Dall’ anziano all’ invecchiamento: il modello dell’ invecchiamento vascolare

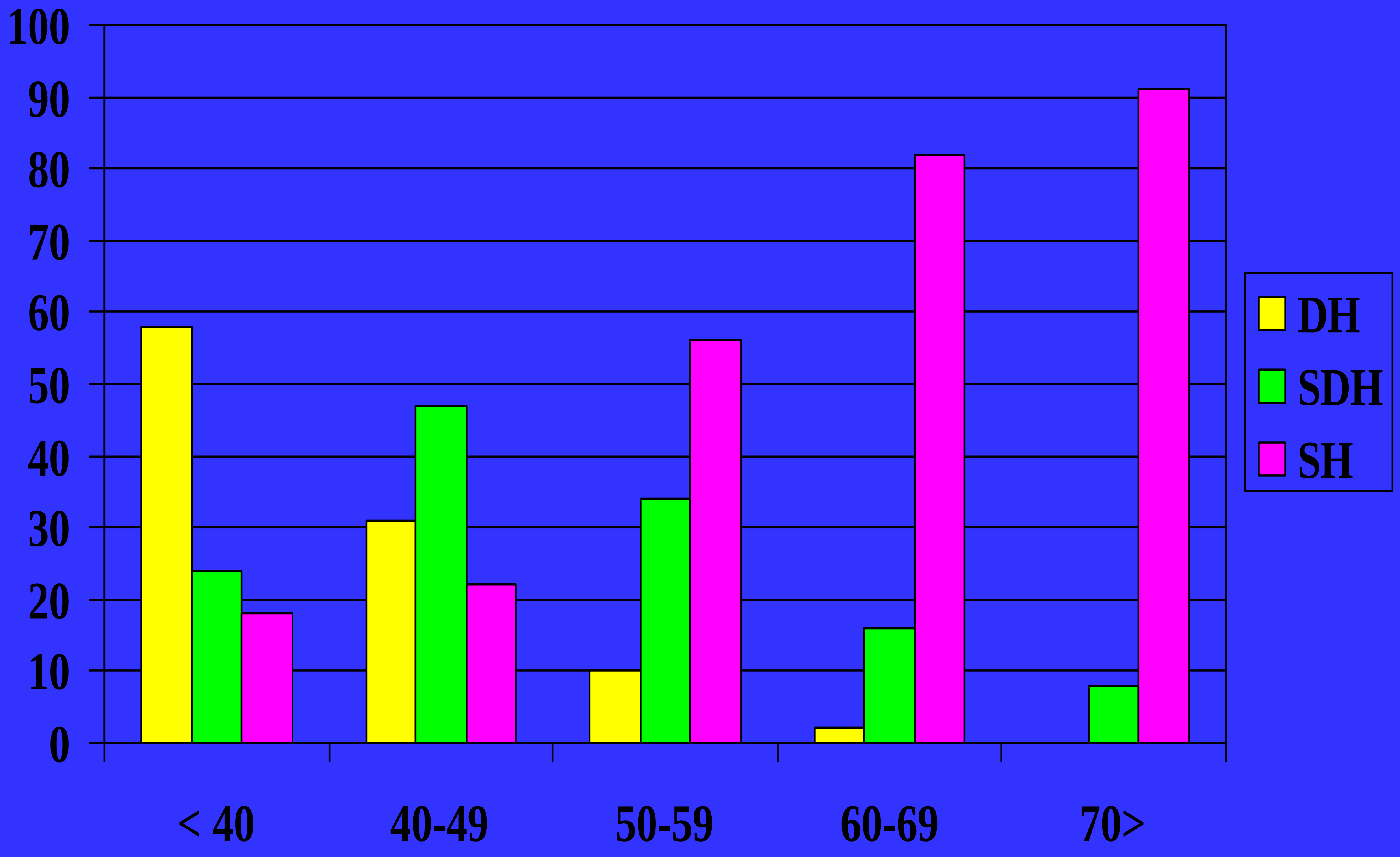
Angelo Scuteri

Professor of Medicine

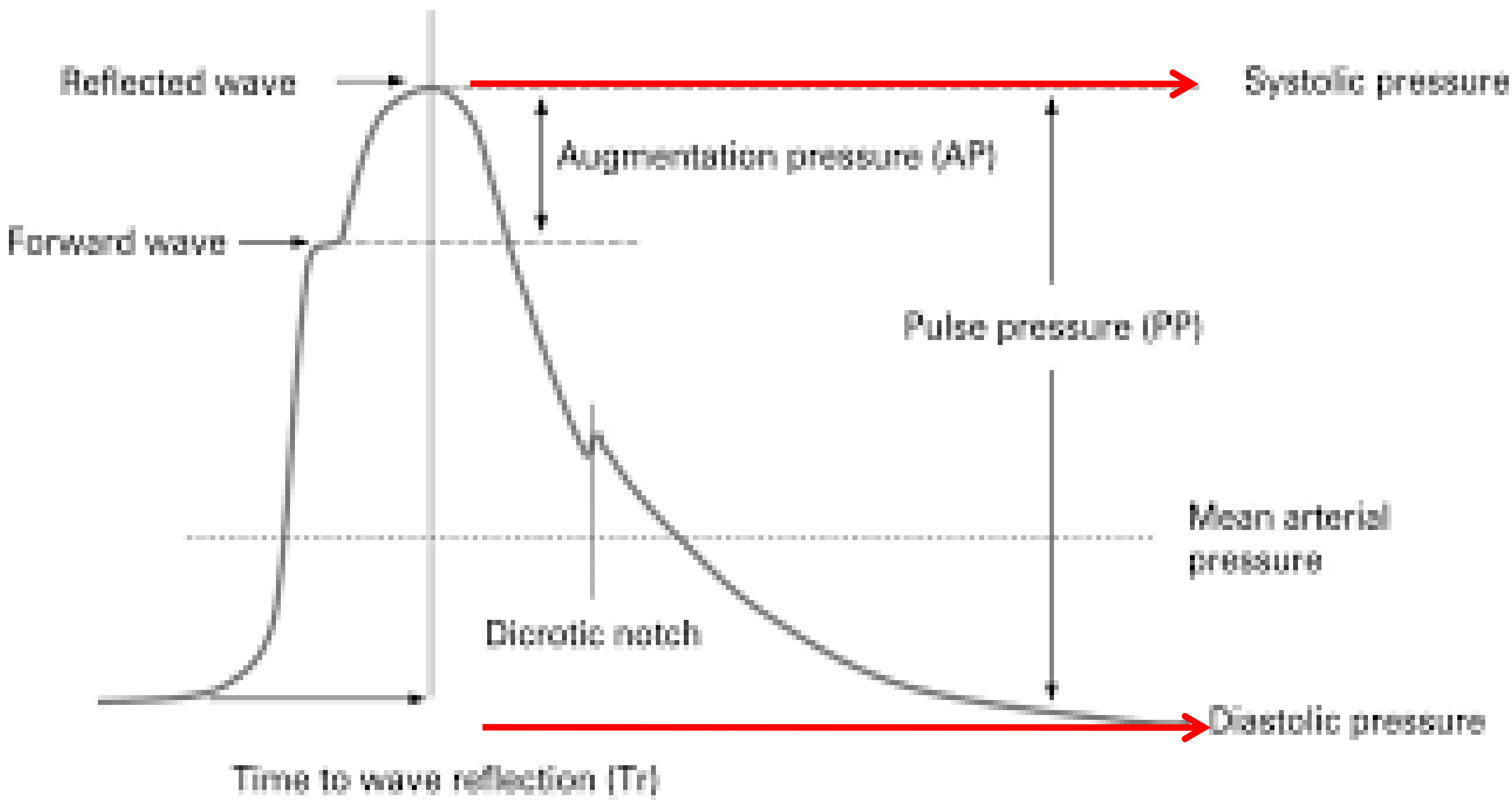
Director Post-Graduate Medical School of Geriatrics

University of Sassari -Sassari (Italy)

SardiNIA Study

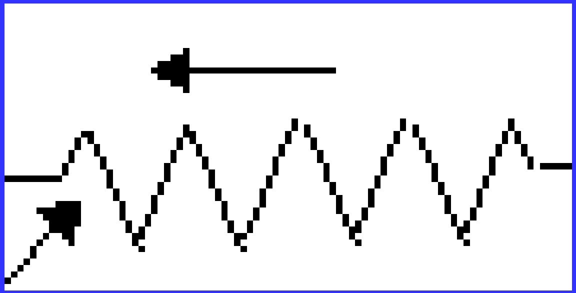


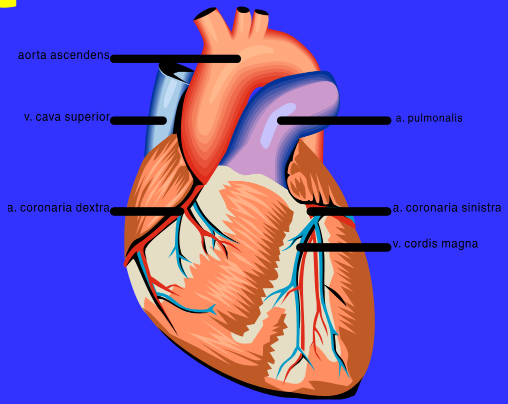
Scipione Riva Rocci
e lo sfigmomanometro di sua invenzione

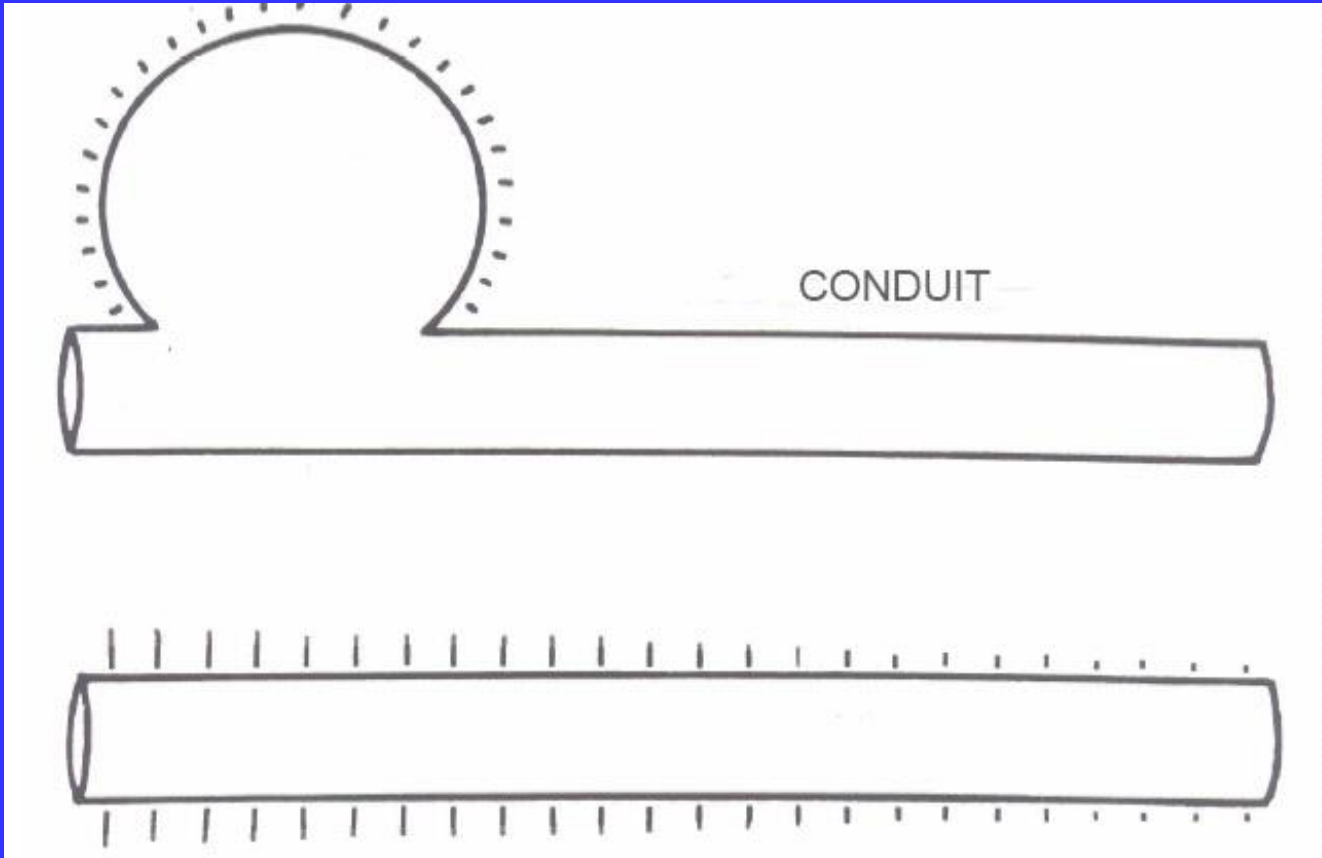


Reflected wave
Systolic pressure
Augmentation pressure (AP)
Forward wave
Pulse pressure (PP)
Mean arterial
pressure
Dicrotic notch
Diastolic pressure
Time to wave reflection (Tr)

$\Delta P = -R*Q$




aorta ascendens
v. cava superior
a. pulmonalis
a. coronaria dextra
a. coronaria sinistra
v. cordis magna


CONDUIT

SOLIDUM PETIT IN PROFUNDIS · UNIVERSITAS ARHUSIENSIS ·

FLVCTVAT NEC MERGITVR

NATIONAL INSTITUTES OF HEALTH

Consiglio
Nazionale delle
Ricerche

Arterial Aging
Is It an Immutable Cardiovascular Risk Factor?

Samer S. Najjar, Angelo Scuteri, Edward G. Lakatta

Hypertension. 2005;46:454-462.

