The relationship between the metabolic syndrome and arterial wall thickness: A mosaic still to be interpreted

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ABSTRACT

Background and aims: We aimed to identify clusters of metabolic syndrome (MetS) components, risky for extremely high intima-media thickness.
Methods: We studied 41,513 volunteers (men and women) from eleven cohorts worldwide, participating in the MARE (Metabolic syndrome and Artery REsearch) Consortium.
Results: Specific clusters of MetS components - high triglycerides-high blood pressure-abdominal obesity (TBW), low HDL cholesterol-high blood pressure-abdominal obesity (HBW), high glucose-high blood pressure-abdominal obesity (GBW) - were accompanied by a 50—90% significantly greater likelihood of presenting extremely high intima-media thickness (via ultrasound of carotid artery, CCA IMT), after controlling for age, sex, smoking, non-HDL cholesterol, and presence of diabetes mellitus. This likelihood is comparable to the effect of being 7—8 years older or of being a cigarette smoker or of having non-HDL cholesterol 50 mg/dl higher.

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Conclusions: The consistent association of specific clusters of MetS components with extremely thick (older) large artery cross-culturally suggests that identification of those clusters in clinical practice will facilitate a personalized health care and a better − i.e. more healthy and cost-effective - prevention of major cardiovascular (CV) events.

1. Introduction

The common carotid artery intima-media thickness (CCA IMT) has been reported to be associated with cardiovascular (CV) risk factors [1] and arterial remodelling [2]. Subsequently, population studies identified CCA IMT as a predictor of CV events, independent of blood pressure, lipids, and glucose levels [3–5]. Ultrasound imaging of CCA IMT is a combined measure of intima and media layers. Over time, there has been a transformation of CCA IMT from a novel and independent CV risk marker into a proxy of arterial aging [6]. In fact, IMT increases from 20 years to 80 years of age [7] and this increase is faster in men than in women [8]. CCA IMT is currently considered expression of Target Organ Damage (TOD) in International Guidelines for treatment of hypertensive subjects [9]. The early identification of subjects with accelerated arterial aging, or Early Vascular Aging (EVA) [10], i.e. with arterial parameters typically observed at older (chronological) age, seems critical to implement effective prevention of CV events and optimal health-care resource allocation. This has particular relevance in the context of growing evidence of a more complex association of traditional CV risk factors with older artery [11].

We selected metabolic syndrome (MetS), a well conceptualized and operationalized model of clustering of multiple CV risk factors, to investigate the impact of specific cluster of MetS components on extremely high intima-media thickness (CCA IMT). The identification of risky-clusters linked to MetS will facilitate a personalized approach to prevention of CV events and CV-related disability.

2. Patients and methods

2.1. The MARE consortium

In 2012, the original MARE (Metabolic syndrome and Artery REsearch) Consortium was established as a collaboration among eleven European and one American centers studying population-based cohorts to identify any cross-cultural differences in clustering of MetS altered components and associations with arterial aging; to disentangle the specific role of genes and lifestyle factors (and their interactions) on the clinical presentation of MetS and on the CV risk attributable to MetS and to develop new strategies to prevent CV events through identification of lifestyle changes (see reference [12] for more details).

In 2014 and 2015, additional participating cohorts joined the MARE Consortium, providing that new data on the MetS components and on arterial properties became available for the recruited subjects. Currently, approximately 75,000 subjects from 22 cohorts worldwide are participating in the MARE Consortium.

Each cohort had been approved by local Institutional Review Board or Ethic Committee and each subject gave informed consent. All studies in the MARE Consortium adhere to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001.

The cohorts participating in the present analysis are briefly described in Supplementary Materials.

