SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

YOUNG EPIDEMIOLOGISTS SIGG yes

UNIVERSITÀ DEGLI STUDI DI NAPOLI FEDERICO II

Hôpitaux de Toulouse

Toulouse GÉRONTOPÔLE

WHO - Collaborating Centre for Frailty, Clinical Research and Geriatric Training

68° CONGRESSO NAZIONALE SIGG

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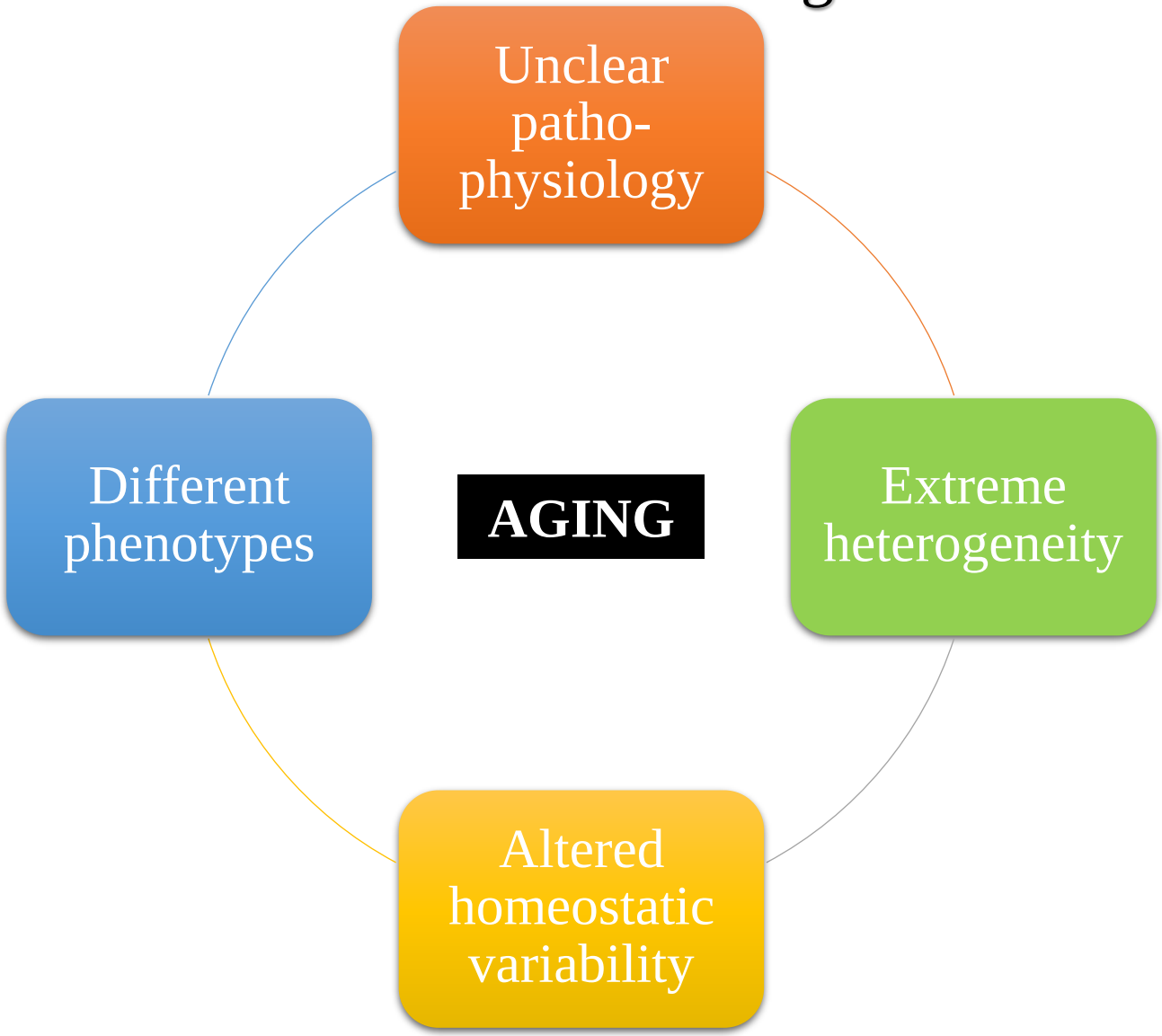
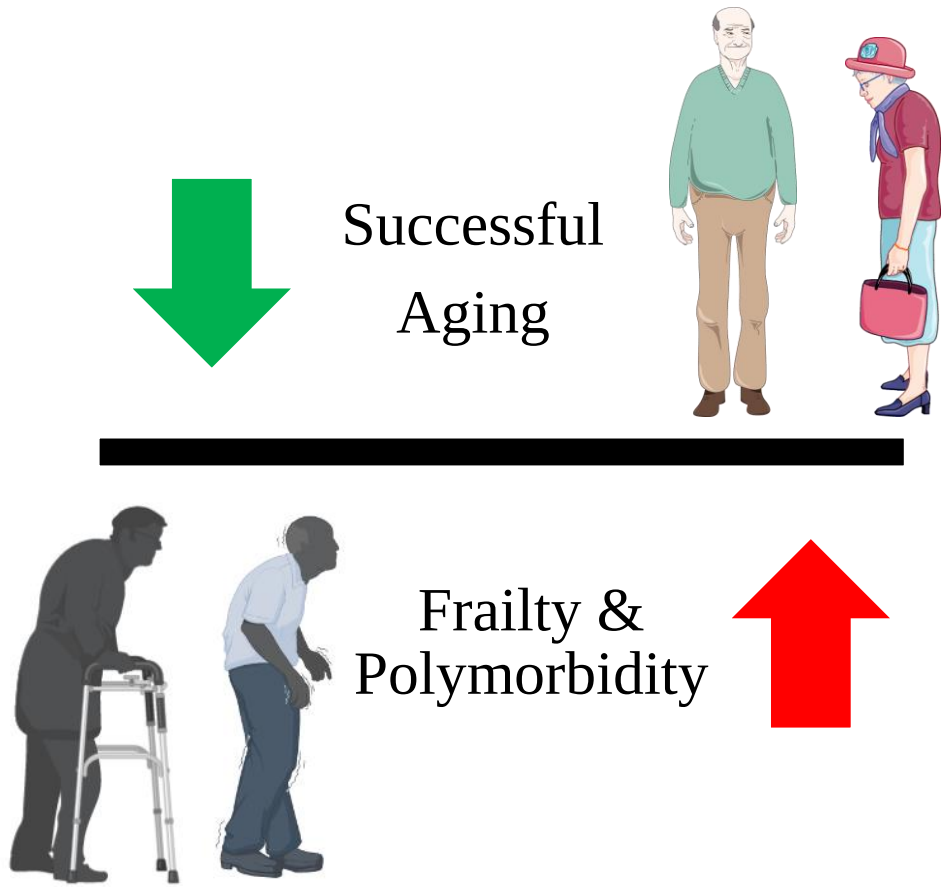
Variabilità della pressione arteriosa e capacità intrinseca negli anziani non istituzionalizzati

