholesterol and triglycerides, two of the components used to diagnose MetS, were not independently associated with cIMT in this current study. HDL-cholesterol is a protective factor for cardiovascular disease [22,30,31]. Kim et al. showed that actually a sub-fraction of HDL, the small and dense HDL particle, is responsible for the significant and inverse association with cIMT, even after adjustment by LDL and all particles of HDL [32]. In our study, we were not able to assess HDL sub-fractions. In addition, the lipid profile is known to be highly associated with atherosclerosis [33,34]. Kawamoto et al. [35] demonstrated not only a positive association of LDL-cholesterol with cIMT but also that MetS amplifies LDL levels. Nonetheless, our data showed that factor 2, composed by total cholesterol and LDL, was not significantly associated with cIMT.

Despite the fact that the cIMT has been already established as a strong predictor of future cardiovascular events [3,5], the heterogeneity regarding its effect in different age strata and the lack of information on younger individuals remained [3,5]. Our findings contribute to this gap because we explored a relatively young sample (average age of 46 ± 16yo), as well as a population without MetS (only 35% had MetS). In addition, our results showed that age is linearly associated with cIMT, even for younger individuals. Although prospective data is essential for cardiovascular risk assessment, the linear relationship between age and cIMT in young individuals pointed out that carotid ultrasound may be a very useful tool for early subclinical atherosclerosis evaluation in young participants.

Our study has limitations. First, the cross-sectional analysis does not allow causal inference. Second, independent associations were tested, and then incomplete adjustment for unmeasured confounders may be taken into account. On the other hand, we conducted a robust statistical analysis in which we assess the contribution of cardiovascular risk factors used to define MetS in the cIMT phenotype, taking into account that many risk factors are highly correlated.

5. Conclusion

In this rural cohort, cIMT showed a linear relationship with increasing age. Higher cIMT values were revealed for those with MetS compared to those without MetS. While analyzing MetS components separately, blood pressure, glucose and obesity were independently associated with cIMT, but not HDL-cholesterol and triglycerides. It appears that hypertension, diabetes, and obesity play a major role in cIMT values compared to the lipid profile. Exploring the contribution of each cardiovascular risk factor for disease development may target specific therapies and point out better practices for disease prevention.

Author contributions

Concept and design: GRG, IPS, SKT and JEK.

Analysis and interpretation of data: GRG, IPS, SKT, LMGG, ACP, and JEK.

Drafting the article or revising it critically for important intellectual content: GRG, IPS, SKT, MJFN, LMGG, GCDG, ACP and JEK.

Final approval: all.

Data sharing statement

Researchers can apply for data and biomaterial by submitting a proposal to the principal investigator, ACP (alexandre.pereira@incor.usp.br).

Funding

Awards from FAPESP (grants 2007/58150-7, 2010/51010-8, 2011/05804-5, 2013/17368-0), from CNPq (150653/2008-5, 481304/2012-6, 400791/2015-5).

Declaration of competing interest

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

Acknowledgments

The authors wish to thank the Municipal Council of Baependi for logistical support and assistance with fieldwork, the dedicated staff at the Field station and the participants of the study.

Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijchy.2020.100043.

Abbreviations

BMI	body mass index
cIMT	carotid intima-media thickness
CVD	cardiovascular disease
DBP	diastolic blood pressure
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
LDL	low-density lipoprotein
MetS	metabolic syndrome
SBP	systolic blood pressure

References

[1] L.E. Chambless, G. Heiss, A.R. Folsom, W. Rosamond, M. Szklo, A.R. Sharrett, et al., Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the atherosclerosis risk in communities (ARIC) study, 1987-1993, Am. J. Epidemiol. 146 (1997) 483–494.

[2] M.L. Bots, A.W. Hoes, P.J. Koudstaal, A. Hofman, D.E. Grobbee, Common Carotid Intima-Media Thickness and Risk of Stroke and Myocardial Infarction. Circulation, vol. 96, Lippincott Williams & Wilkins, 1997, pp. 1432–1437.

[3] M.W. Lorenz, H.S. Markus, M.L. Bots, M. Rosvall, M. Sitzer, Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis, Circulation 115 (2007) 459–467.

[4] M. Amato, F. Veglia, U. de Faire, P. Giral, R. Rauramaa, A.J. Smit, et al., Carotid Plaque-Thickness and Common Carotid IMT Show Additive Value in Cardiovascular Risk Prediction and Reclassification, vol. 263, Atherosclerosis. Elsevier Ltd, 2017, pp. 412–419.