3. Definition of the metabolic syndrome

The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) [13] defined the MetS as an alteration in three or more of the following five components: abdominal obesity (W), high triglycerides (T), low HDL cholesterol (H), elevated blood pressure (systolic or diastolic) (B), and elevated fasting glucose (G). The following cut-off values are used to define each altered component: triglycerides $\geq$150 mg/dl HDL cholesterol <40 mg/dl for men or <50 mg/dl for women, blood pressure $\geq$130/$\geq$85 mmHg, fasting glucose $\geq$110 mg/dl, and waist circumference >102 cm for men or >88 cm for women. For Asian subjects, an elevated waist circumference is defined as $\geq$80 cm for women and $\geq$90 cm for men [14]. In 2009, a revised definition of MetS has been proposed [14]. In this definition the cut-off values to define elevated fasting glucose were lowered to $\geq$100 mg/dl, and ethnic specific cut-offs have been defined for waist circumference [14].

To allow comparability with previous studies, we adopted the original ATP II definition of MetS for primary analyses and the revised definition of MetS for secondary confirmatory analyses.

Because MetS is defined by the presence of three or more altered components, subjects with MetS may have diagnosed based on different combinations of the individual components of MetS.

3.1. CCA IMT measurements

High-resolution B-mode carotid ultrasonography was performed for measurement of CCA IMT. The subject lay in the supine position in a dark, quiet room. The right CCA was examined with the head tilted slightly upward in the midline position. The transducer was manipulated so that the near and far walls of the CCA were parallel to the transducer footprint and the lumen diameter was maximized in the longitudinal plane. A region 1.5 cm proximal to the carotid bifurcation was identified, and the IMT of the far wall was evaluated as the distance between the luminal-intimal interface and the medial-adventitial interface. IMT was measured in areas without plaques or calcification (at least 1 mm distance from the plaque shoulder, if plaque was present).

Some details of the IMT measurement differed across Centers as illustrated in Table 1.

3.2. Statistical analysis

All analyses were performed using the SAS package for Windows (9.1 Version Cary, NC, US). ANOVA analysis followed by Bonferroni test was adopted to compare means amongst subgroups of subjects. Least square means ($\pm$standard error, SEM) were calculated with ANCOVA analysis in order to compare CCA IMT values across clusters of MetS components, after controlling for covariates (age, sex, non-HDL cholesterol levels, current smoking, presence of diabetes mellitus, and study center for CCA IMT).

Multivariable logistic regression analyses were used to identify which clusters of MetS components were significantly associated with extremely high intima-media thickness. Extremely high

Table 1
Characteristics of the MARE cohorts included according to measurement of CCA IMT.

	Asklepios	LitHiR	Rotterdam	SardiNIA	SHIP	BLSA	Namwon	Dong-gu	Kingmen Aging Study	MDC-CV	Moscow
Country	Belgium	Lithuania	The Netherlands	Italy	Germany	USA	South Korea	South Korea	Taiwan	Sweden	Russia
N	2522	1417	3733	6049	2395	759	10262	9092	1305	3692	287
Years CCA IMT measured	2002-	2007–2015	1990–93	2001–2004 (baseline)	1997–2001 (baseline)	1958-	2004–2007	2007–2010	1992–1993		2012–2013
Site measured	Near & far wall Left & right	Far wall Left & right	Near & far wall Left & right	Far wall Right	Far wall Left & right	Far wall Right at end-diastole	Far wall Left & right	Far wall Left & right	Far wall Right at end-diastole	Far wall Right	Far wall Left & right
Device	VIVID 7, GE Vingmed Ultrasound, Horten, (Norway).	High-resolution echo-tracking technology (Art.Lab, Esaote Europe B.V., Maastricht, the Netherlands)	Duplex scanner (ATL UltraMark IV)	High-resolution Bmode carotid ultrasonography was performed by use of a lineararray5- to 7.5- MHz transducer (HDI 3500-ATLUltramark Inc)	B-Modeultrasonography was performed using a 5 MHz linear array transducer with an axial resolution of less than 0.5 mm and a high resolution instrument (Diasonics VST Gateway, Santa Clara, California, USA).	5- to 10-MHz transducer (Ultramark 9 HDI, Advanced Technology Laboratories, Inc)	B-mode ultrasound scanners (SONOACE 9900; Medison, Seoul, Korea) with an electrical linear transducer (7.5 MHz).	B-mode ultrasound scanners (SONOACE 9900; Medison, Seoul, Korea) with an electrical linear array transducer (7.5 MHz).	Hewlett-Packard SONOS 500 U (Hewlett-Packard, Andover, MA) 7-MHz vascular probe		High-resolution B-mode 17, 5-MHz linear-type probe (PHILIPS iU22)

Table 2
Characteristic of cohorts participating the MARE Consortium with available IMT measurements.