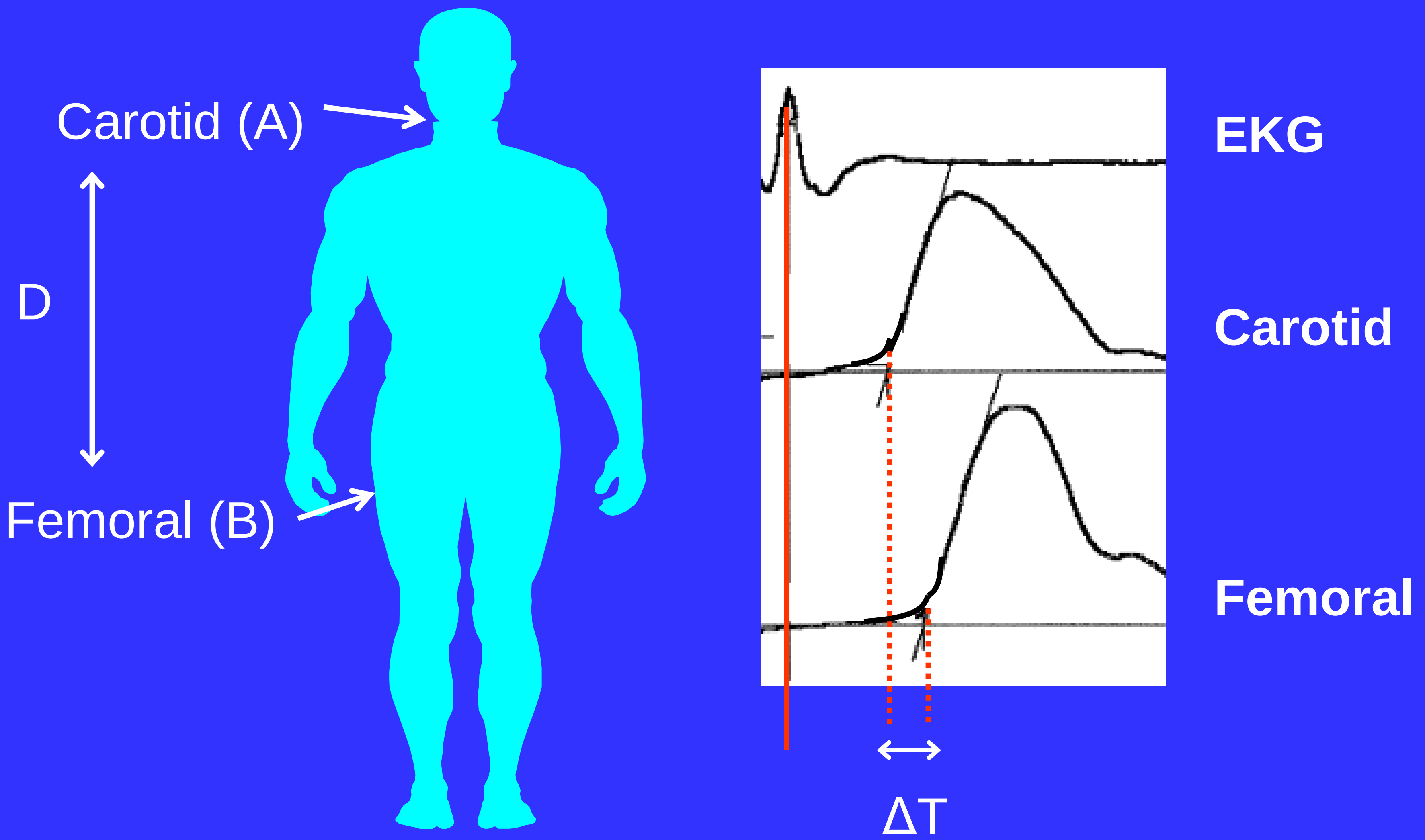
Con l’ invecchiamento le grandi arterie

si dilatano

si ispessiscono

si irrigidiscono

Assessment of PWV



PWV = D/ ΔT

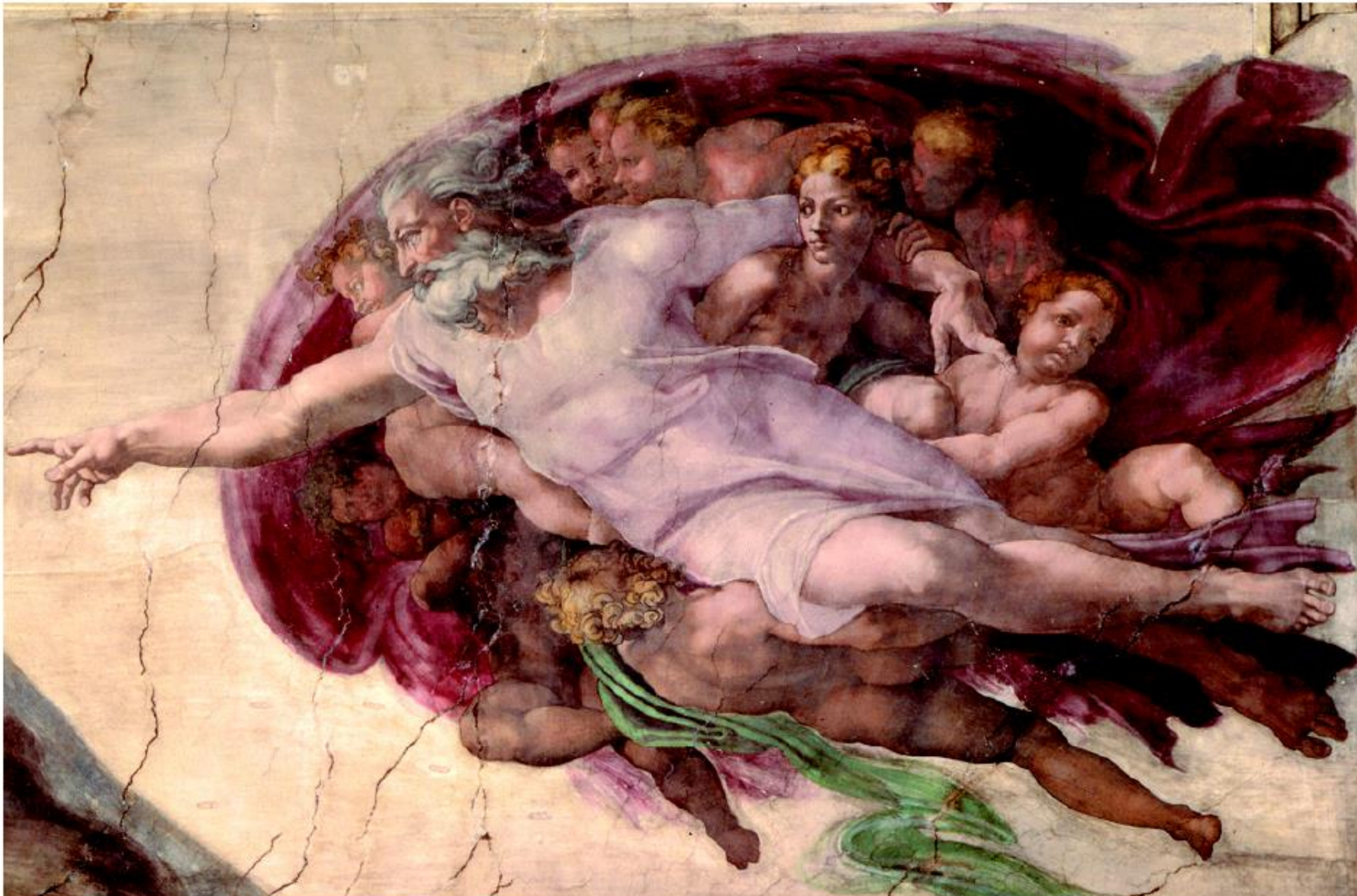
Arterial aging is risky

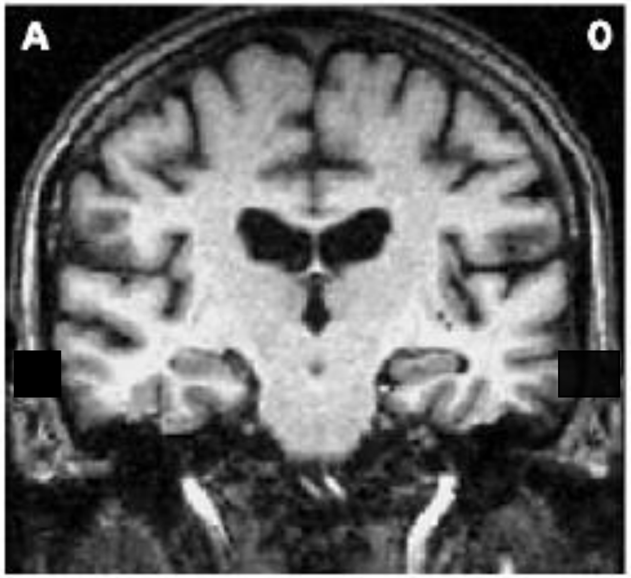
Table 1	Pooled Adjusted Hazard Ratios (95% CIs) of a 1-SD Increase in Log_e-Transformed aPWV for All-Cause Mortality, CVD Mortality, CHD Events, Stroke Events, and CVD Events		
	Model 1*	Model 2*	Model 3*
CHD events (n = 1,195)	1.35 (1.22–1.50)	1.32 (1.18–1.48)	1.23 (1.11–1.35)
CVD events (n = 1,785)	1.45 (1.30–1.61)	1.37 (1.23–1.52)	1.30 (1.18–1.43)
Stroke events (n = 641)	1.54 (1.34–1.78)	1.37 (1.21–1.54)	1.28 (1.16–1.42)
CVD mortality (n = 395)	1.41 (1.27–1.56)	1.35 (1.20–1.53)	1.28 (1.15–1.43)
All-cause mortality (n = 2,041)	1.22 (1.16–1.27)	1.20 (1.15–1.26)	1.17 (1.11–1.22)

*Model 1 adjusts for sex and age group; model 2 adjusts for sex, age group, and systolic blood pressure; and model 3 additionally adjusts for other risk factors (cholesterol, high-density lipoprotein cholesterol, smoking status, presence of diabetes, and antihypertensive medication), stratified by race in the Sutton-Tyrell study (27). Not all studies had data on every risk factor.

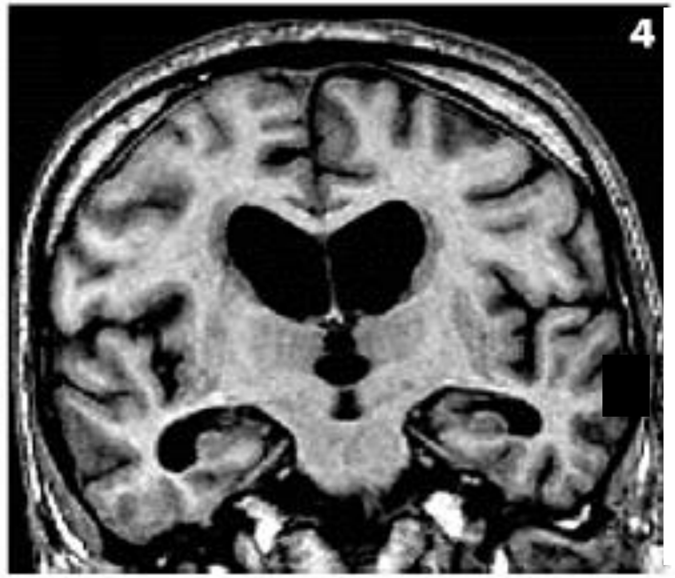
aPWV = aortic pulse wave velocity; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease.

Ben-Sholmo Y JACC 2014; 63: 636-646

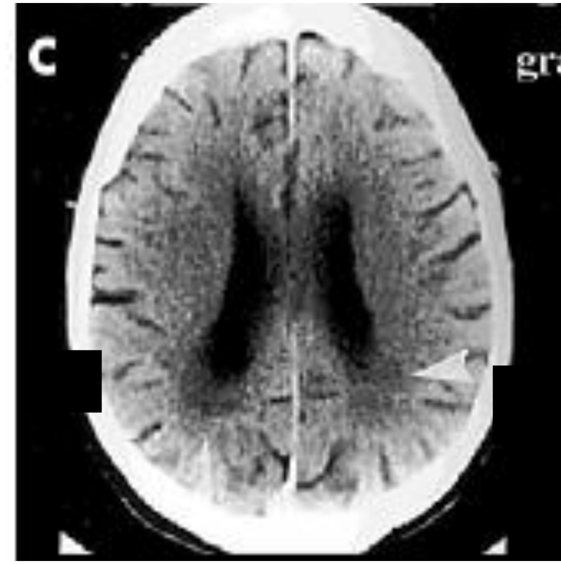




normal

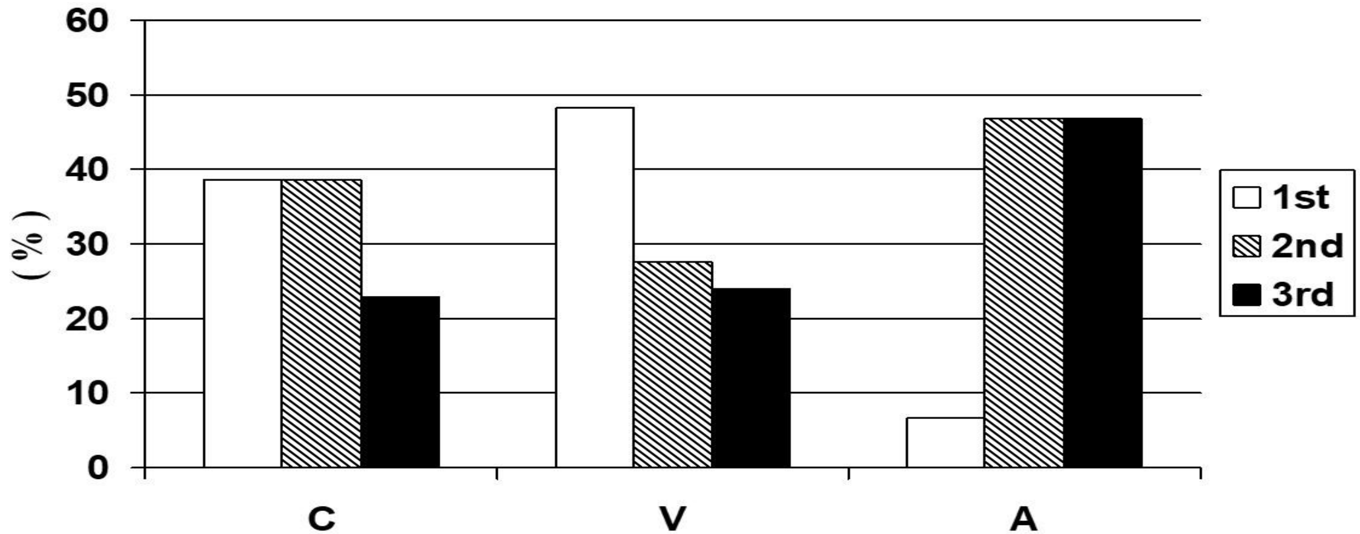


atrophy萎缩



microvascular lesion

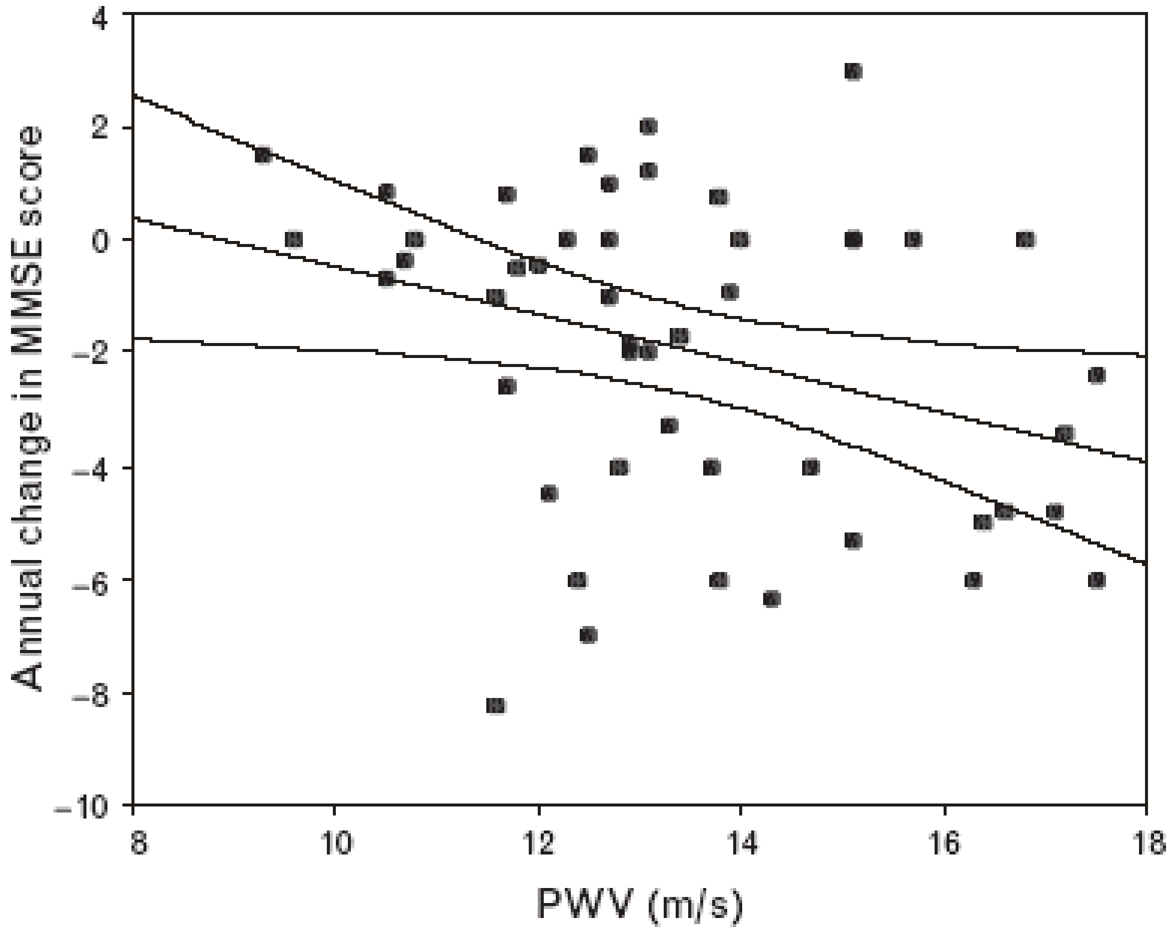
PWV tertiles distribution
According to brain CT lesions



Scuteri A et al. J Hypertens 2005

Arterial stiffness as an independent predictor of longitudinal changes in cognitive function in the older individual

Angelo Scuteri[a], Manfredi Tesauro[b], Sergio Appolloni[a], Francesca Preziosi[a],
Anna Maria Brancati[a] and Massimo Volpe[c,d]



Determinants of dementia (MMSE <21/ 30) in 400 subjects (70% women) with mean age 79 years (range 65-95)

	OR	95% CI	*P*-value
Age	1.06	1.01–1.11	0.03
Female sex	1.10	0.58–2.07	0.42
MBP	0.99	0.96–1.02	0.39
Antihypertensive drugs	0.84	0.43–1.62	0.42
LVMI			
1st quartile	1.00	Reference	0.01
2nd quartile	1.75	0.76–4.29	
3rd quartile	1.77	0.76–3.87	
4th quartile	2.72	1.20–6.12	

Scuteri A et al. Eur Heart J 2009

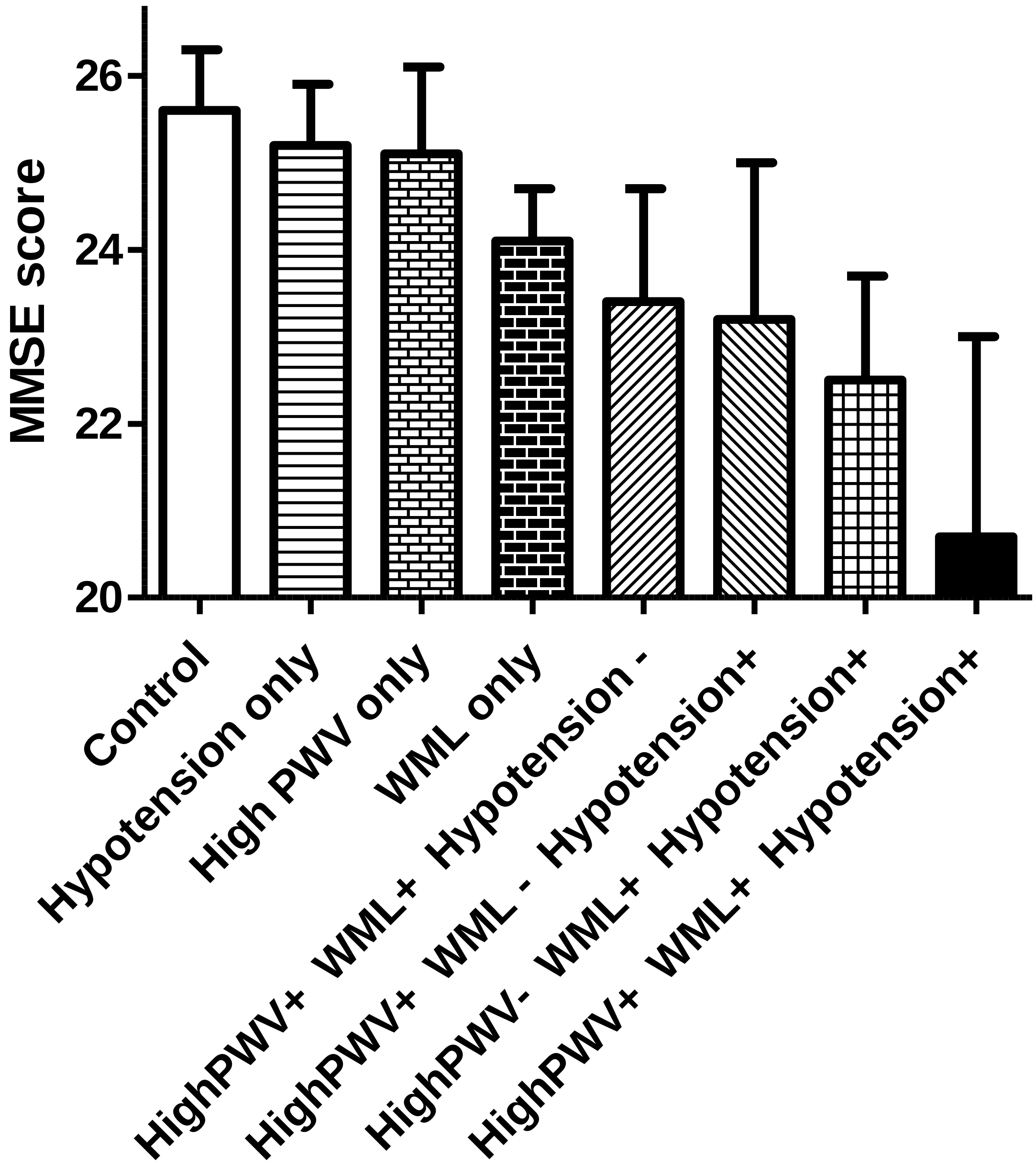
Microvascular brain damage with aging and hypertension: pathophysiological consideration and clinical implications

Angelo Scuteri[a], Peter M. Nilsson[b], Christopher Tzourio[c], Josep Redon[d] and Stephane Laurent[e]

J Hypertens 2011; 29: May

	All (n= 588)	Men (n=185)	Women (n=403)
24h hypotension (%)	50.3	45.9	52.4
Dirunal hypotension (%)	39.8	32.4	43.2 **
Nocturnal hypotension (%)	31.3	30.3	31.8
≥10% registrations with SBP <100 mmHg during 24h (%)	19.2	15.3	20.9