CONFLICT OF INTEREST DISCLOSURE

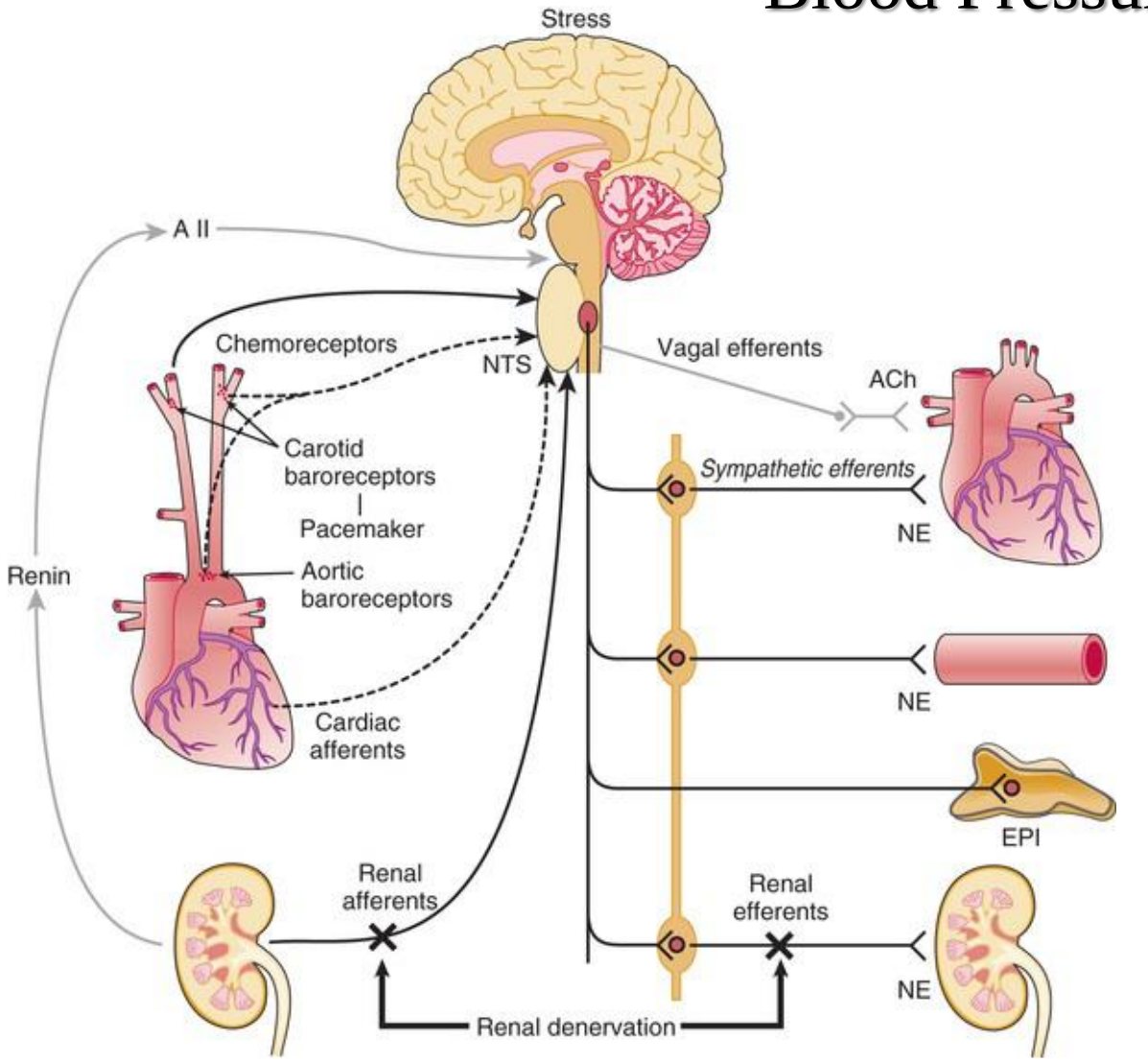
I have no potential conflict of interest to report