	Asklepios	LitHiR	Rotterdam	SardiNIA	SHIP	BLSA	Namwon	Dong-gu	Kingmen Aging Study	MDC-CV	Moscow
Country	Belgium	Lithuania	The Netherlands	Italy	Germany	USA	South Korea	South Korea	Taiwan	Sweden	Russia
N	2522	1417	3733	6049	2395	759	10262	9092	1305	3692	287
Age (years)	46 ± 6	55 ± 6	72 ± 7	44 ± 17	61 ± 9	66 ± 14	62 ± 8	65 ± 8	52 ± 13	72 ± 6	52 ± 13
Women (%)	48.5	34.2	42.0	57.5	48.9	48.2	60.5	59.9	46.4	59.3	66.9
Waist (cm)	87.1 ± 12.7	105.3 ± 11.4	93.5 ± 11.4	84.8 ± 13.1	93.6 ± 12.7	91.6 ± 12.0	86.1 ± 8.4	88.1 ± 8.6	85.0 ± 9.0	92.3 ± 12.5	89.7 ± 15.2
BMI (Kg/m^2)	25.8 ± 4.3	31.9 ± 5.1	26.8 ± 39.5	25.4 ± 4.7	28.5 ± 4.6	27.0 ± 4.7	24.3 ± 3.0	24.4 ± 2.9	24.8 ± 3.0	26.9 ± 4.4	27.3 ± 5.1
Glucose (mg/dl)	91.4 ± 12.3	112.2 ± 25.5	106.9 ± 26.6	90.1 ± 23.6	108.0 ± 37.3	94.8 ± 17.4	104.9 ± 24.6	109.7 ± 25.2	98.8 ± 15.7	110.9 ± 26.2	103.7 ± 25.9
Total cholesterol (mg/dl)	216.5 ± 36.6	258.9 ± 52.8	225.0 ± 37.8	208.6 ± 42.2	235.2 ± 45.4	191.1 ± 38.4	189.3 ± 36.9	201.3 ± 39.6	197.5 ± 36.7	201.0 ± 41.3	219.8 ± 44.4
nonHDL cholesterol (mg/dl)	153.6 ± 38.0	209.1 ± 51.2	171.4 ± 37.9	145.3 ± 38.8	179.6 ± 45.2	134.3 ± 36.1	142.8 ± 34.8	150.5 ± 37.0	147.3 ± 36.4	146.6 ± 37.9	172.9 ± 45.3
HDL cholesterol (mg/dl)	63.6 ± 17.2	50.0 ± 12.3	53.9 ± 15.4	64.2 ± 14.9	55.8 ± 17.2	58.6 ± 16.5	47.6 ± 11.9	51.6 ± 11.9	50.9 ± 12.9	55.2 ± 16.7	47.2 ± 12.0
Triglycerides (mg/dl)	109.8 ± 71.1	195.2 ± 113.4	133.7 ± 64.0	85.2 ± 52.7	173.9 ± 105.3	104.3 ± 61.7	154.8 ± 97.3	140.8 ± 87.4	123.0 ± 85.2	56.6 ± 30.7	65.6 ± 44.1
SBP (mmHg)	126.9 ± 14.1	139.7 ± 15.6	143.4 ± 21.2	125.9 ± 18.5	144.4 ± 21.3	121.5 ± 15.6	126.0 ± 18.4	123.4 ± 16.9	138.9 ± 23.7	135.8 ± 17.3	125.4 ± 16.6
DBP (mmHg)	80.0 ± 10.0	86.0 ± 9.7	75.2 ± 11.1	77.6 ± 10.5	86.0 ± 11.3	66.4 ± 9.1	80.4 ± 10.2	74.4 ± 10.2	87.9 ± 14.6	75.7 ± 8.7	78.2 ± 10.3
MetS (%)	9.0	62.2	29.8	6.8	30.1	14.4	39.2	34.8	32.4	22.2	28.3
Hypertension (%)	28.8	58.3	55.1	29.0	69.6	16.6	39.8	44.7	50.3	70.0	25.8
Diabetes mellitus (%)	1.6	23.6	13.5	4.9	18.3	12.0	12.2	20.0	5.4	17.7	26.8
Antihypertensive medication (%)	10.5	N/A	N/A	9.5	75.4	4.7	21.6	35.7	—	56.8	N/A
CCA IMT (mm)	0.60 ± 0.11	0.67 ± 0.10	0.87 ± 0.15	0.55 ± 0.11	0.79 ± 0.18	0.59 ± 0.08	0.74 ± 0.14	0.72 ± 0.15	1.03 ± 0.26	0.92 ± 0.22	0.76 ± 0.20
CCA IMT 95th % (mm)	0.81	0.84	1.15	0.77	1.10	0.72	0.97	1.00	1.50	1.30	1.11