Scuteri A J Gerontol 2012



Scuteri A Int J Cardiol 2013

BRAIN

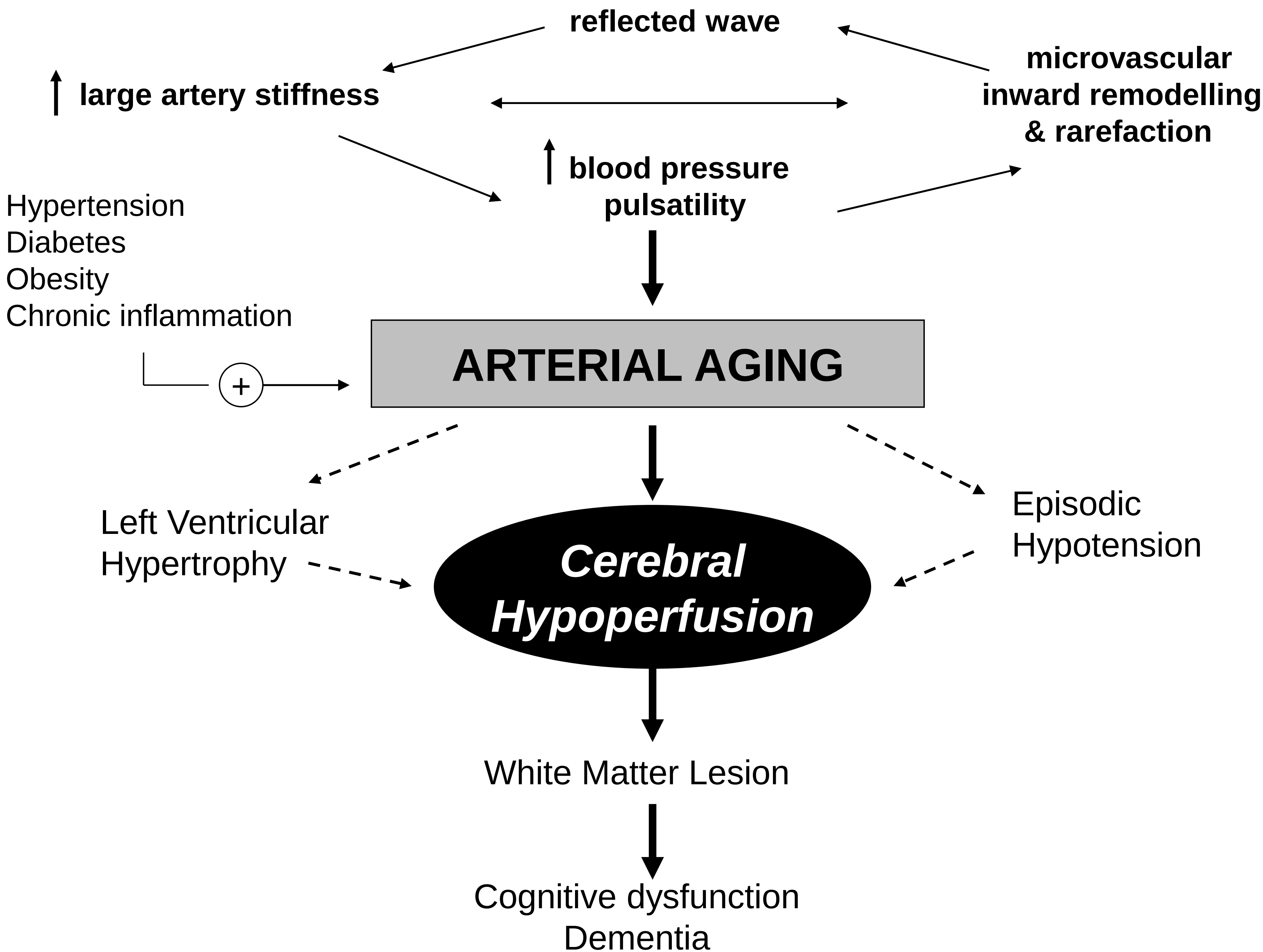
- 2% of body weight
- 20% of body O2 consumption
- 25% of body total glucose utilization

Yet…

It lacks energy reserves

Its normal function depends upon perfusion

that provides optimal nutrient delivery.


reflected wave
↑ large artery stiffness
microvascular inward remodelling & rarefaction
↑ blood pressure pulsatility
Hypertension
Diabetes
Obesity
Chronic inflammation
+
ARTERIAL AGING
Left Ventricular Hypertrophy
Episodic Hypotension
Cerebral Hypoperfusion
White Matter Lesion
Cognitive dysfunction
Dementia

AHA/ASA Scientific Statement

Vascular Contributions to Cognitive Impairment and Dementia

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

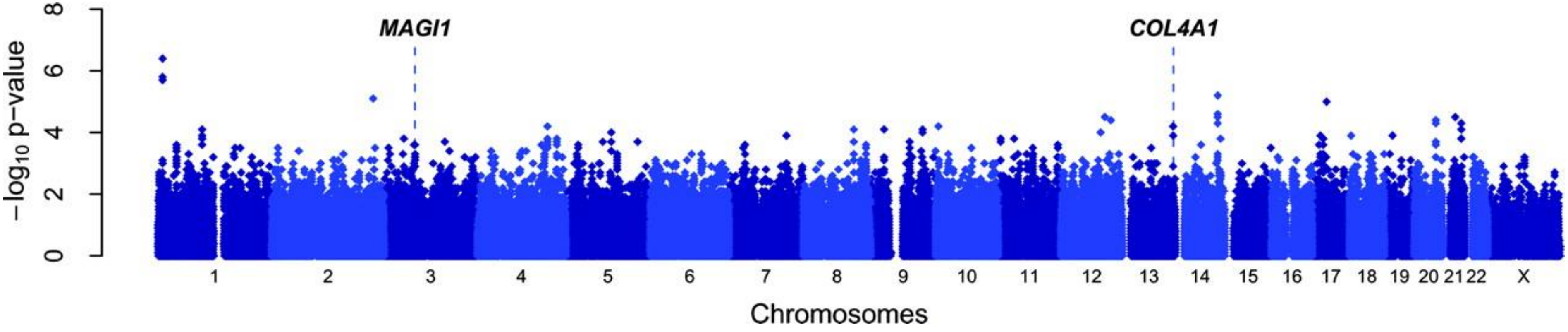
The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

The Alzheimer's Association participated in the development of this statement to advance knowledge and understanding of the causes of dementia and the factors that contribute to its progression.

Philip B. Gorelick, MD, MPH, FAHA, Co-Chair; Angelo Scuteri, MD, PhD, Co-Chair; Sandra E. Black, MD, FRCPC, FAHA*; Charles DeCarli, MD*; Steven M. Greenberg, MD, PhD, FAHA*; Costantino Iadecola, MD, FAHA*; Lenore J. Launer, MD*; Stephane Laurent, MD*; Oscar L. Lopez, MD*; David Nyenhuis, PhD, ABPP-Cn*; Ronald C. Petersen, MD, PhD*; Julie A. Schneider, MD, MS*; Christophe Tzourio, MD, PhD*; Donna K. Arnett, PhD, MSPH, FAHA; David A. Bennett, MD; Helena C. Chui, MD, FAHA; Randall T. Higashida, MD, FAHA; Ruth Lindquist, PhD, RN, ACNS-BC, FAHA; Peter M. Nilsson, MD, PhD; Gustavo C. Roman, MD; Frank W. Sellke, MD, FAHA; Sudha Seshadri, MD; on behalf of the American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia

…altre piccole soddisfazioni

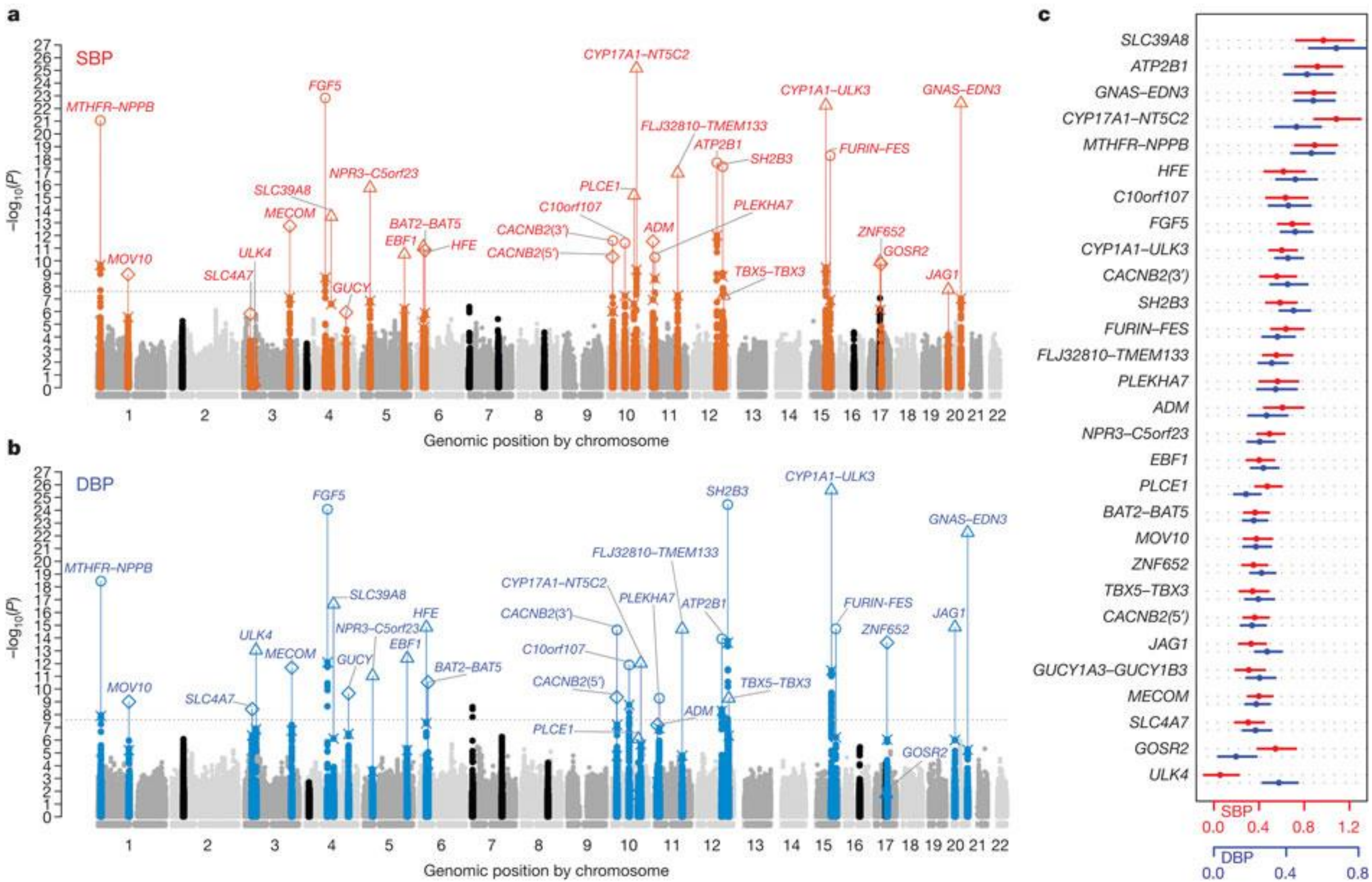
Summary of GWAS for PWV in the SardiNIA study cohort.



Tarasov K V et al. Circ Cardiovasc Genet 2009;2:151-158

Genome-wide $-\log_{10}$ *P*-value plots and effects for significant loci.

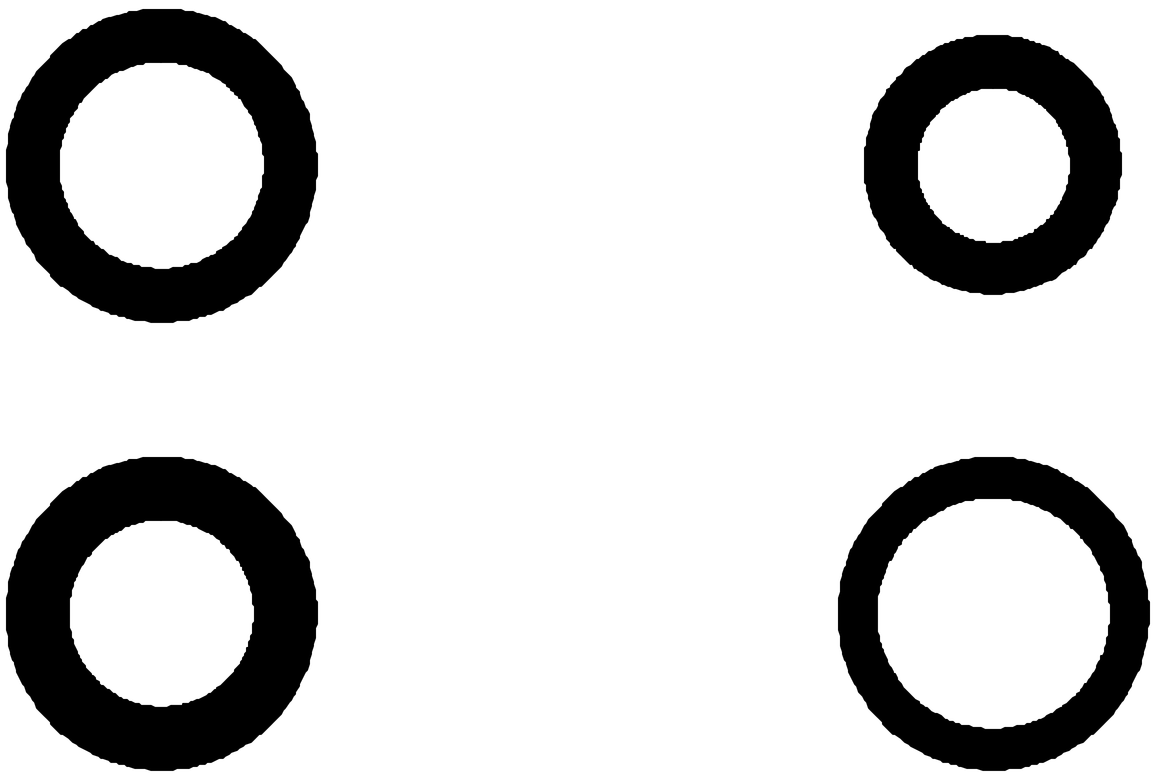
multi-stage design in 200,000 individuals of European descent



nature

Carotid Geometric Phenotype (CGP)

top:
left, normal (CGP1); right, concentric remodelling (CGP2)
bottom:
left, concentric hypertrophy (CGP3); right, hypertrophy with dilation (CGP4)

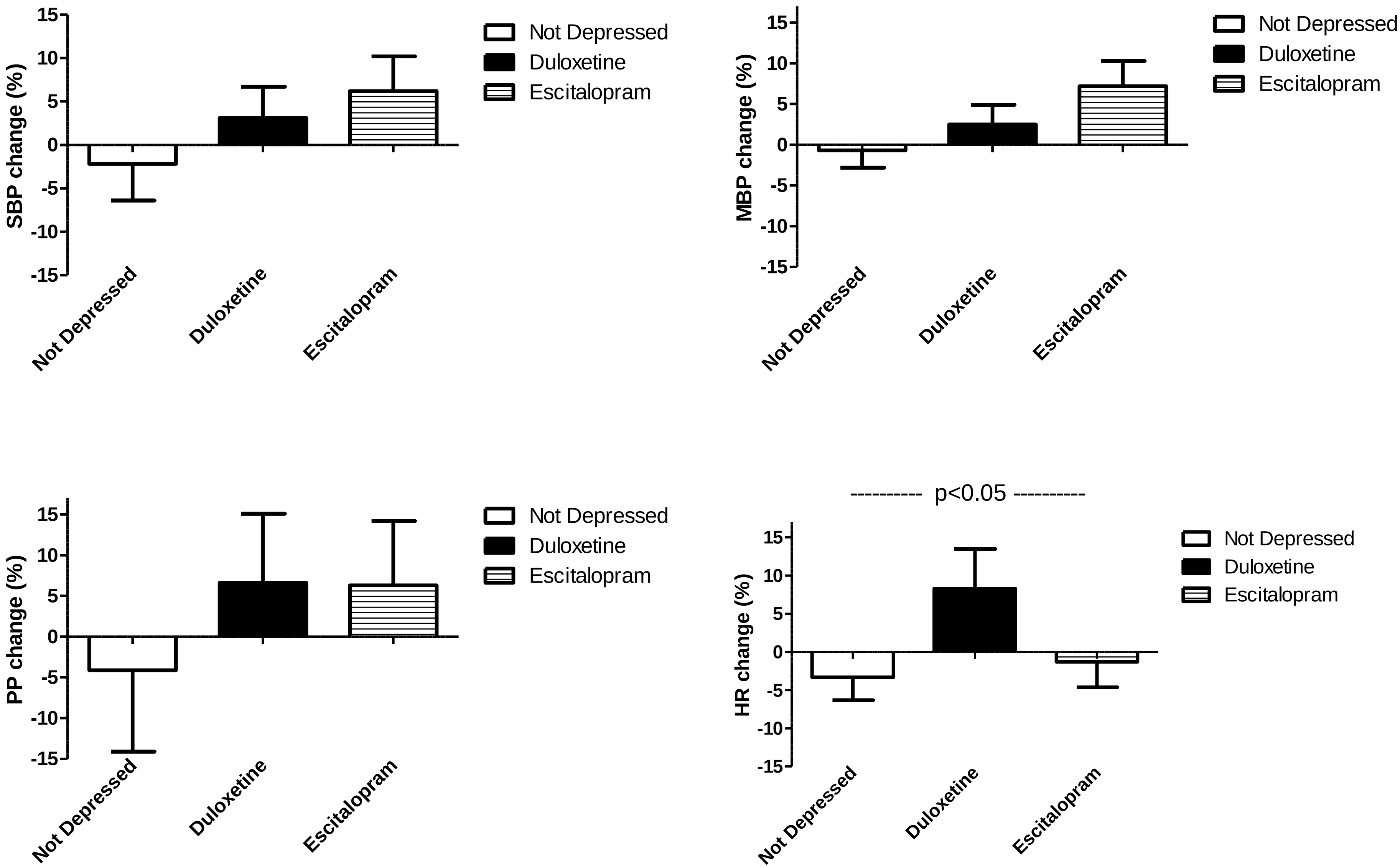


	CGP1 (83.4%)	CGP2 (5.5%)	CGP3 (2.2%)	CGP4 (8.9%)
Age (yrs)	52 ± 13	62 ± 9*	54 ± 15	55 ± 11
SBP (mmHg)	134 ± 23	133 ± 23	142 ± 24	156 ± 26*
DBP (mmHg)	84 ± 13	79 ± 11	84 ± 13	95 ± 16*
CCA D (mm)	6.4 ± 0.7	5.5 ± 0.5*	6.1 ± 0.6	7.4 ± 0.9*
CCA IMT (mm)	0.96 ± 0.20	1.35 ± 0.16*	1.77 ± 0.35*	1.37 ±0.17*
CCA W/L	0.30 ± 0.07	0.51 ± 0.07*	0.58 ± 0.13*	0.38± 0.06*
CCA VM	11.1 ± 2.7	13.6 ± 2.3*	20.7 ± 5.3*	18.4 ± 3.2*
CCA stress (mmHg)	30.4± 8.4	49.2 ± 7.1*	60.0 ± 14.3*	43.4 ± 9.3*
CCA Dist (µm/ mmHg/mm)	110 ± 65	151 ± 125*	156 ± 97*	86 ± 58*
CCA AGI (%)	19.1 ± 23.8	19.3 ± 24.3	23.7 ± 22.3	33.7± 24.3*
PWV (cm/sec)	979 ± 220	981 ± 278	1135 ± 428*	1076± 282*