[5] M.W. Lorenz, S. Von Kegler, H. Steinmetz, H.S. Markus, M. Sitzer, Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS), Stroke 37 (2006) 87–92.

[6] I.C.L. van den Munckhof, H. Jones, M.T.E. Hopman, J. de Graaf, J. Nyakayiru, B. van Dijk, et al., Relation between age and carotid artery intima-medial thickness: a systematic review, Clin. Cardiol. 41 (2018) 698–704.

[7] M.L. Bots, K.A. Groenewegen, T.J. Anderson, A.R. Britton, J.M. Dekker, G. Engström, et al., Common carotid intima-media thickness measurements do not improve cardiovascular risk prediction in individuals with elevated blood pressure: the USE-IMT collaboration, Hypertension 63 (2014) 1173–1181.

[8] M. Herder, S.H. Johnsen, K.A. Arntzen, E.B. Mathiesen, Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromsø study, Stroke 43 (2012) 1818–1823.

[9] H. Bixby, J. Bentham, B. Zhou, M. Di Cesare, C.J. Paciorek, et al., NCD Risk Factor Collaboration (NCD-RisC). Rising rural body-mass index is the main driver of the global obesity epidemic in adults, Nature 569 (7755) (2019 May) 260–264, https://doi.org/10.1038/s41586-019-1171-x. Epub 2019 May 8.

[10] I. Lambrinoudaki, A. Kazani, E. Armeni, D. Rizos, A. Augoulea, G. Kaparos, et al., The metabolic syndrome is associated with carotid atherosclerosis and arterial stiffness in asymptomatic, nondiabetic postmenopausal women, Gynecol. Endocrinol. 34 (2018) 78–82.

[11] E.S. Ford, Prevalence of the metabolic syndrome defined by the international diabetes federation among adults in the U.S, Diabetes Care 28 (2005) 2745–2749.

[12] D.R. Pokharel, D. Khadka, M. Sigdel, N.K. Yadav, S. Acharya, R.C. Kafle, et al., Prevalence of metabolic syndrome in Nepalese type 2 diabetic patients according to WHO, NCEP ATP III, IDF and Harmonized criteria, J. Diabetes Metab. Disord. 13 (2014).

[13] C. Cuspidi, C. Sala, F. Provenzano, M. Tadic, E. Gherbesi, G. Grassi, et al., Metabolic syndrome and subclinical carotid damage: a meta-analysis from population-based studies, J. Hypertens. 36 (2018) 23–30.

[14] K.J. Egan, M. Von Schantz, A.B. Negrão, H.C. Santos, A.R.V.R. Horimoto, N.E. Duarte, et al., Cohort profile: the Baependi Heart Study - a family-based, highly admixed cohort study in a rural Brazilian town, BMJ Open 6 (10) (2016) e011598, https://doi.org/10.1136/bmjopen-2016-011598. PMID: 27797990.

[15] C.M. de Oliveira, A.C. Pereira, M. de Andrade, J.M. Soler, J.E. Krieger, Heritability of cardiovascular risk factors in a Brazilian population: Baependi Heart Study, BMC Med. Genet. 9 (2008) 32.

[16] C.M. De Oliveira, A.Z. Ulbrich, F.S. Neves, F.A.L. Dias, A.R.V.R. Horimoto, J.E. Krieger, et al., Association between anthropometric indicators of adiposity and hypertension in a Brazilian population: Baependi Heart Study, PloS One 12 (2017).

[17] D Tobin Martin, Nuala A. Sheehan, Katrina J. Scurrah, Paul R. Burton, Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure, Stat. Med. 24 (19) (2005 Oct 15) 2911–2935, https://doi.org/10.1002/sim.2165.

[18] Executive summary of the third report of the national cholesterol education Program (NCEP) expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment Panel III), J. Am. Med. Assoc. 285 (19) (2001 May 16) 2486–2497.

[19] [I Brazilian guidelines on diagnosis and treatment of metabolic syndrome], [Article in Portuguese] Arq. Bras. Cardiol. 84 (Suppl 1) (2005 Apr) 1–28.

[20] A. Horimoto, C.M. Oliveira, S.R. Giolo, J.P. Soler, M. de Andrade, J.E. Krieger, A.C. Pereira, Genetic analyses of smoking initiation, persistence, quantity, and age-at-onset of regular cigarette use in Brazilian families: the Baependi Heart Study, BMC Med. Genet. 13 (2012 Jan 30) 9, https://doi.org/10.1186/1471-2350-13-9.