intima-media thickness was defined based upon the 95th percentile of CCA IMT distribution within each cohort. Age, sex, non-HDL cholesterol levels, current smoking status, and presence of diabetes mellitus were introduced as covariates.

A two-sided *p* value < 0.05 indicated statistical significance.

4. Results

Complete data were available for 41,513 subjects (18,501 men and 22,932 women) from eleven cohorts, whose characteristics are briefly summarized in Tables 1 and 2. MetS had an overall prevalence of 27.3% (11,325 subjects) and unexpectedly indicated a greater prevalence in Asian cohorts.

Average values and 95th percentile for CCA IMT showed wide differences across studies and the acquisition methods of CCA IMT varied at each study site (year, equipment, ECG-gating, etc), as illustrated in Table 1. This greater variability across studies further supports the choice of the study-specific 95th percentile in CCA IMT to identify extremely high intima-media thickness. Notably, the interaction term between study site and cluster of MetS component was not significant at ANCOVA analysis — indicating that the impact of specific clusters of MetS components on CCA IMT did not significantly differ across the sites.

By adopting the within cohort 95th CCA IMT percentile subgroup to define subjects with extremely high intima-media thickness, after controlling for age, sex, smoking, non-HDL cholesterol, and presence of diabetes mellitus, specific clusters of MetS components were relatively more associated with the occurrence of extreme values of CCA IMT (Table 3 left columns). Counterintuitively, when affected subjects were compared to those without MetS, not all the clusters of MetS components were associated with extremely high intima-media thickness. Specific clusters (for instance TBW, HBW, GBW) were accompanied by a 50–90% significantly greater likelihood of presenting extremely thick arteries — which was comparable to that associated with the simultaneous alteration in all the five MetS components. This likelihood is comparable to the effect of being 7–8 years older or being a

smoker or having a non-HDL cholesterol 50 mg/dl higher. When the presence of diabetes mellitus was not included amongst the covariates, the impact of MetS cluster including glucose on CCA IMT was greater (Table 3 right columns).

Confirmatory analyses conducted with the 2009 harmonizaed MetS definition [14] yielded findings similar to what reported for ATP III MetS definition, as illustrated in Table 4.

5. Discussion

The metabolic syndrome (MetS) remains a controversial entity and its conceptual construct has been criticized [15,16]. The main and fundamental criticism concerning the CV risk associated with CV is that the whole is not greater than the sum of the parts. In other terms, a large number of scientists suggested that current evidence does not support clinical usefulness of MetS diagnosis, as it does not imply any action that would otherwise be ignored or missed (not in the therapeutic approach, not in the presence of CV greater risk, not in patient's attitude towards a healthier lifestyle and/or a greater adherence to therapy). Notably, they still recommend that more research is needed to understand the cause of risk-factor clustering rather than pursuing MetS diagnosis [15].