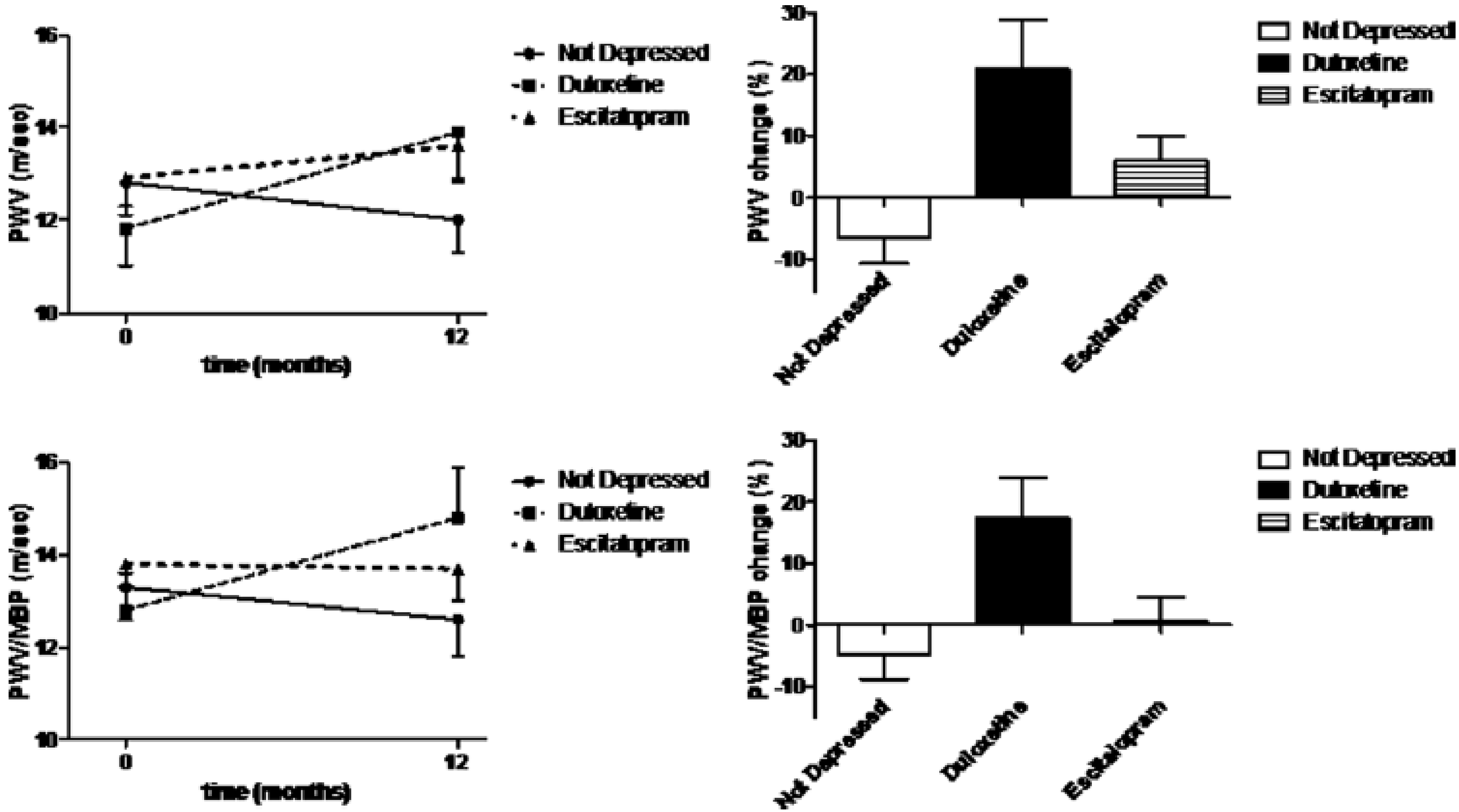
* p< 0.05 vs CGP1

Scuteri A et al Hypertension 2001

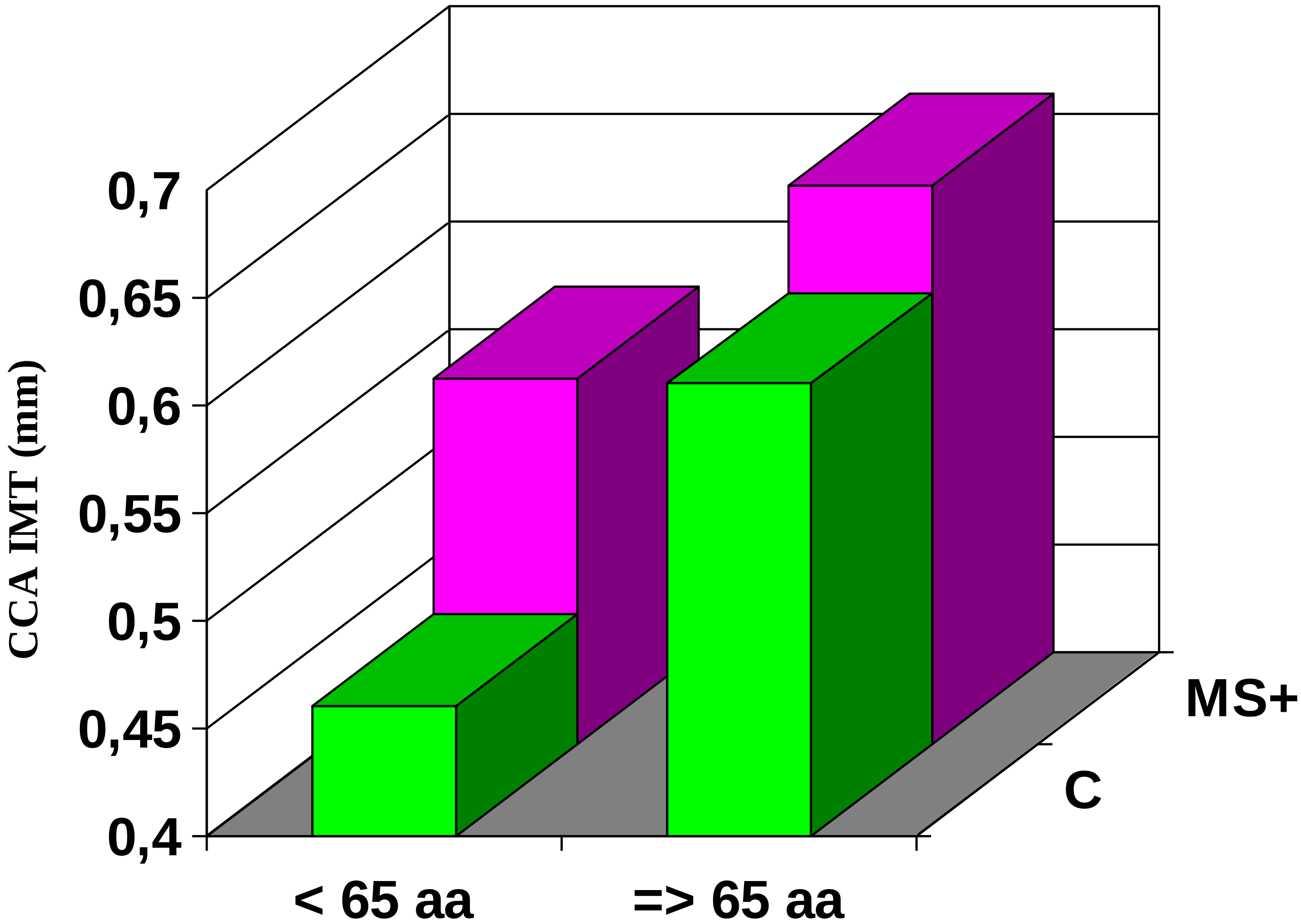
Can we slow down arterial aging?



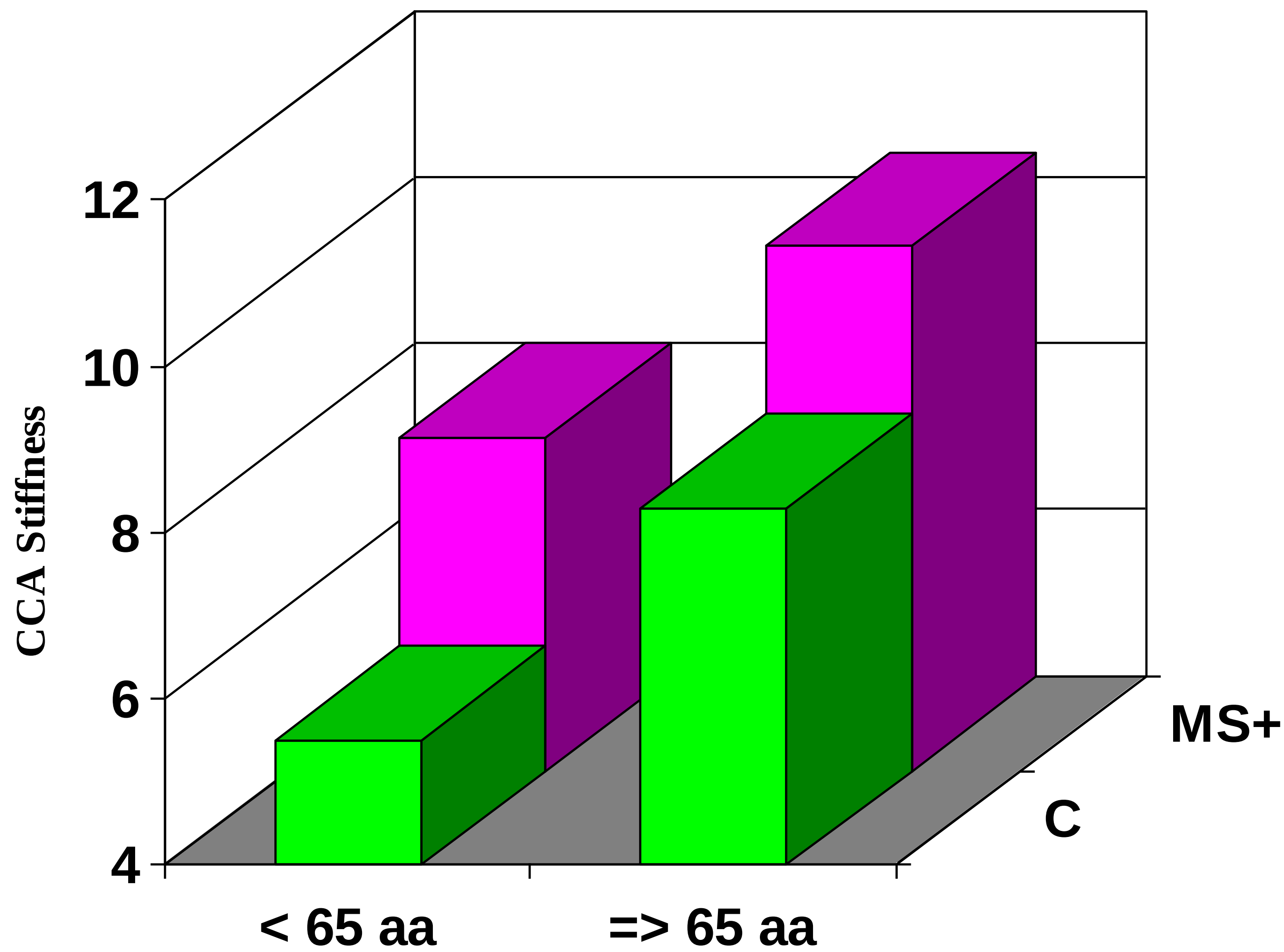
Scuteri A et al. J Gerontol 2012



Scuteri A et al. J Gerontol 2012



Scuteri A et al. JACC 2004



Scuteri A et al. JACC 2004

Dall’ anziano
all’ invecchiamento:

Aging is …

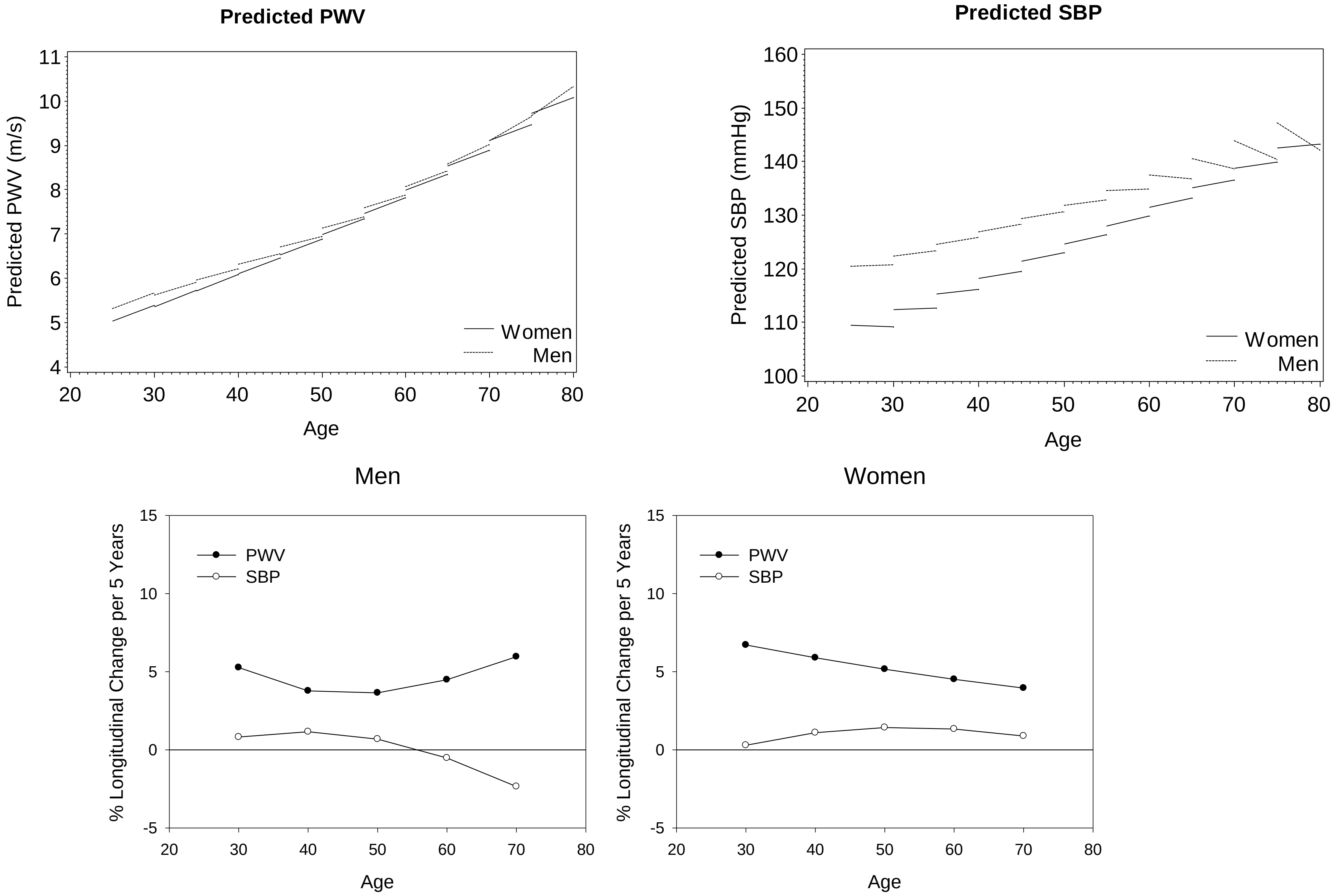
- *a process*
- *dynamic*
- *heterogenous*
- *systemic*
- (partially) *adaptive*

Aging is …

- ***a process***
- ***dynamic***
- ***heterogenous***
- ***systemic***
- **(partially) *adaptive***

Longitudinal changes in PWV and SBP at various ages

Scuteri A et al Hypertension 2014



Aging is …

- *a process*
- *dynamic*
- *heterogenous*
- *systemic*
- (partially) *adaptive*

Metabolic Syndrome NCEP- ATP III

GLUCOSE (G)

Fasting plasma glucose ≥ 110 mg/dl

HDL-CHOLESTEROL (H)

HDL-Chol < 40 mg/dl (M), < 50 mg/dl (F)

TRIGLYCERIDES (T)

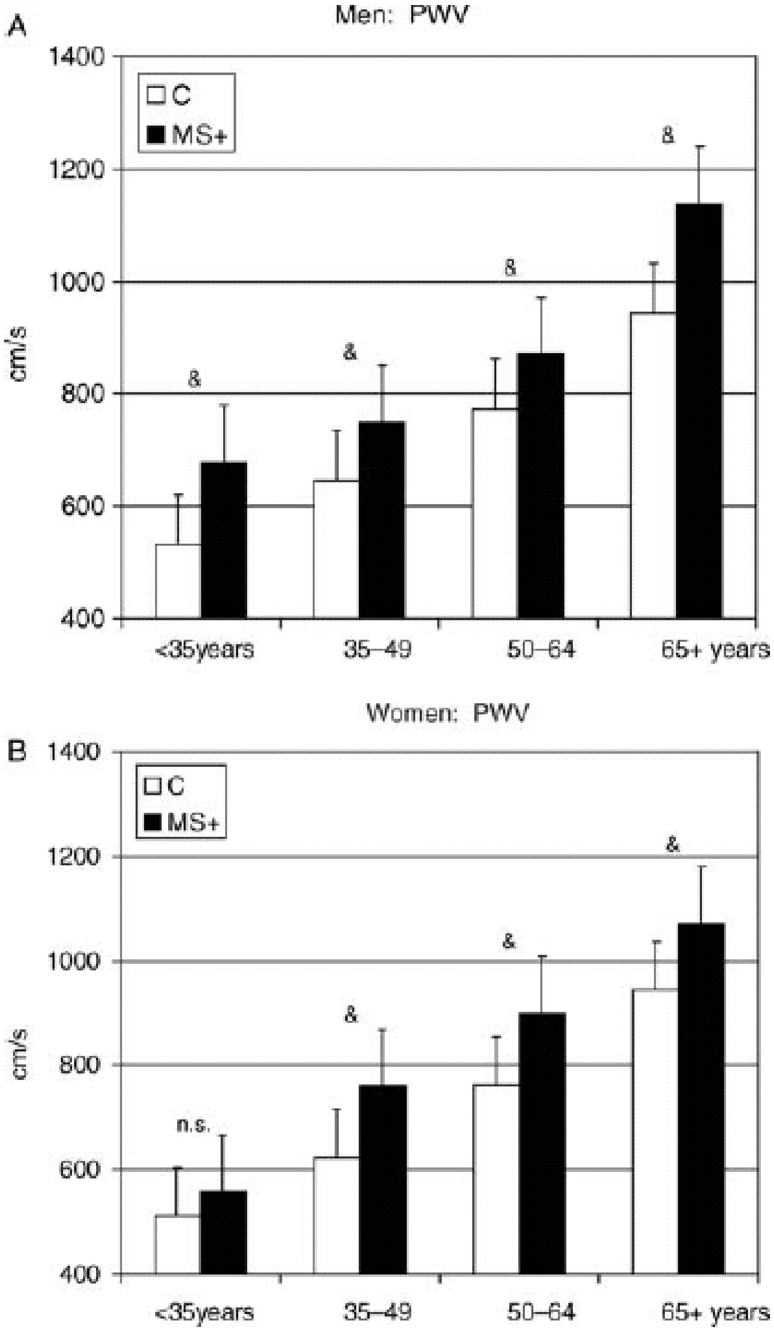
Triglycerides ≥ 150 mg/dl

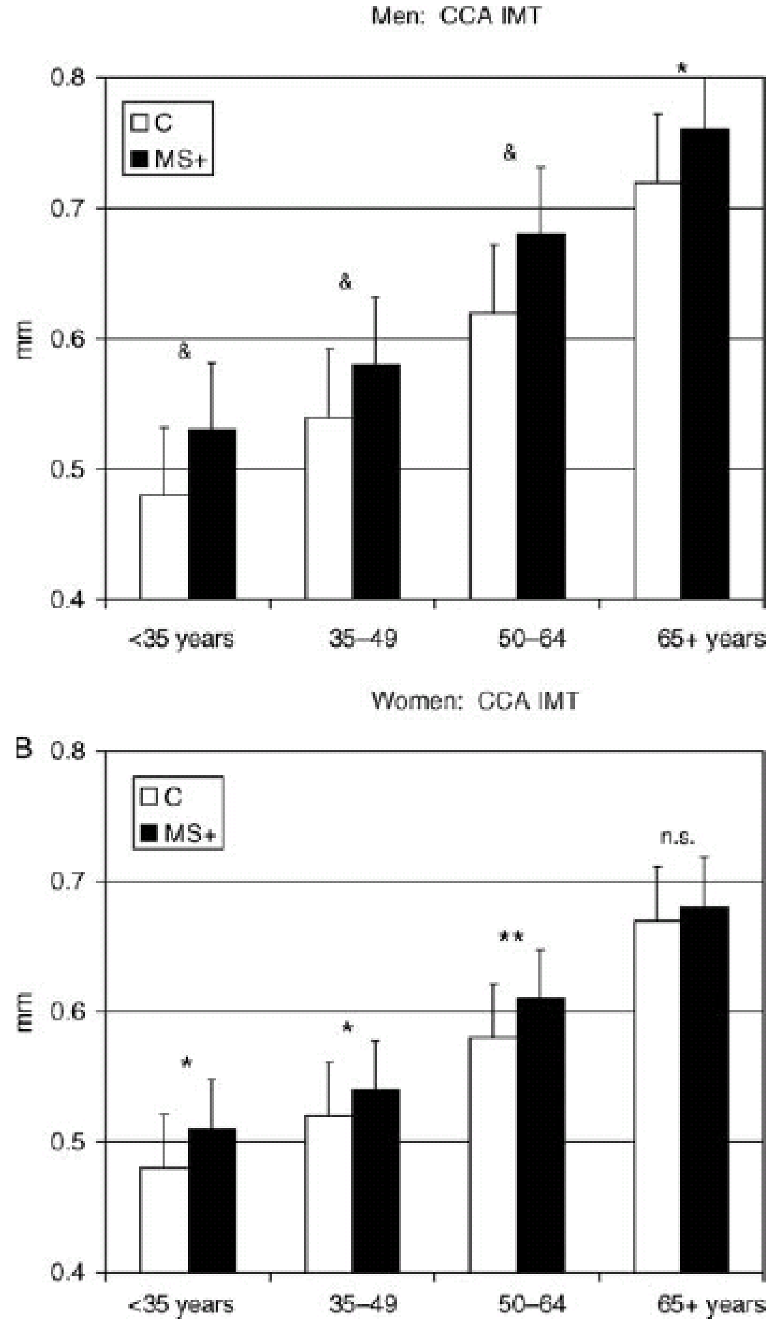
BLOOD PRESSURE (B)

SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg

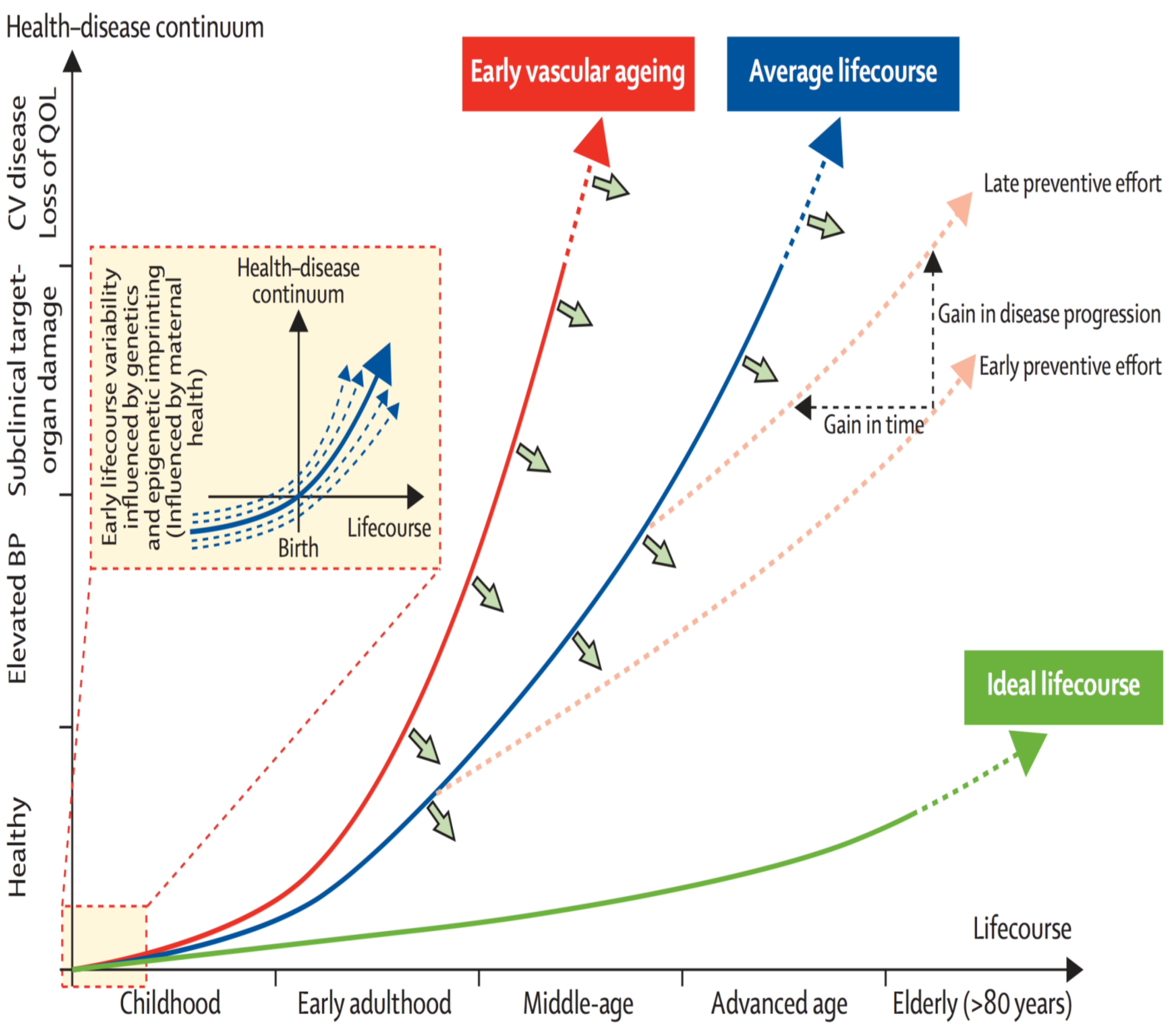
ABDOMINAL OBESITY (W)

Waist circumference > 102 cm (M), > 88 cm (F)


A
Men: PWV
1400
1200
1000
800
600
400
cm/s
C
MS+
&
<35years
35–49
50–64
65+ years
B
Women: PWV
n.s.

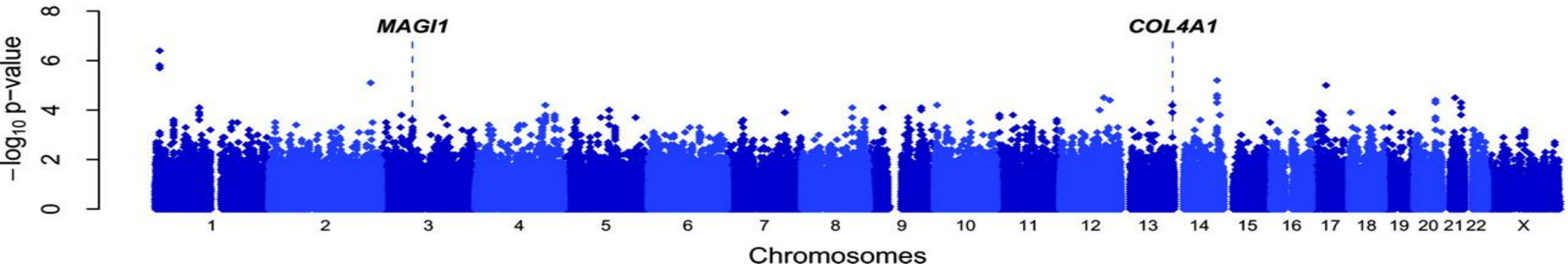

Men: CCA IMT
0.8
0.7
0.6
0.5
0.4
mm
C
MS+
&
*
<35 years
35–49
50–64
65+ years
B
Women: CCA IMT
**
n.s.

The life-course approach *(2)*



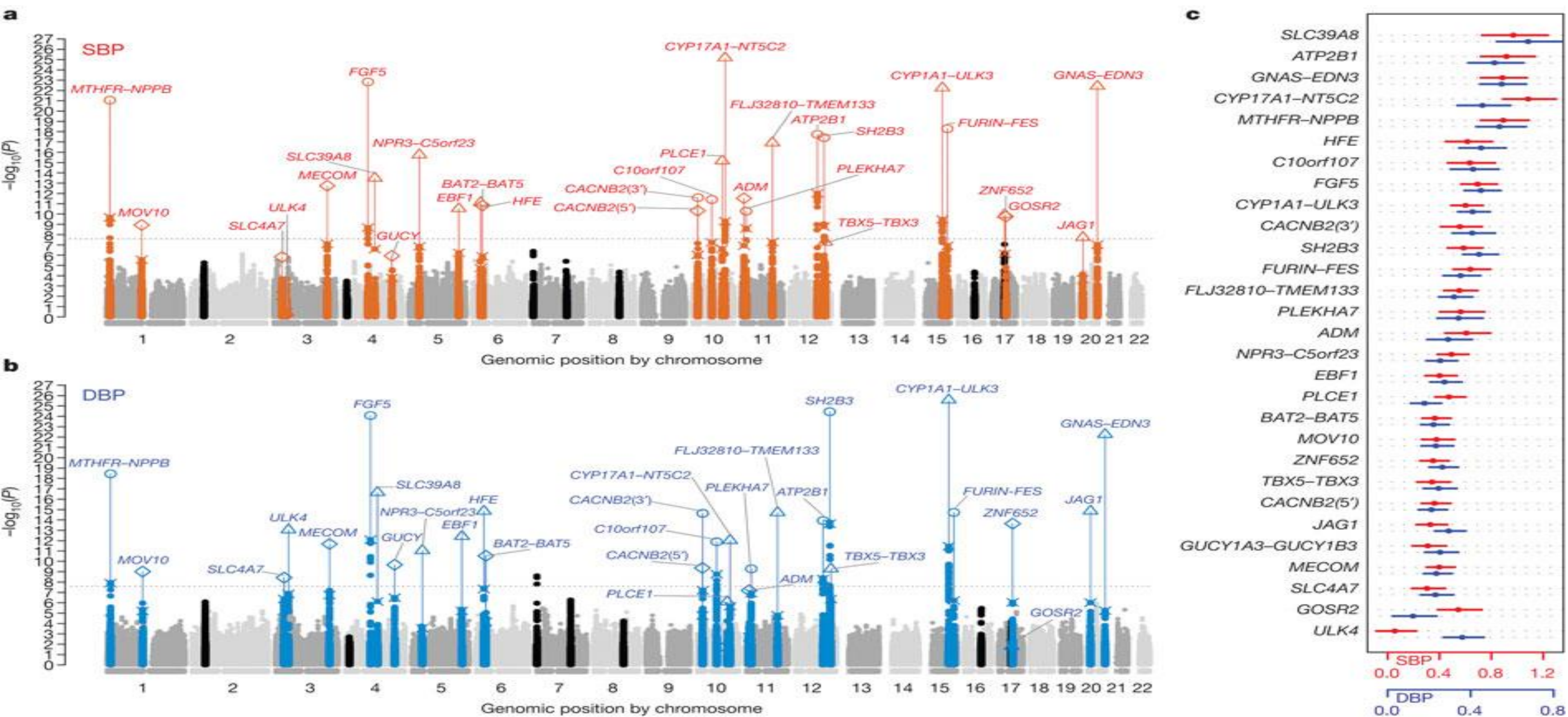
Summary of GWAS for PWV in the SardiNIA study cohort.

Tarasov K V et al. Circ Cardiovasc Genet 2009;2:151-158



Summary of GWAS for SBP (top) and DBP (bottom)

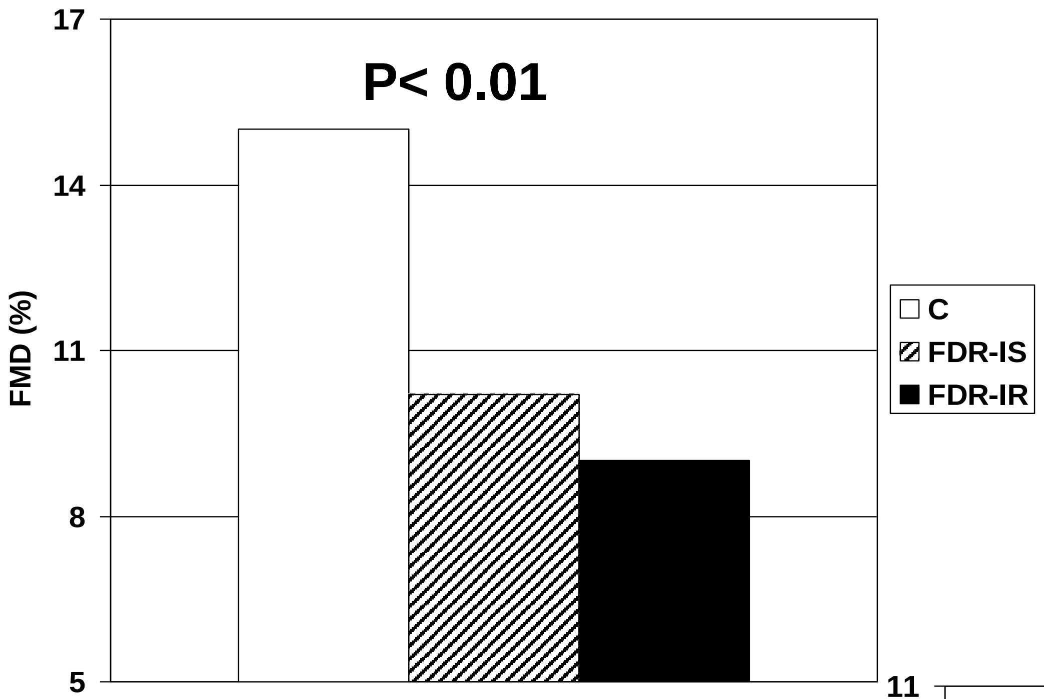
Nature. **2011** Sep 11;478(:103-9

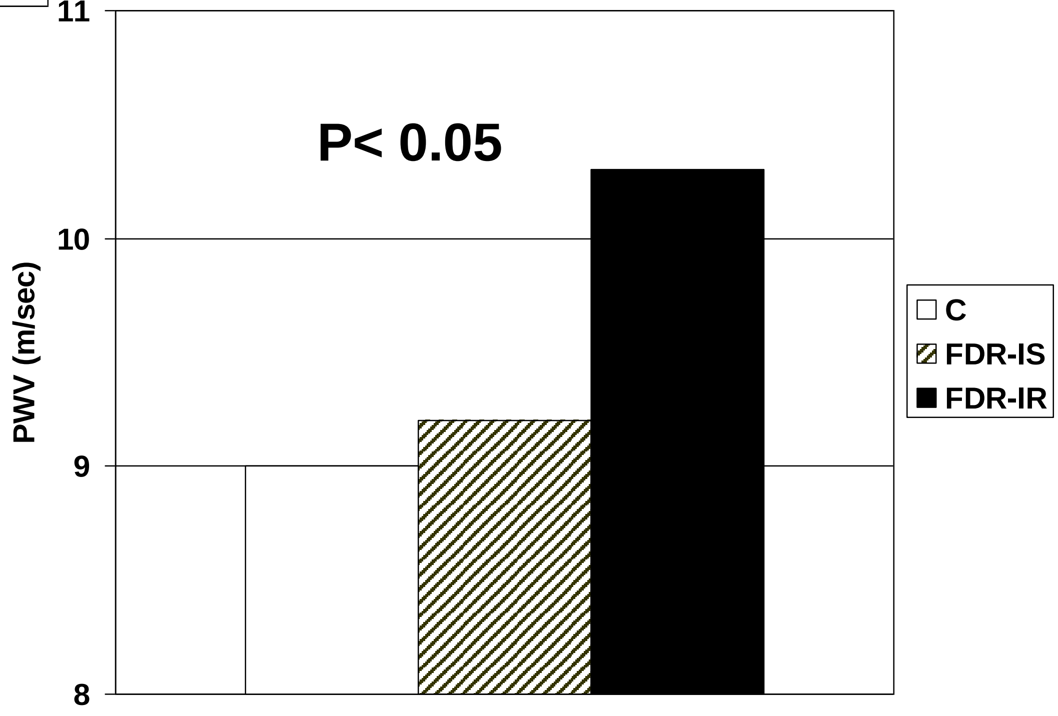


PWV is an Independent Predictor of Incident HT

	Hazard Ratio	95%CI	P-value
SBP (per 10 mmHg)	1.40	0.99-1.08	0.08
PWV (per 1 m/s)	1.10	1.01-1.30	0.03

Multivariate Cox Proportional Hazards models
Other variables included in model: Age, Sex, BMI, MAP, LDL, HDL, Trig



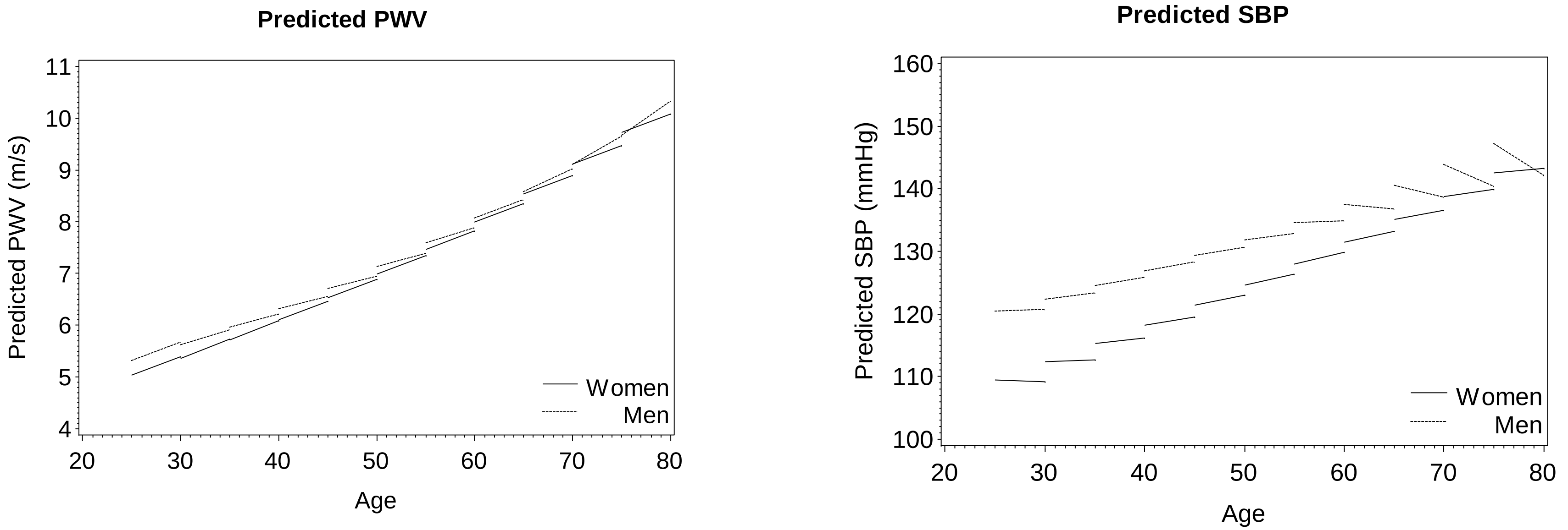


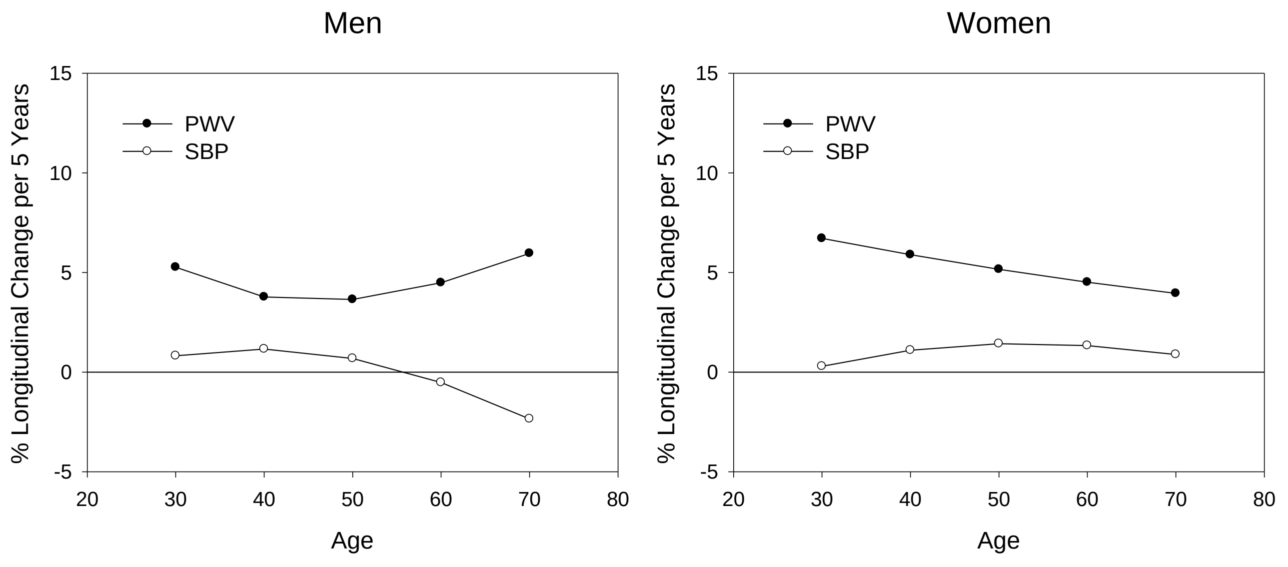
Scuteri A et al

Nutr Metab CV Disease 2008; 18:349-56.