[21] I.S. Santos, M.S. Bittencourt, I.R.S. Oliveira, A.G. Souza, D.P. Meireles, T. Rundek, et al., Carotid intima-media thickness value distributions in the Brazilian longitudinal study of adult health (ELSA-Brasil), Atherosclerosis 237 (2014) 227–235.

[22] T. Gordon, W.P. Castelli, M.C. Hjortland, W.B. Kannel, T.R. Dawber, High density lipoprotein as a protective factor against coronary heart disease. The Framingham study, Am. J. Med. 62 (5) (1977) 707–714, https://doi.org/10.1016/0002-9343(77)90874-9. PMID: 193398.

[23] P.J. Touboul, M.G. Hennerici, S. Meairs, H. Adams, P. Amarenco, N. Bornstein, et al., Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011), Cerebrovasc. Dis. 34 (2012) 290–296.

[24] S.D.J.M. Kanters, A. Algra, M.S. Van Leeuwen, J.D. Banga, Reproducibility of in vivo carotid intima-media thickness measurements: a review, Stroke (1997) 665–671.

[25] G.F.N. Berkelmans, Y. van der Graaf, J.A.N. Dorresteijn, G.J. de Borst, M.J. Cramer, L.J. Kappelle, et al., Decline in risk of recurrent cardiovascular events in the period 1996 to 2014 partly explained by better treatment of risk factors and less subclinical atherosclerosis, Int. J. Cardiol. 251 (2018) 96–102.

[26] T. Rundek, S.H. Blanton, S. Bartels, C. Dong, A. Raval, R.T. Demmer, et al., Traditional risk factors are not major contributors to the variance in carotid intima-media thickness, Stroke 44 (2013) 2101–2108.

[27] T.-W. Wu, C.-L. Hung, C.-C. Liu, Y.-J. Wu, L.-Y. Wang, H.-I. Yeh, Associations of cardiovascular risk factors with carotid intima-media thickness in middle-age adults and elders, J. Atherosclerosis Thromb. 24 (2016) 677–686.

[28] M. Łoboz-Rudnicka, J. Jaroch, Z. Bociąga, B. Rzyczkowska, I. Uchmanowicz, J. Polański, et al., Impact of cardiovascular risk factors on carotid intima–media thickness: sex differences, Clin. Interv. Aging (2016) 721.

[29] T. Mannami, M. Konishi, S. Baba, N. Nishi, A. Terao, Prevalence of Asymptomatic Carotid Atherosclerotic Lesions Detected by High-Resolution Ultrasonography and its Relation to Cardiovascular Risk Factors in the General Population of a Japanese City. Stroke, vol. 28, Lippincott Williams & Wilkins, 1997, pp. 518–525.

[30] G. Assmann, A.M. Gotto Jr., HDL cholesterol and protective factors in atherosclerosis, Circulation 109 (23 Suppl 1) (2004 Jun 15) III8–14.

[31] B.G. Nordestgaard, A. Varbo, Triglycerides and cardiovascular disease, Lancet 384 (9943) (2014 Aug 16) 626–635, https://doi.org/10.1016/S0140-6736(14)61177-6, submitted for publication.

[32] D.S. Kim, Y.K. Li, G.A. Bell, A.A. Burt, T. Vaisar, P.M. Hutchins, et al., Concentration of smaller high-density lipoprotein particle (HDL-P) is inversely correlated with carotid intima media thickening after confounder adjustment: the multi ethnic study of atherosclerosis (MESA), J Am Heart Assoc 5 (2016) 1–12.

[33] B.A. Ference, H.N. Ginsberg, I. Graham, K.K. Ray, C.J. Packard, E. Bruckert, et al., Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel, Eur. Heart J. 38 (32) (2017) 2459–2472, https://doi.org/10.1093/eurheartj/ehx144. PMID: 28444290.

[34] M. Alique, C. Luna, J. Carracedo, R. Ramírez, LDL biochemical modifications: a link between atherosclerosis and aging, Food Nutr. Res. 59 (eCollection 2015) (2015) 29240, https://doi.org/10.3402/fnr.v59.29240. PMID: 26637360.

[35] R. Kawamoto, H. Tomita, Y. Oka, A. Kodama, A. Kamitani, Metabolic syndrome amplifies the LDL-cholesterol associated increases in carotid atherosclerosis, Intern. Med. 44 (2006) 1232–1238.