A major limitation to the current approach to MetS is that, by definition, any cluster of three or more of its components is sufficient to diagnose MetS. In other terms, the unproven assumption is that any combination of three MetS components carries a similar CV risk. However, this point has scarcely been investigated [16]. We firstly reported that specific clusters of altered MetS components - rather than MetS *per se* - were associated with accelerated arterial aging in the SardiNIA Study [7]. The observation was confirmed for arterial stiffness, indexed as Pulse Wave Velocity, in multiple cohorts from different countries participating the MARE Consortium [17]. Specifically, MetS clusters TBW, GBW, and GTBW were associated with extremely stiff large artery [17]. Notably, only specific clusters of altered MetS components conferred a higher risk of CV events in the Framingham Study [18].

The present study identified specific clusters of MetS

Table 3
Specific clusters of MetS components as determinants of extremely high intima-media thickness as compared to Control (no MetS) subjects.

	Prevalence within		Prevalence of extremely high CCA IMT (%)	Controlling for age, sex, diabetes mellitus, non-HDL cholesterol, smoking, and study site			Controlling for age, sex, non-HDL cholesterol, smoking, and study site		
	Whole population (%)	Subjects with MetS (%)		OR	95% CI	*p* <	OR	95% CI	*p* <
Age (per 10 years of age)				**1.78**	**1.70–1.86**	0.0001	**1.78**	**1.70–1.86**	0.0001
Male sex				**1.78**	**1.61–1.98**	0.0001	**1.81**	**1.63–2.01**	0.0001
Current smoking				**1.22**	**1.13–1.30**	0.0001	**1.21**	**1.02–1.43**	0.0001
Diabetes mellitus				**2.17**	**1.80–2.61**	0.0001\	—	—	—
Non-HDL cholesterol (per 40 mg/dl)				**1.24**	**1.18–1.30**	0.0001	**1.24**	**1.18–1.30**	0.0001
Control (no MetS)	69.9	—	4.4	1.0			1.0		
TBW	2.7	9.0	6.1	**1.38**	**1.05–1.81**		**1.33**	**1.02–1.75**	
HBW	3.2	10.8	7.1	**1.94**	**1.54–2.45**		**1.87**	**1.48–2.35**	
HTW	3.3	11.0	4.2	1.15	0.87–1.51		1.11	0.84–1.46	
HTB	1.2	4.1	9.5	**1.69**	**1.21–2.36**		**1.63**	**1.16–2.27**	
HTBW	3.4	11.4	7.5	**1.95**	**1.57–2.42**		**1.89**	**1.52–2.35**	
GBW	3.1	10.4	5.8	**1.41**	**1.13–1.77**		**1.74**	**1.40–2.14**	
GTBW	1.8	6.0	8.5	1.24	0.92–1.68		**1.59**	**1.19–2.13**	
GHBW	1.7	5.6	9.5	**1.59**	**1.19–2.12**		**1.99**	**1.51–2.63**	
GHTBW	2.3	7.8	8.8	**1.46**	**1.12–1.90**		**1.89**	**1.47–2.43**	
Other MetS clusters	7.2	24.0	6.7	0.95	0.80–1.15		**1.21**	**1.02–1.43**	

TBW,high trilycerides-high blood pressure-abdominal obesity; HBW,low HDL cholesterol-high blood pressure-abdominal obesity; HTW,low HDL cholesterol - high triglycerides - abdominal obesity; HTB,low HDL cholesterol - high triglycerides - high blood pressure; HTBW, low HDL cholesterol - high triglycerides - high blood pressure-abdominal obesity; GBW,high glucose-high blood pressure-abdominal obesity; GTBW,high glucose-high triglycerides - high blood pressure-abdominal obesity; GHBW,high glucose-low HDL cholesterol - high blood pressure-abdominal obesity; GHTBW,high glucose-low HDL cholesterol - high triglycerides - high blood pressure-abdominal obesity.