Longitudinal changes in PWV and SBP at various ages

Scuteri A et al Hypertension 2014





Aging is …

- *a process*
- *dynamic*
- *heterogenous*
- *systemic*
- (partially) *adaptive*

Factors impacting on heterogeneity of arterial aging: the model of MetS

Table 3 Occurrence of specific clustering of the components of the MetS in men and women when compared with the expected prevalence calculated on the basis of gender-specific prevalence of each MetS component (see Methods for details)

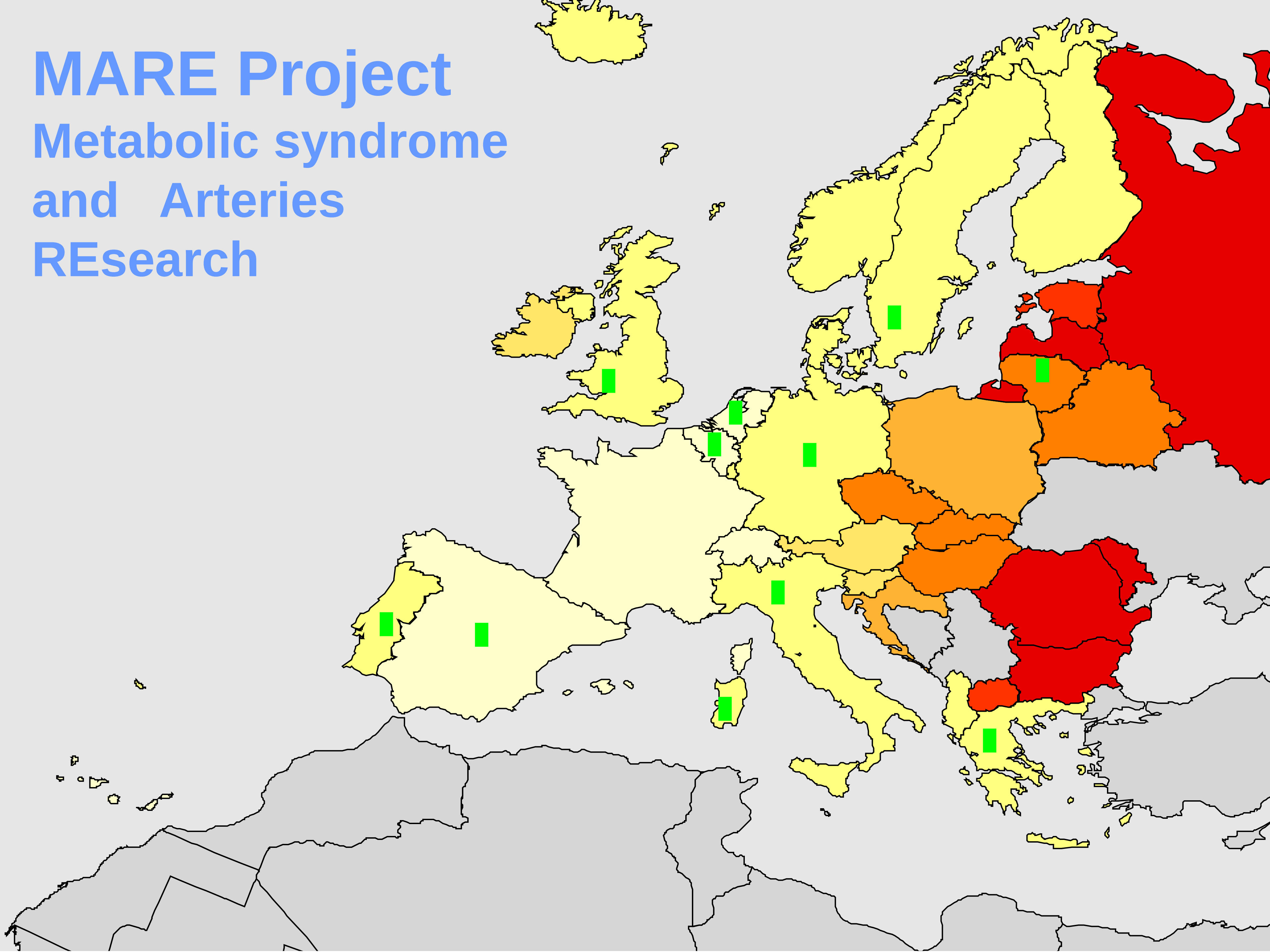
	Men		Women	
	Expected	Observed	Expected	Observed
T–B–W	29.2	20.0	18.4	21.0
H–B–W	7.9	4.3	6.4	15.9
H–T–W	1.6	1.1	4.9	2.3
H–T–B	7.9	4.3	5.0	0
H–T–B–W	1.4	2.2	1.9	3.7
G–B–W	18.1	28.7	17.3	29.0
G–T–W	3.6	4.3	2.7	6.5
G–T–B	18.1	12.4	2.7	0.5
G–T–B–W	3.2	15.1	1.0	5.6
G–H–B	4.9	2.2	4.7	0.5
G–H–W	1.0	0	4.6	4.7
G–H–B–W	0.9	2.2	1.8	4.7
G–H–T	1.0	0.5	0.7	0
G–H–T–B	0.9	1.1	0.3	0.5
G–H–T–W	0.2	0	27.4	2.3
G–H–T–B–W	0.2	1.6	0.1	2.8

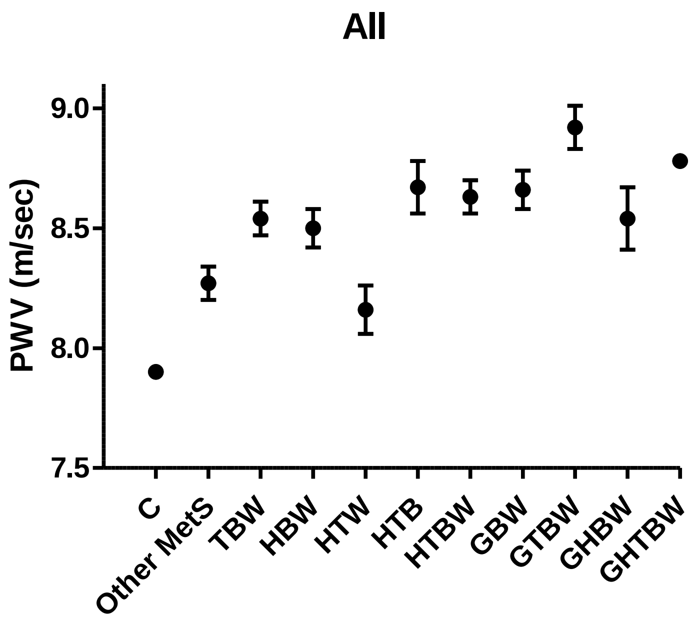
G, elevated glucose component; H, low HDL cholesterol component; T, elevated triglycerides component; B, elevated blood pressure component; W, abdominal obesity.

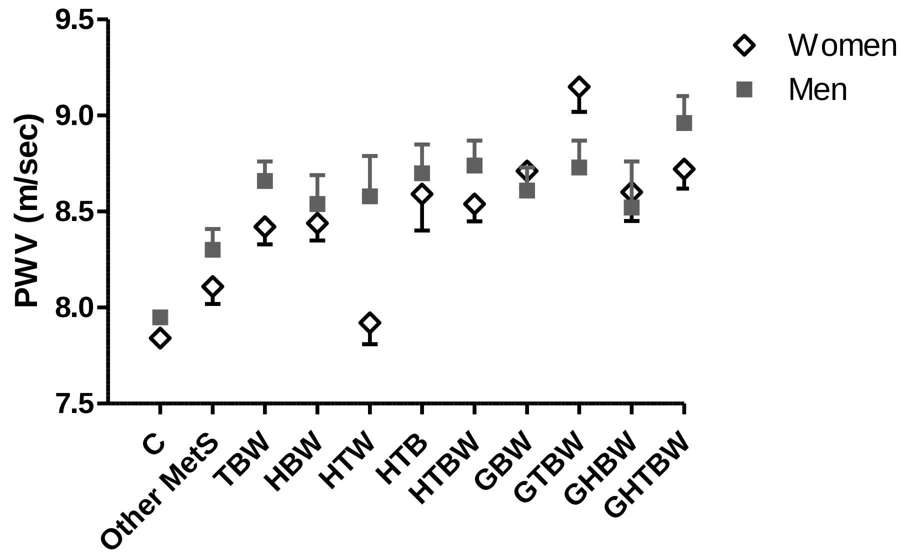
	T–B–W		H–B–W		G–B–W		G–T–B(–W)		G–H–B(–W)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
APWV > 95th percentile										
Univariate	**3.72**	2.03–6.81	**3.23**	1.35–7.73	**6.68**	4.29–10.4	**6.11**	3.38–11.0	**8.99**	3.39–23.8
Age, sex adjust.	**2.72**	1.17–4.21	2.13	0.81–5.64	**2.06**	1.28–3.32	**2.57**	1.35–4.92	2.64	0.91–7.68
Age, sex, DM	**2.38**	1.25–4.52	2.17	0.82–5.73	**1.60**	0.98–2.81	**2.11**	1.08–4.12	1.98	0.67–5.84
Age, sex, DM, LDL-cholesterol, current smoking	**2.31**	1.21–4.40	2.22	0.84–5.86	1.58	0.93–2.69	**2.10**	1.07–4.10	2.08	0.70–6.19
Age, sex, DM, LDL-cholesterol, current smoking excluding prevalent CV disease	**2.39**	1.25–4.59	2.19	0.83–5.79	1.47	0.84–2.57	**2.03**	1.01–4.07	1.46	0.41–5.21

MARE Project

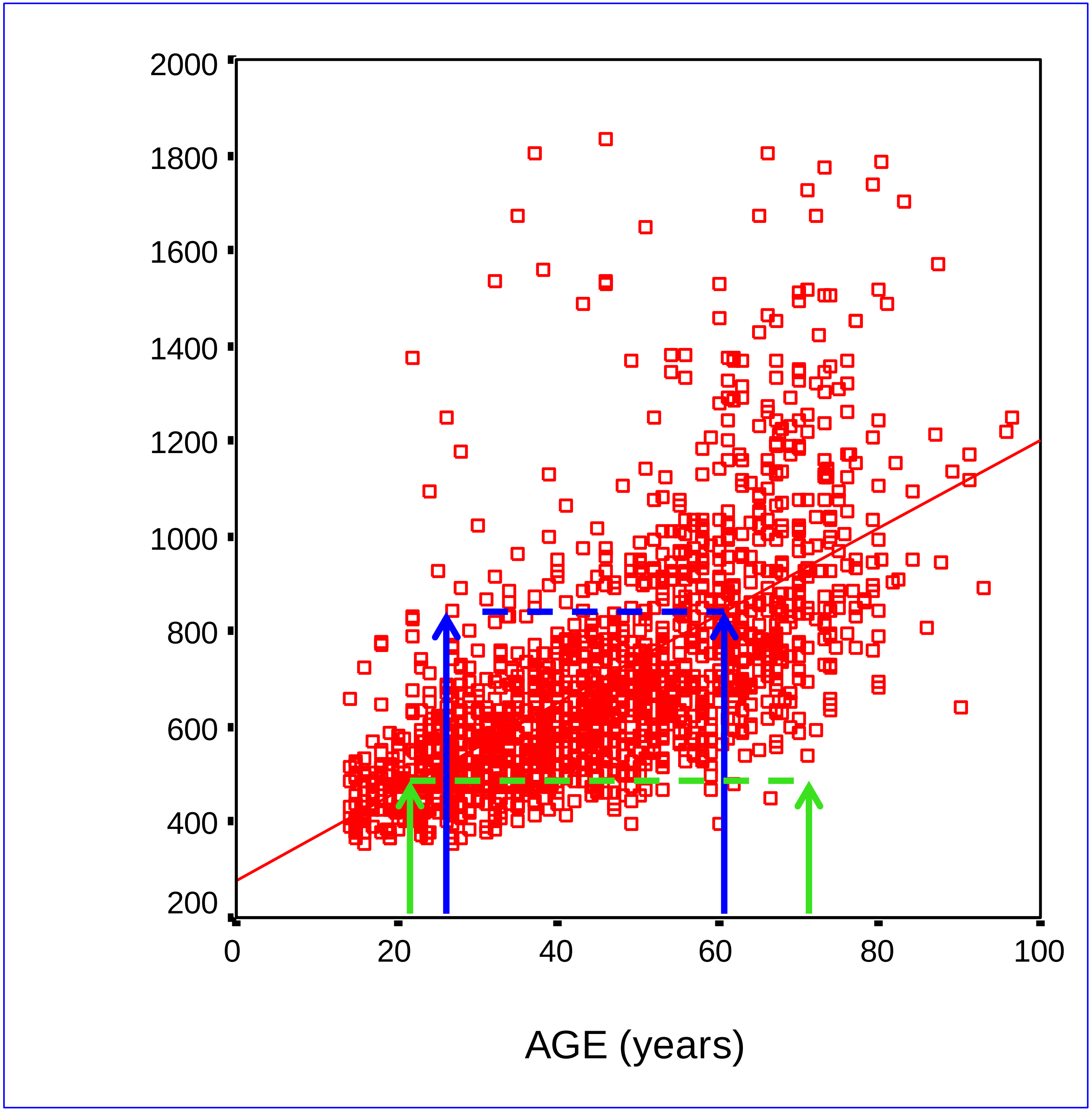
Metabolic syndrome and Arteries REsearch

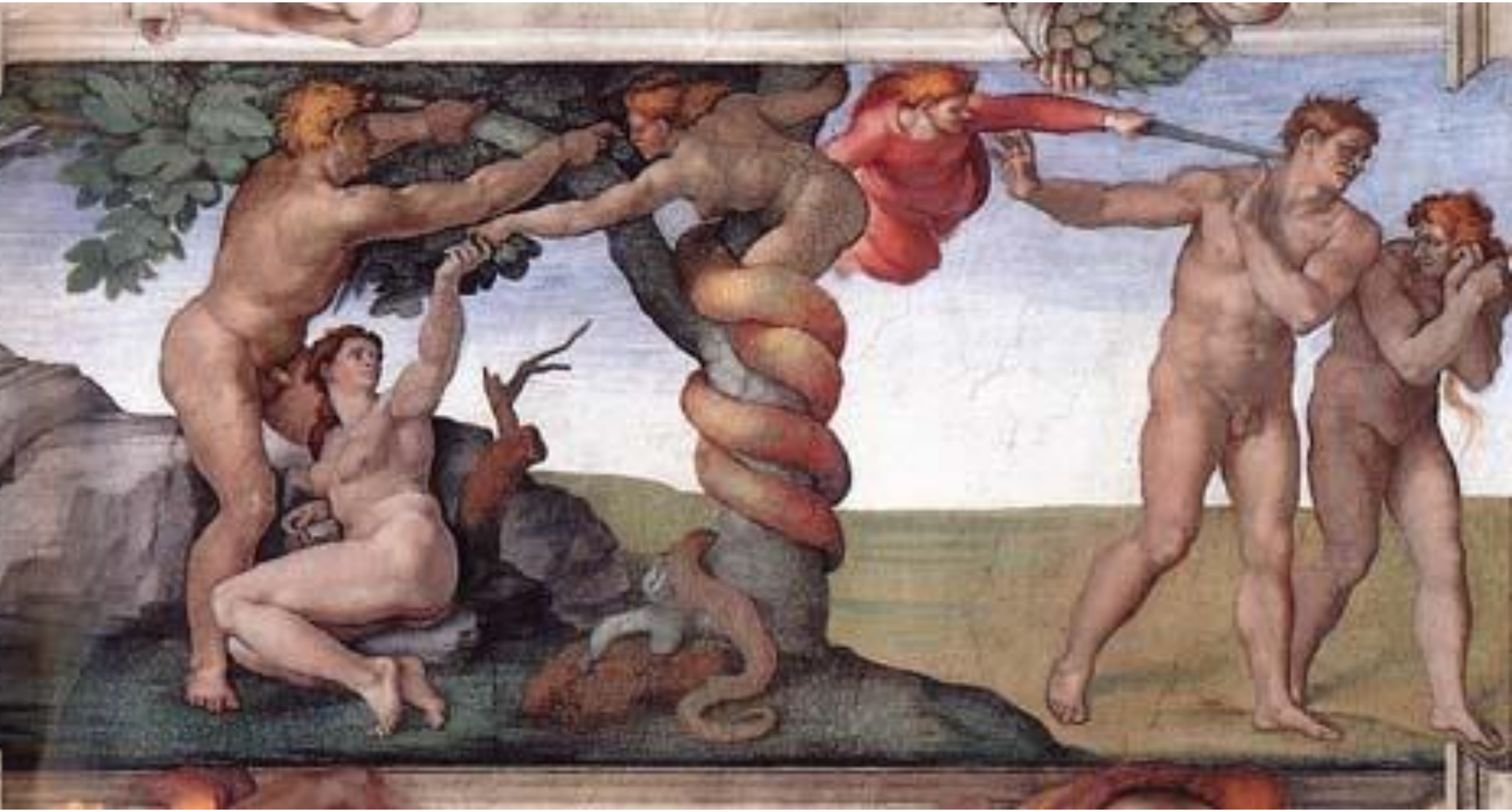


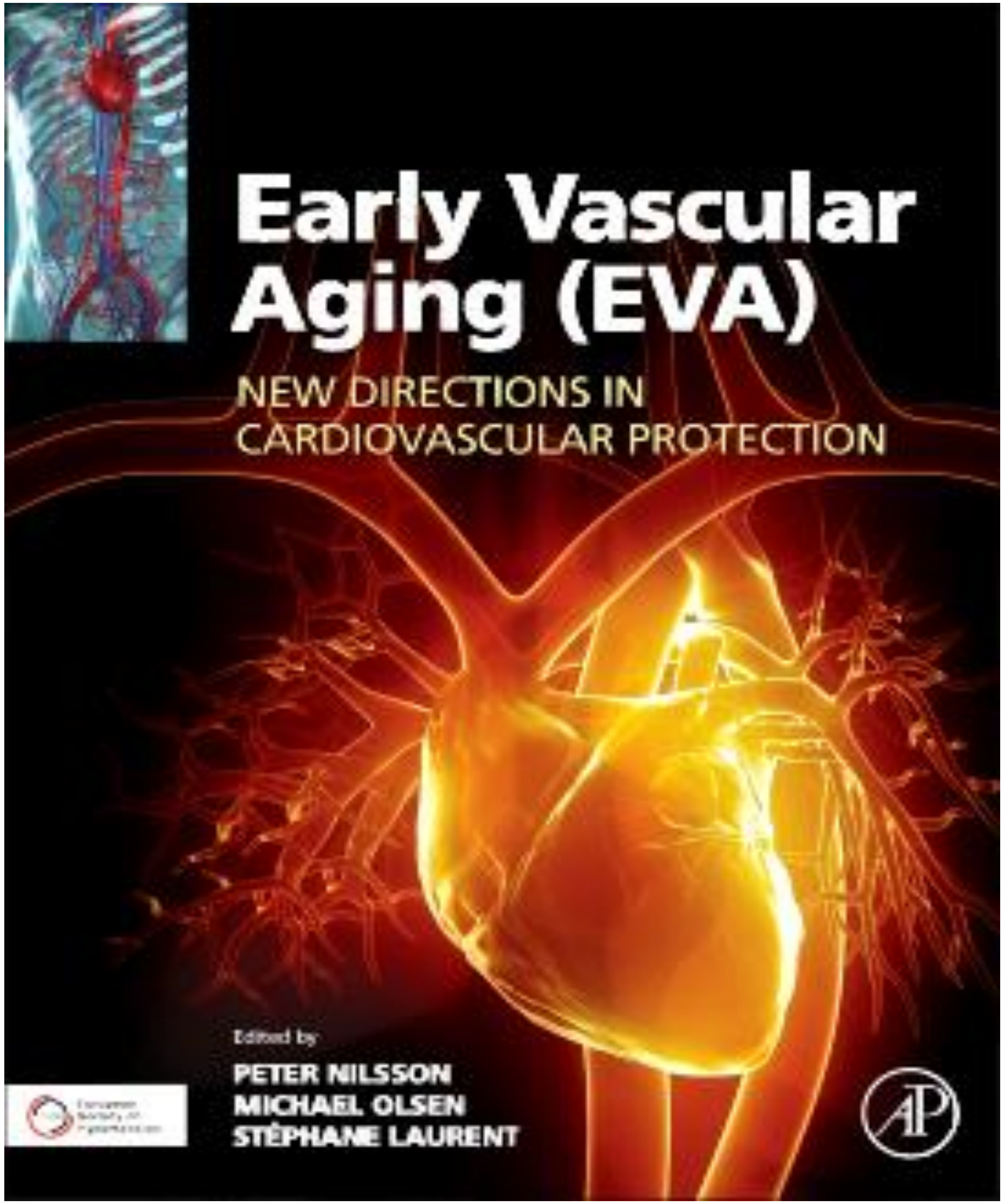




Scuteri A for the MARE Consortium
Atherosclerosis 2014


2000
1800
1600
1400
1200
1000
800
600
400
200
0
20
40
60
80
100
AGE (years)




Early Vascular Aging (EVA)
NEW DIRECTIONS IN CARDIOVASCULAR PROTECTION
Edited by
PETER NILSSON
MICHAEL OLSEN
STÉPHANE LAURENT

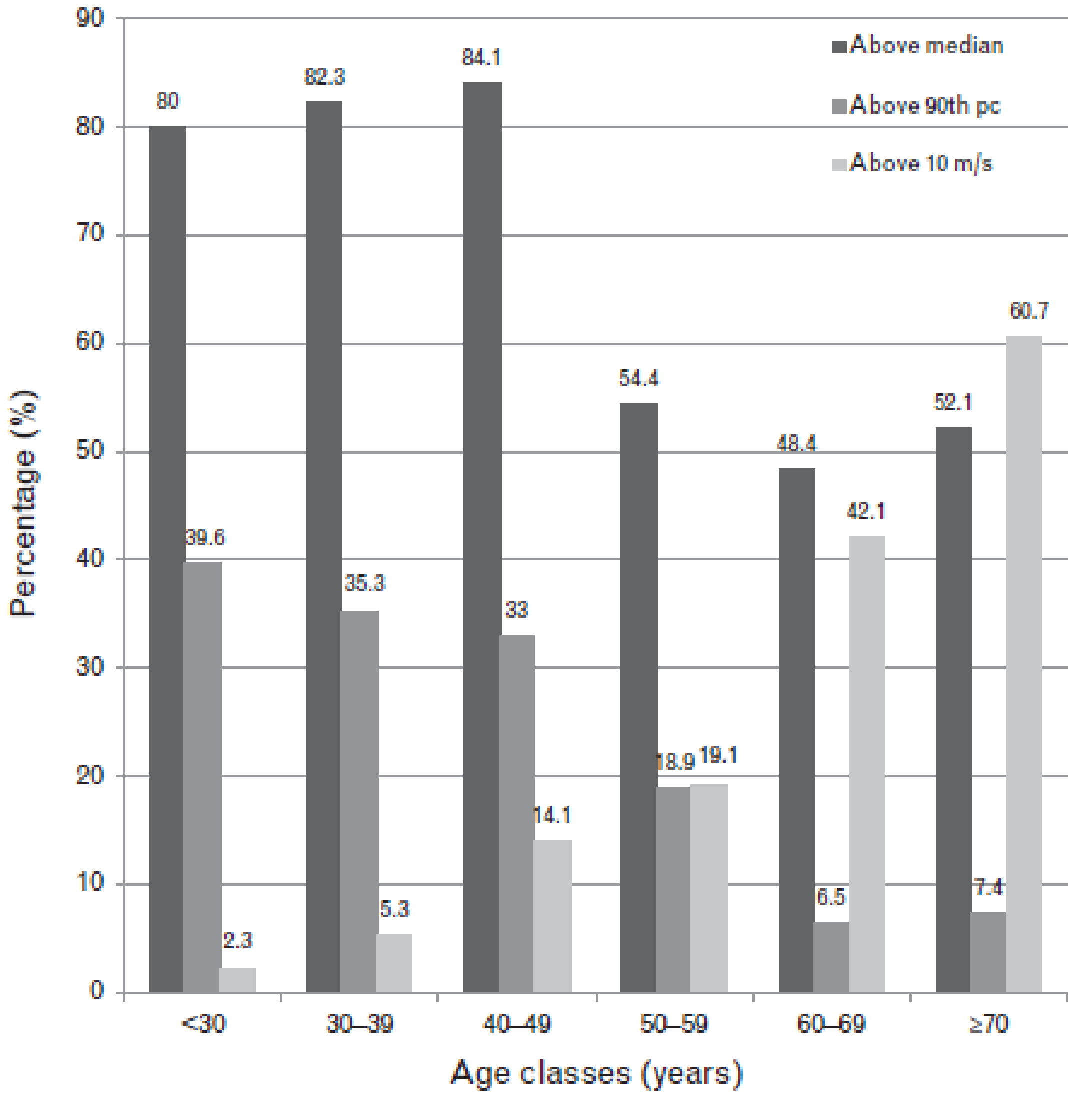
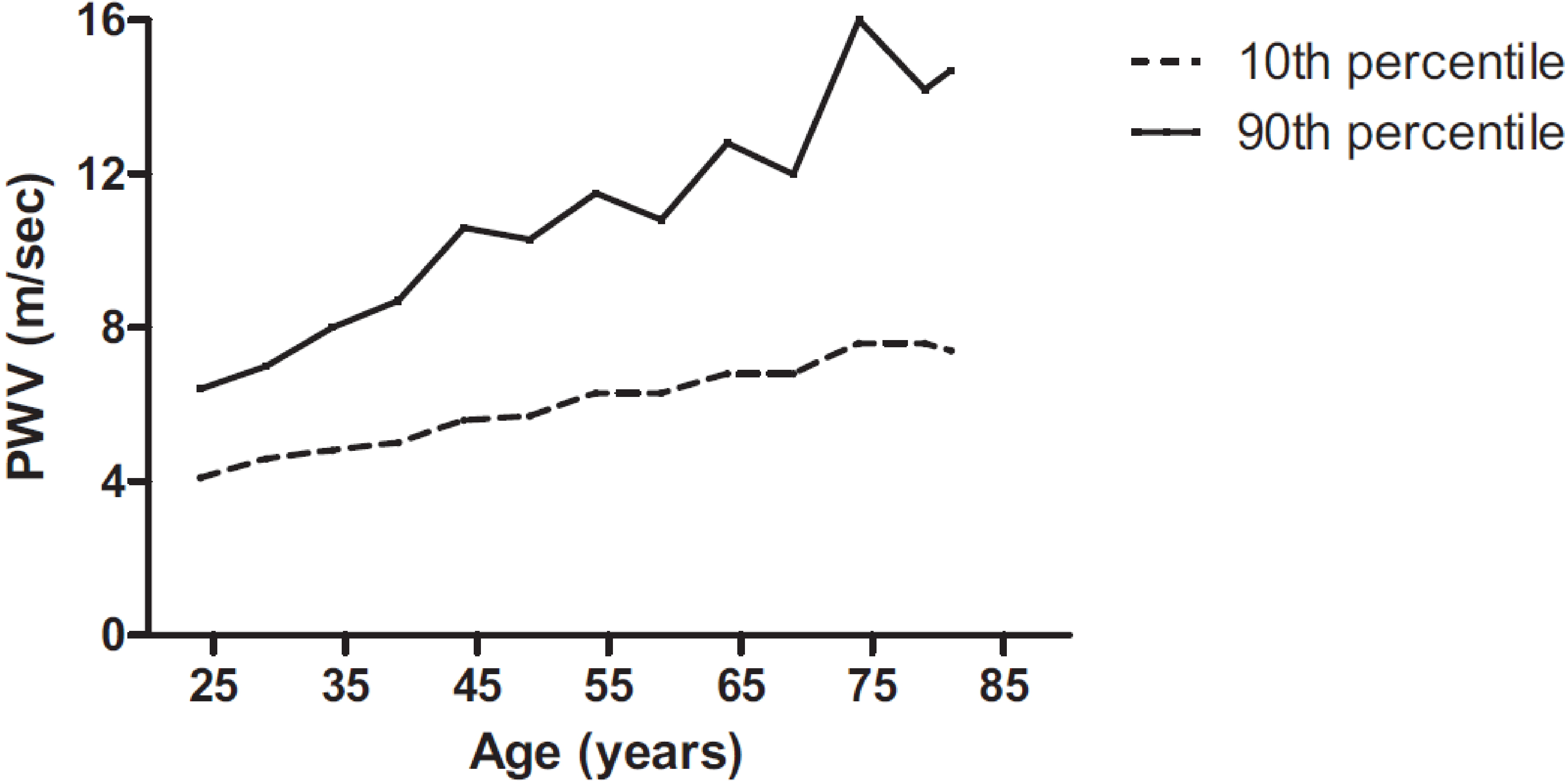


FIGURE 3 Percentage of individuals above the median and above the 90th percentile of the normal pulse wave velocity value expected for age, and above the 10 m/s cutoff (stratified by age decade). pc, percentile.

Cunha P et al J Hypertens 2015



Nilsson PN et al for the MARE Consortium J Hypertens 2018

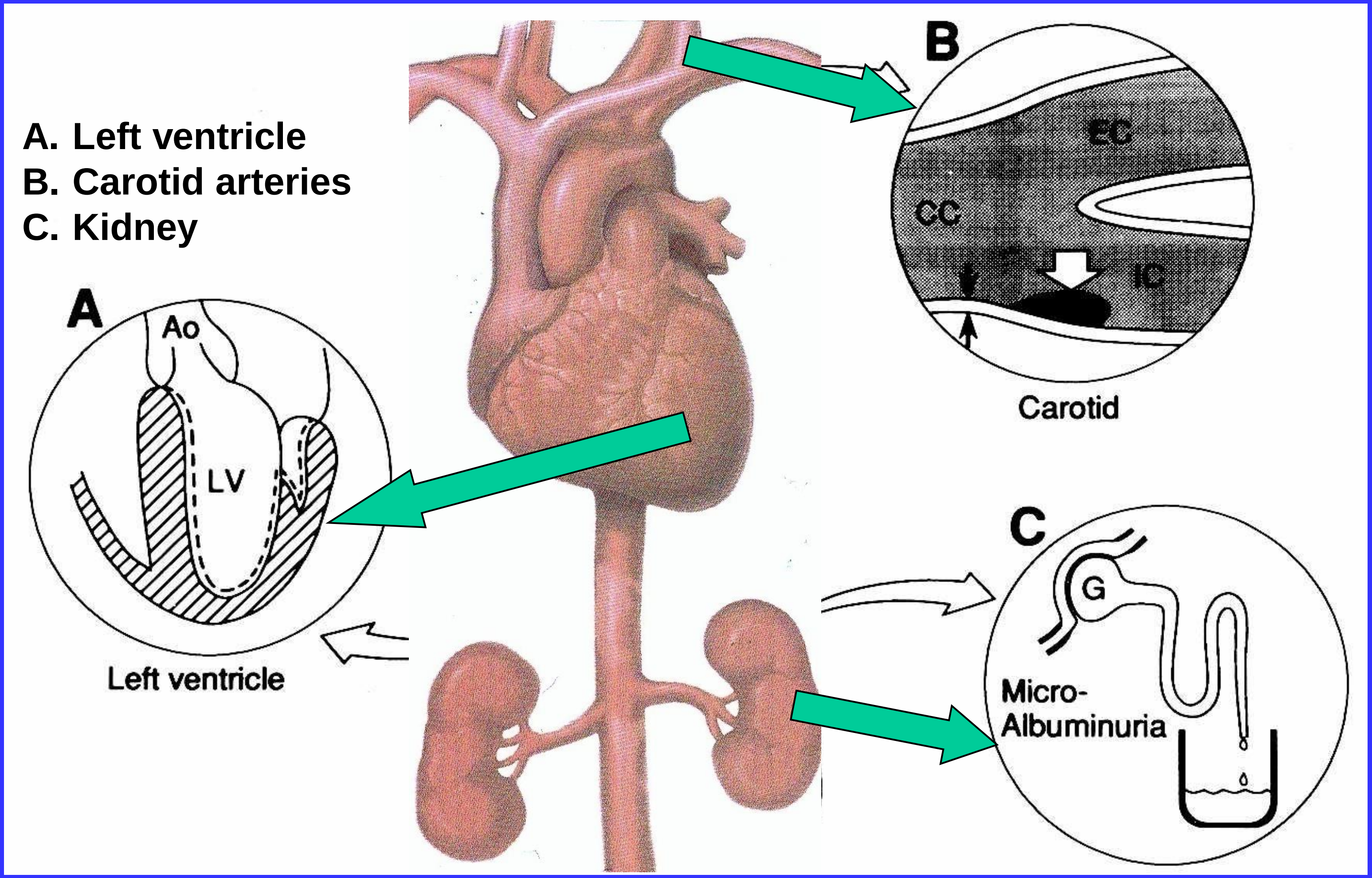
	HVA defined as PWV value below the age-quintile specific 10th percentile		
	Control ($n = 16803$)	HVA ($n = 1723$)	*P* value
Age (years)	52.5 ± 16.5	52.4 ± 17.1	0.76
Women (%)	57.0	59.4	.05
BMI (kg/m^2)	27.1 ± 5.2	25.2 ± 4.2	.0001
Waist circumference (cm)	91.0 ± 14.0	85.1 ± 12.8	0.0001
Fasting glucose (mg/dl)	96.1 ± 24.6	88.9 ± 18.2	0.0001
Total cholesterol (mg/dl)	218.4 ± 50.2	204.3 ± 41.8	0.0001
HDL cholesterol (mg/dl)	58.4 ± 18.7	63.4 ± 17.5	0.0001
Non-HDL cholesterol (mg/dl)	160.1 ± 51.9	140.9 ± 40.7	0.0001
Triglycerides (mg/dl)	117.4 ± 123.9	87.1 ± 59.2	0.0001
SBP (mmHg)	131.5 ± 19.5	120.5 ± 16.7	0.0001
DBP (mmHg)	79.7 ± 11.5	73.3 ± 10.2	0.0001
MAP (mmHg)	96.8 ± 13.0	89.0 ± 11.3	0.0001
PP (mmHg)	52.0 ± 14.1	47.4 ± 12.4	0.0001
HR (bpm)	67.7 ± 11.1	64.6 ± 10.2	0.0001
Central SBP (mmHg)[a] (*n*)	125.7 ± 19.8 (8354)	117.3 ± 18.5 (367)	0.0001
Central PP (mmHg)[a]	43.7 ± 14.4	41.4 ± 14.5	0.01
PP amplification (%)[a]	131.7 ± 30.7	128.2 ± 21.9	0.05
Serum creatinine (mg/ml)[a] (*n*)	0.85 ± 0.26 (13632)	0.84 ± 0.19 (1685)	0.01
PWV (m/s)	8.8 ± 2.9	5.5 ± 0.9	0.0001
PWV/MBP	9.2 ± 2.8	6.3 ± 1.2	0.0001
CCA IMT (mm)[a] (*n*)	0.70 ± 0.25 (9916)	0.58 ± 0.13 (1349)	0.0001
Hypertension (%)	41.8	21.0	0.0001
Diabetes mellitus (%)	10.1	4.7	0.0001
Overweight (%)	14.2	17.0	0.01
Obesity (%)	23.4	12.5	0.0001
Metabolic syndrome	23.0	8.4	0.0001

Nilsson PN et al for the MARE Consortium J Hypertens 2018

Aging is …

- *a process*
- *dynamic*
- *heterogenous*
- *systemic*
- (partially) *adaptive*

“Windows” through which preclinical cardiovascular disease can be assessed non-invasively



Modified from Devereux and Alderman, Circulation 1993; 88:1444-1455

Target organ damage: Definitions

- **HEART**

Echocardiographic LVH:

LVMI >50 g/m2.7 in either sex

- **COMMON CAROTID ARTERY**

an intimal-media thickness(IMT) > 0.9 mm and/or presence of plaque

- **KIDNEY:**

eGFR<60 ml/min/1.73 m2 (stage 3)

Determinants of SHATS.