Table 4
Likelihood of extremely high intima-media thickness as compared to Control (no MetS) subjects,following adjustment for age, sex, diabetes mellitus, non-HDL cholesterol, smoking, and study site,according to specific clusters of components of ATP II [13] (left columns) or harmonized definition of MetS [14] (right columns).

	ATP III definition			Harmonized definition		
	OR	95% CI	*p<*	OR	95% CI	*p<*
Age (per 10 years of age)	**1.78**	**1.70–1.86**	0.0001	**1.78**	**1.70–1.86**	0.0001
Male sex	**1.78**	**1.61–1.98**	0.0001	**1.78**	**1.61–1.98**	0.0001
Current smoking	**1.22**	**1.13–1.30**	0.0001	**1.22**	**1.13–1.30**	0.0001
Diabetes mellitus	**2.17**	**1.80–2.61**	0.0001	**2.17**	**1.80–2.61**	0.0001
Non-HDL cholesterol (per 40 mg/dl)	**1.24**	**1.18–1.30**	0.0001	**1.24**	**1.18–1.30**	0.0001
Control (no MetS)	1.0			1.0		
TBW	**1.38**	**1.05–1.81**		**1.47**	**1.01–2.15**	
HBW	**1.94**	**1.54–2.45**		**1.99**	**1.46–2.73**	
HTW	1.15	0.87–1.51		1.29	0.91–1.83	
HTB	**1.69**	**1.21–2.36**		**2.19**	**1.46–3.29**	
HTBW	**1.95**	**1.57–2.42**		**2.39**	**1.82–3.14**	
GBW	**1.41**	**1.13–1.77**		**1.31**	**1.08–1.58**	
GTBW	1.24	0.92–1.68		1.21	0.93–1.59	
GHBW	**1.59**	**1.19–2.12**		**1.47**	**1.14–1.89**	
GHTBW	**1.46**	**1.12–1.90**		**1.31**	**1.03–1.68**	
Other MetS clusters	0.95	0.80–1.15		0.97	0.84–1.12	

Legend: as in Table 3.

components (for instance, TBW, HBW, HTBW, and GBW) that are consistently associated with extremely thick large artery (CCA IMT) across cohorts. This association is independent of age, sex, and other established CV risk factors. Thus, it is plausible that the association with greater arterial wall thickness is not exclusively driven by the number of altered MetS components, but rather by the selective combination of specific cluster of MetS components.

The MARE Consortium included several population-based studies from different countries around the world. Average CCA IMT values differed across studies (Table 2). This may be also attributable to heterogeneity in the techniques of CCA IMT acquisition and measurement (Table 1). We have aimed to avoid most of this "noise" by adopting the within-each cohort 95th percentile to define extremely thick arteries.

Our findings may have attained statistical significance by chance. Yet, the MARE Consortium included a very large population, that, together with the consistent findings that only selected clusters of MetS components are associated with older arteries, suggest that chance *per se* is unlikely a plausible explanation for the reported observations.

Another possibility is that the association of specific clusters of MetS components with arterial wall thickness is driven by a greater prevalence of diabetes mellitus in those clusters. In fact, endothelial dysfunction is observable in diabetic subjects prior to metabolic alterations [19]. Endothelial dysfunction and decreased nitric oxide bioavailability promote blood pressure increase [20], greater CCA IMT [21], and vascular complication in diabetic subjects [22].

Nonetheless, adjustment for diabetes mellitus reduced the magnitude but did not change the significance of the odds ratio of the association between the specific MetS cluster and extremely high CCA IMT.

In these regards, a major limitation of the current study design is represented by the possibility to explore pathophysiological mechanisms that may support the findings with a biological interpretation.

However, our study confirms that MetS can no longer be regarded as a unique syndrome, impacting equally on large arteries, and, thus, on a greater CV risk [2–5,17,18]. Additional research is needed to characterize pathophysiological cascades linking specific cluster of components of currently defined MetS to older artery.

In conclusion, the consistent association of specific clusters of MetS components with extremely high intima-media thickness (older large arteries) cross-culturally suggests that identification of those clusters in clinical practice may facilitate identification of subjects at greater CV risk and thus, a potential for cost-effective prevention of major CV events.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at 10. 1016/j.atherosclerosis.2016.10.032.

References

[1] P. Pignoli, E. Tremoli, A. Poli, P. Oreste, R. Paoletti, Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging, Circulation 74 (1986) 1399—1406.

[2] A. Scuteri, C.H. Chen, F.C.P. Yin, T.T. Chih, H.A. Spurgeon, E.G. Lakatta, Functional correlates of central arterial geometric phenotypes, Hypertension 38 (2001) 1471—1475.

[3] D.H. O'Leary, J.F. Polak, R.A. Kronmal, T.A. Manolio, G.L. Burke, S.K. Wolfson Jr., Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group, N. Engl. J. Med. 340 (1999) 14—22.

[4] L.E. Chambless, A.R. Folsom, L.X. Clegg, A.R. Sharrett, E. Shahar, F.J. Nieto, et al., Carotid wall thickness is predictive of incident clinicalstroke: the Atherosclerosis Risk in Communities (ARIC) study, Am. J. Epidemiol. 151 (2000) 478—487.

[5] A. Iglesias del Sol, M.L. Bots, D.E. Grobbee, A. Hofman, J.C.M. Witteman, Carotid intima-media thickness at different sites: relation to incident myocardial infarction; the Rotterdam Study, Eur. Heart J. 23 (2002) 934—940.

[6] S.S. Najjar, A. Scuteri, E.G. Lakatta, Arterial aging: is it an immutable cardiovascular risk factor? Hypertension 46 (2005) 454—462.

[7] A. Scuteri, S.S. Najjar, M. Orru', G. Usala, M.G. Piras, L. Ferrucci, A. Cao, D. Schlessinger, M. Uda, E.G. Lakatta, The central arterial burden of the metabolic syndrome is similar in men and women: the SardiNIA Study, Eur. Heart J. 31 (2010) 602—613.

[8] J.H. Stein, C.E. Korcarz, R.T. Hurst, E. Lonn, C.B. Kendall, E.R. Mohler, et al., Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine, J. Am. Soc. Echocardiogr. 21 (2008) 93—111.

[9] ESH/ESC Task Force for the Management of Arterial Hypertension, 2013 practice guidelines for the management of arterial hypertension of the european society of hypertension (ESH) and the european society of cardiology (ESC): ESH/ESC task force for the management of arterial hypertension, J. Hypertens. 31 (2013) 1925—1938.

[10] P.M. Nilsson, P. Boutouyrie, P. Cunha, V. Kotsis, K. Narkiewicz, G. Parati, et al., Early vascular ageing in translation: from laboratory investigations to clinical applications in cardiovascular prevention, J. Hypertens. 31 (2013) 1517—1526.

[11] A. Scuteri, C.H. Morrell, M. Orrù, J.B. Strait, K.B. Tarasov, L.A. Ferreli, F. Loi, M.G. Pilia, A. Delitala, H. Spurgeon, S.S. Najjar, M. AlGhatrif, E.G. Lakatta, Longitudinal perspective on the conundrum of central arterial stiffness, blood pressure, and aging, Hypertension 64 (2014) 1219—1227.

[12] A. Scuteri, S. Laurent, S. Cucca, J. Cockcroft, P.G. Cunha, L. Rodriguez Manas, F.U. Mattace Raso, M.L. Muiesan, L. Ryliškyte, E. Rietzschel, J. Strait, C. Vlachopoulos, H. Voelzke, E.G. Lakatta, P.M. Nilsson, for the Metabolic Syndrome and Arteries Research (MARE) Consortium, Metabolic syndrome across Europe: different clusters of risk factors, Eur. J. Prev. Cardiol. (2014), http://dx.doi.org/10.1177/2047487314525529.