Bottom up approach			
Traditional CV risk factors (sex, smoking, BMI, SBP, DBP; LDL and HDL cholesterol, diabetes) Plus Antihypertensive, antidiabetic, and lipid-lowering medications Plus 24 h BP variability measures			
variable name	OR	95% CI	p value
BMI (per Kg/m2)	**1.10**	1.02–1.18	0.01
DBP (per mmHg)	**0.97**	0.95–0.99	0.05
24 h SBP SD	**1.18**	1.05–1.32	0.01
24 h DBP SD	**0.81**	0.68–0.97	0.05
SBP Dipper	**0.18**	0.06–0.57	0.001
Model accuracy		c = 0.77	

Top down approach			
PWV > 10 m/s Plus 24 h BP variability measures			
variable name	OR	95% CI	p value
PWV >10 m/s	**3.41**	1.49–7.76	0.01
24 h SBP SD	**1.16**	1.04–1.29	0.01
24 h DBP SD	**0.82**	0.54–0.98	0.05
SBP Dipper	**0.19**	0.06–0.60	001
		c = 0.79	

Int J Cardiol
2018; 263: 132-137

	SHATS "score"					
	1		2		3	
	OR	95% CI	OR	95% CI	OR	95% CI
PWV >10 m/s	**2.23** **	1.01–4.94	**5.87** **	2.57–13.4	**10.6** **	3.76–29.8
Use of antiHT meds	1.21	0.53–2.78	**3.25 &**	1.31–8.10	**3.74** *	1.27–11.1
24 h DBP SD	1.08	0.90–1.28	**0.81 &**	0.67–0.99	**0.75** *	0.59–0.95
SBP Dipper	0.92	0.39–2.16	**0.31** **	0.12–0.77	**0.09** **	0.02–0.32

Int J Cardiol 2018; 263: 132-137

…and so stiffer arteries

are a marker

of systemic alteration & damage

in the whole arterial tree

CONCLUSIONS

Measuring arterial aging

Arterial aging is risky

Arteries:
aging
not atherosclerosis,
not hypertension

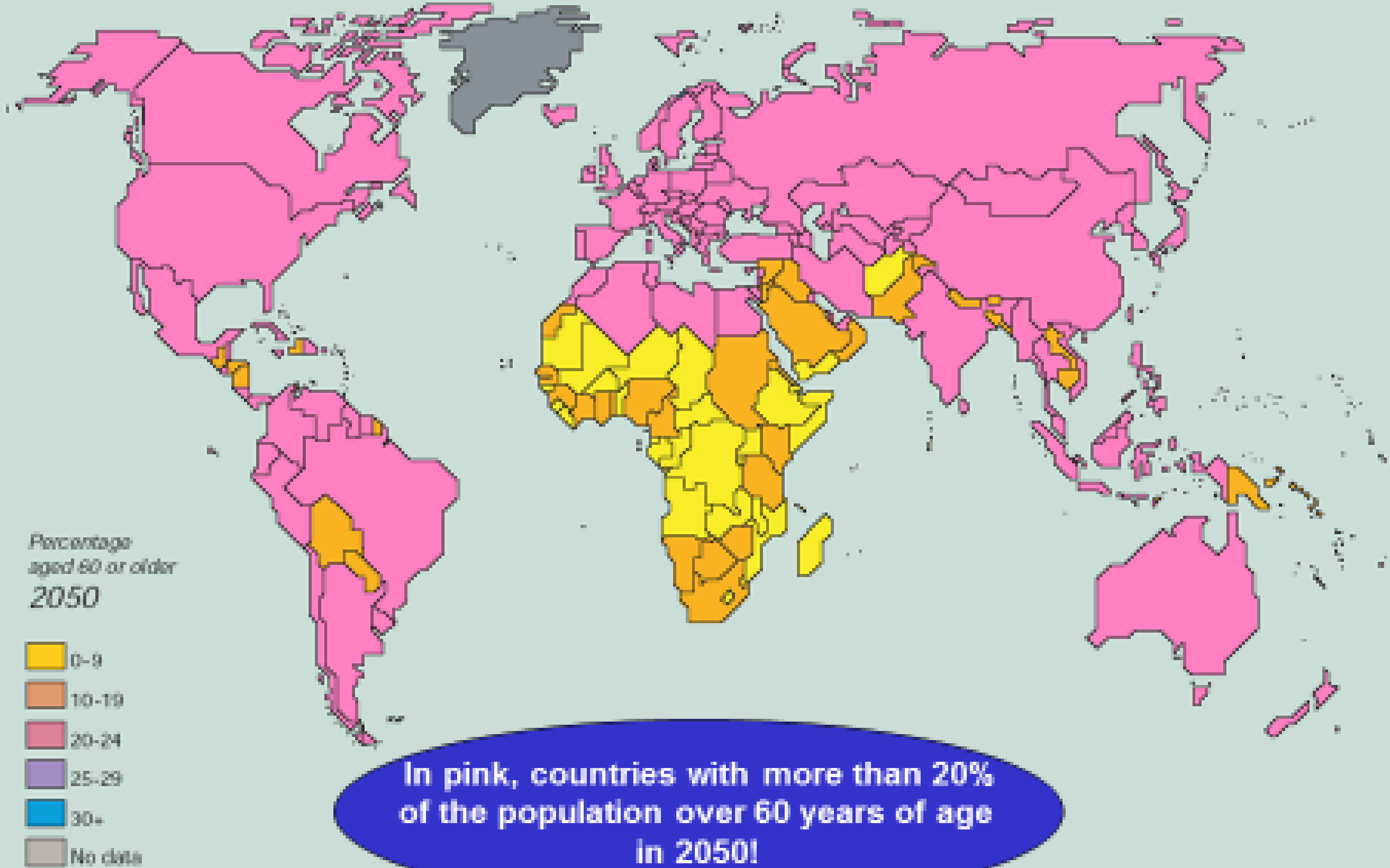
Aging is …

- *a process*
- *dynamic*
- *heterogenous*
- *systemic*
- (partially) *adaptive*

How early arterial aging can be identified?

Can we slow down arterial aging?

Percentage of total population aged 60 years or older 2050



In pink, countries with more than 20% of the population over 60 years of age in 2050!

http://www.un.org/esa/population/publications/ageing/Graph.pdf

THE LANCET

UNIVERSITY OF SOUTHERN DENMARK

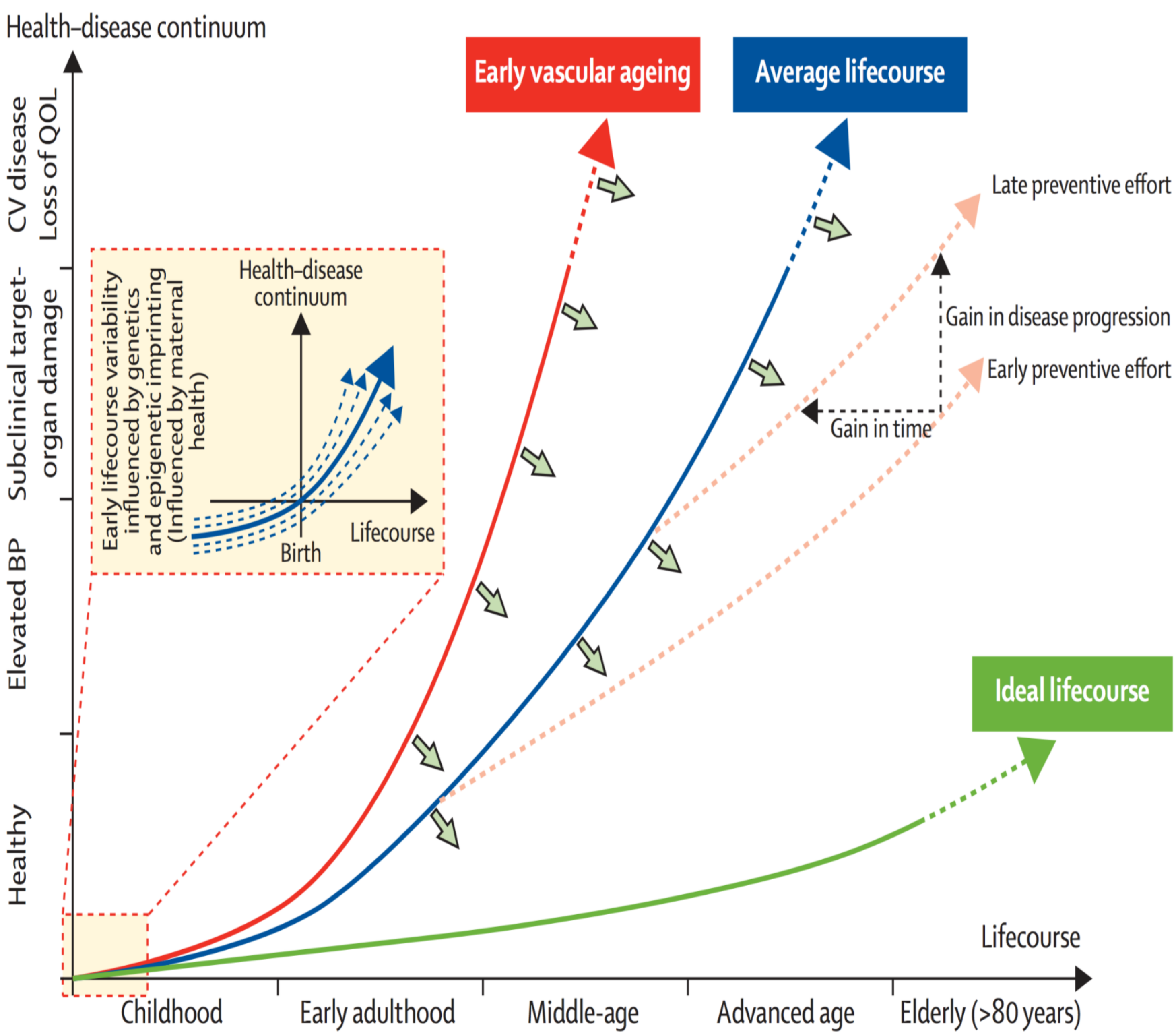
International Society of Hypertension | 50 YEARS 1966 | 2016

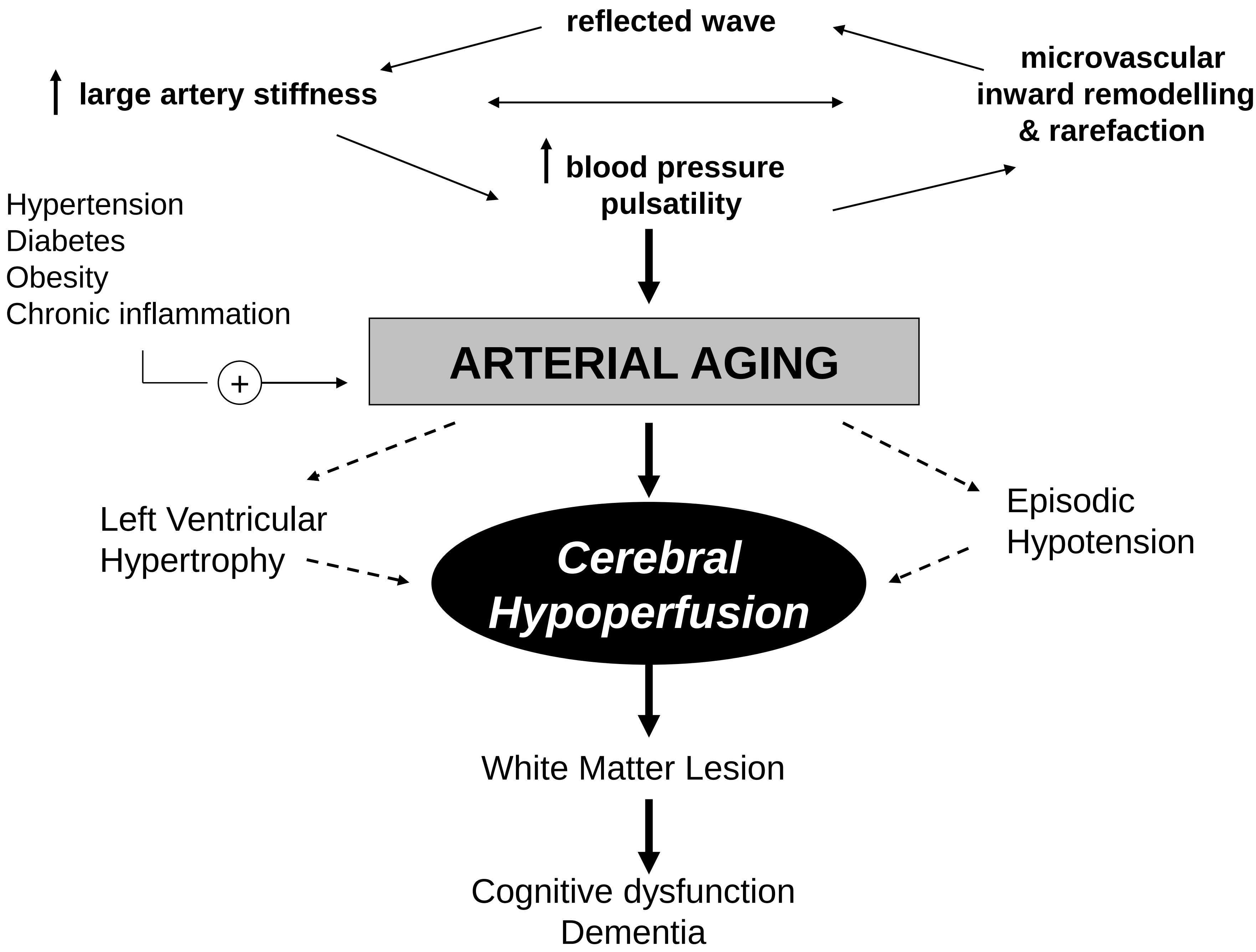
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the *Lancet* Commission on hypertension

Michael H Olsen, Sonia Y Angell, Samira Asma, Pierre Boutouyrie, Dylan Burger, Julio A Chirinos, Albertino Damasceno, Christian Delles, Anne-Paule Gimenez-Roqueplo, Dagmara Hering, Patricio López-Jaramillo, Fernando Martinez, Vlado Perkovic, Ernst R Rietzschel, Giuseppe Schillaci, Aletta E Schutte, Angelo Scuteri, James E Sharman, Kristian Wachtell, Ji Guang Wang*

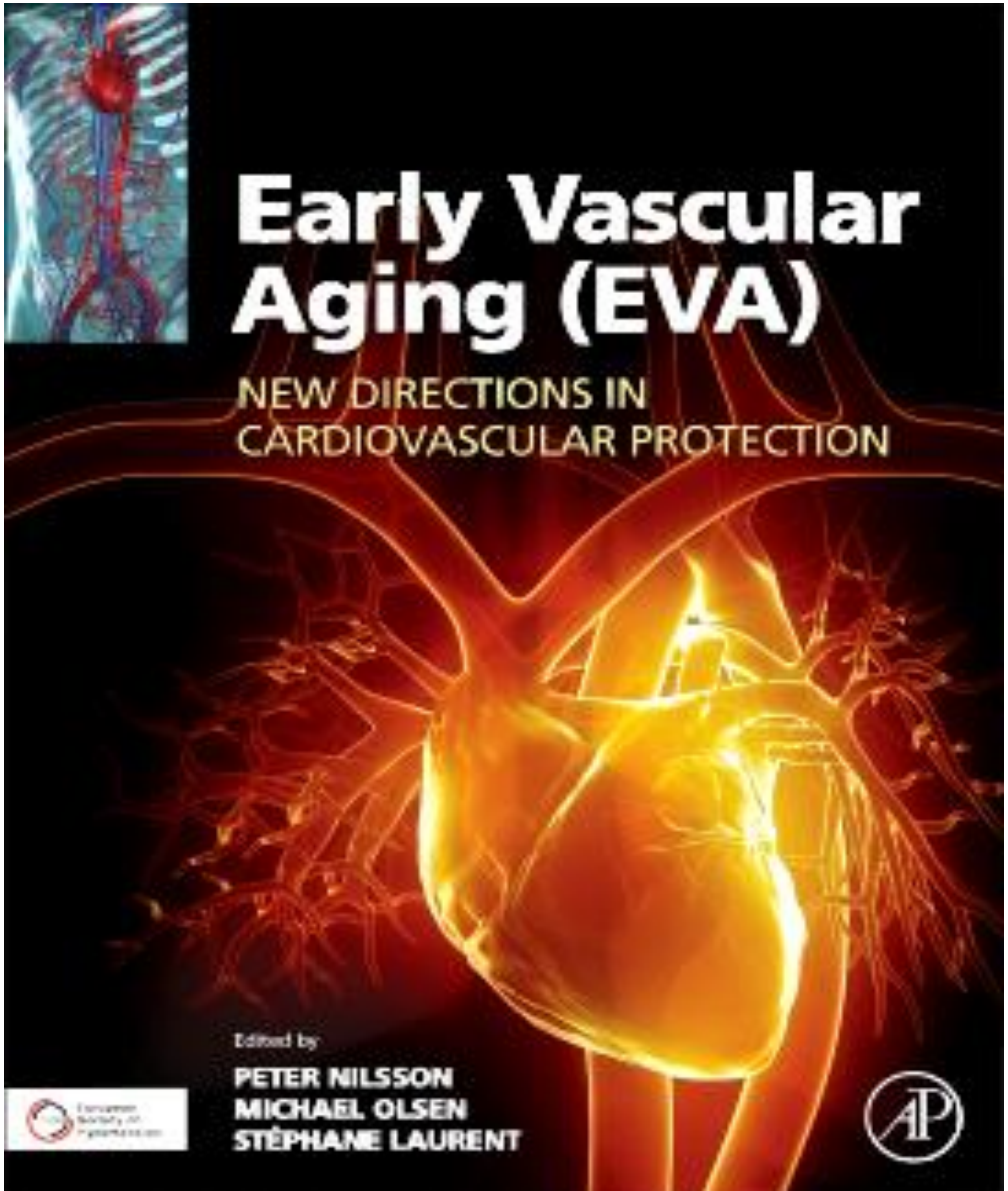
The life-course approach *(2)*





reflected wave
large artery stiffness
microvascular inward remodelling & rarefaction
blood pressure pulsatility
Hypertension
Diabetes
Obesity
Chronic inflammation
+
ARTERIAL AGING
Left Ventricular Hypertrophy
Episodic Hypotension
Cerebral Hypoperfusion
White Matter Lesion
Cognitive dysfunction
Dementia

Routinely measuring arterial aging as early as possible …with recurrent follow-up



An increasing number of years is lived with some disability….
…and novel functional otucomes become relevant

Source: **Istat, Italian Life tables and survey «Indagine Aspetti della vita quotidiana»**


Measles induces immune amnesia pp. 560 & 599
Russia debates a plan to make gene-edited babies p. 562
Finding a hidden black hole p. 637
Science
$15
1 NOVEMBER 2019
AAAS
GENE FLOW
Hybridization boosts butterfly genome complexity pp. 570 & 594

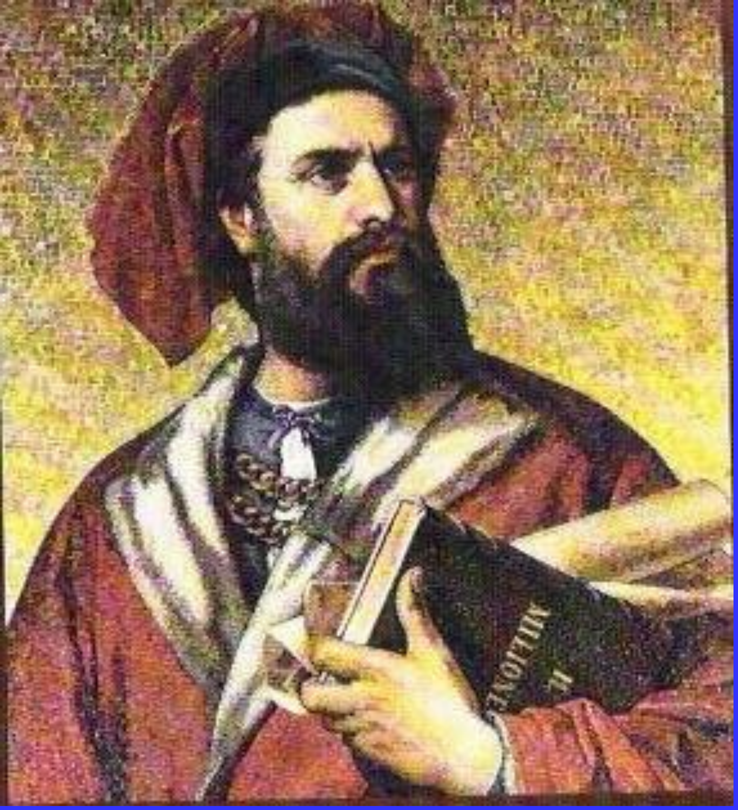
POLICY FORUM

AGING

To help aging populations, classify organismal senescence

Comprehensive disease classification and staging is required to address unmet needs of aging populations

By **Stuart R. G. Calimport, Barry L. Bentley, Claire E. Stewart, Graham Pawelec, Angelo Scuteri, Manlio Vinciguerra, Cathy Slack, Danica Chen, Lorna W. Harries, Gary Marchant, G. Alexander Fleming, Michael Conboy, Adam Antebi, Gary W. Small, Jesus Gil, Edward G. Lakatta, Arlan Richardson, Clifford Rosen, Karoly Nikolich, Tony Wyss-Coray, Lawrence Steinman, Thomas Montine, João Pedro de Magalhães, Judith Campisi, George Church**



Io parlo parlo, ma chi mi ascolta ritiene solo le parole che aspetta. […]

Chi comanda il racconto non e’ la voce:

e’ l’ orecchio.

I. Calvino

Save the Date

MEto

Meet the Expert on Ageing, Hypertension and Co-Morbidities An update 2020

ALGHERO, SARDINIA - ITALY
APRIL 23-24, 2020

Supported by the International Society of Hypertension - Regional Activity Group (ISH-RAG) for Europe

https://www.aristea.com/mastercourse2020/

Soffio antichissimo del mare,
vento del mare a notte:
a nessuno tu vieni;
per chi vegli
resisterti
e’ una prova

RM Rilke ***Canto del mare***