[13] 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).Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults, JAMA 285 (2001) 2486—2497.

[14] K.G. Alberti, R.H. Eckel, S.M. Grundy, P.Z. Zimmet, J.I. Cleeman, et al., International diabetes federation task force on epidemiology and prevention; national Heart, lung, and blood Institute; american Heart association; world Heart federation; international atherosclerosis society; international association for the study of obesity. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national Heart, lung, and blood Institute; american Heart association; world Heart federation; international atherosclerosis society; and international association for the study of obesity, Circulation 120 (2009) 1640—1645.

[15] R. Kahn, Metabolic syndrome—what is the clinical usefulness? Lancet 371 (2008) 1892—1893.

[16] R. Kahn, J. Buse, E. Ferranini, M. Stern, The metabolic syndrome: time for a critical appraisal, Diabetes Care 28 (2005) 2289—2304.

[17] A. Scuteri, P.G. Cunha, E. Agabiti Rosei, J. Badariere, S. Bekaert, J.R. Cockcroft, J. Cotter, F. Cucca, M.L. De Buyzere, T. De Meyer, L. Ferrucci, O. Francom, N. Gale, T.H. Gillebert, A. Hofman, M. Langlois, A. Laucevicius, S. Laurent, F.U.S. Mattace Raso, C.H. Morrell, M.L. Muiesan, M.M. Munnery, R. Navickas, P. Oliveira, M. Orru', M.G. Pilia, E.R. Rietzschel, L. Ryliskyte, M. Salvetti, D. Schlessinger, N. Sousa, C. Stefanadis, J. Strait, C. Van daele, I. Villa, C. Vlachopoulos, J. Wittemanm, P. Xaplanteris, P.M. Nilsson, E.G. Lakatta, for the MARE Consortium, Arterial stiffness and influences of the metabolic syndrome: a cross-countries study, Atherosclerosis 233 (2014) 654—660.

[18] O.H. Franco, J.M. Massaro, J. Civil, M.R. Cobain, B. O'Malley, R. D'Agostino, Trajectoreis of entering the metabolic syndrome. The Framingham Heart study, Circulation 120 (2009) 1943—1950.

[19] A. Scuteri, M. Tesauro, S. Rizza, M. Iantorno, M. Federici, D. Lauro, U. Campia, M. Turriziani, A. Fusco, G. Cocciolillo, R. Lauro, Endothelial dysfunction and arterial stiffness in normotensive normoglycemic first degree relatives of diabetic patients are independent of the metabolic syndrome, Nutr. Metab. Cardiovasc Dis. 18 (2008) 349—356.

[20] A. Scuteri, M.C. Stuehlinger, J.P. Cooke, J.G. Wright, E.G. Lakatta, D.E. Anderson, J.L. Fleg, Nitric oxide inhibition as a mechanism for blood pressure increase during salt loading in normotensive postmenopausal women, J. Hypertens. 21 (2003) 1339—1346.

[21] T. Ganz, J. Wainstein, S. Gilad, R. Limor, M. Boaz, N. Stern, Serum ADMA and arginine levels predict micro- and macrovascular complications in type 2 diabetes mellitus, Diabetes Metab. Res. Rev. (2016 Jul 8), http://dx.doi.org/10.1002/dmrr. 2836 ([Epub ahead of print]).

[22] K. Furuki, H. Adachi, H. Matsuoka, M. Enomoto, A. Satoh, A. Hino, Y. Hirai, T. lmaizumi, Plasma levels of asymmetric dimethylarginine (ADMA) are Relat. to intima-media thickness of the carotid artery an epidemiological study, Atherosclerosis 191 (2007) 206—210. Epub 2006 May 2.