Higher variability in aging

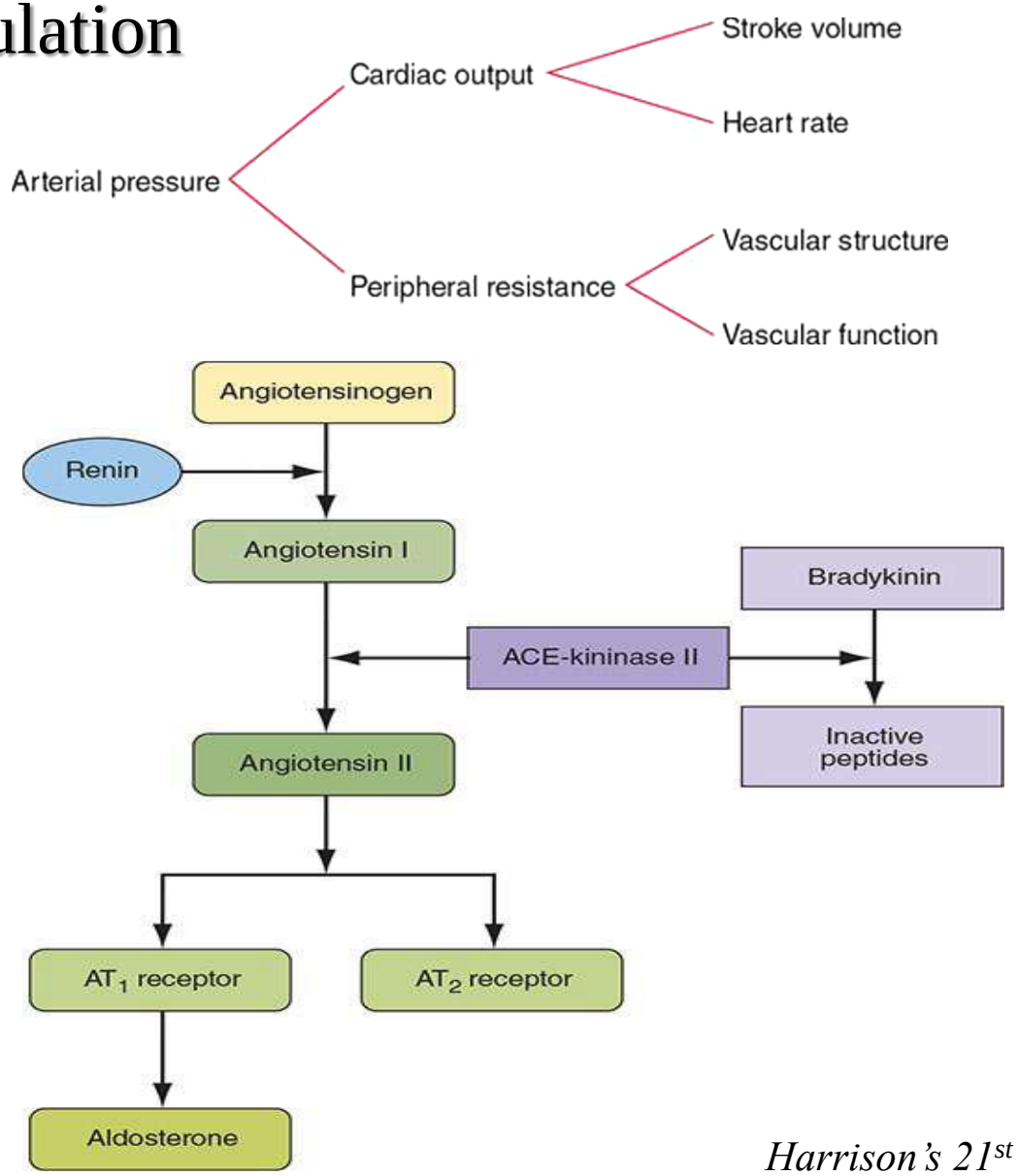




Blood Pressure Regulation

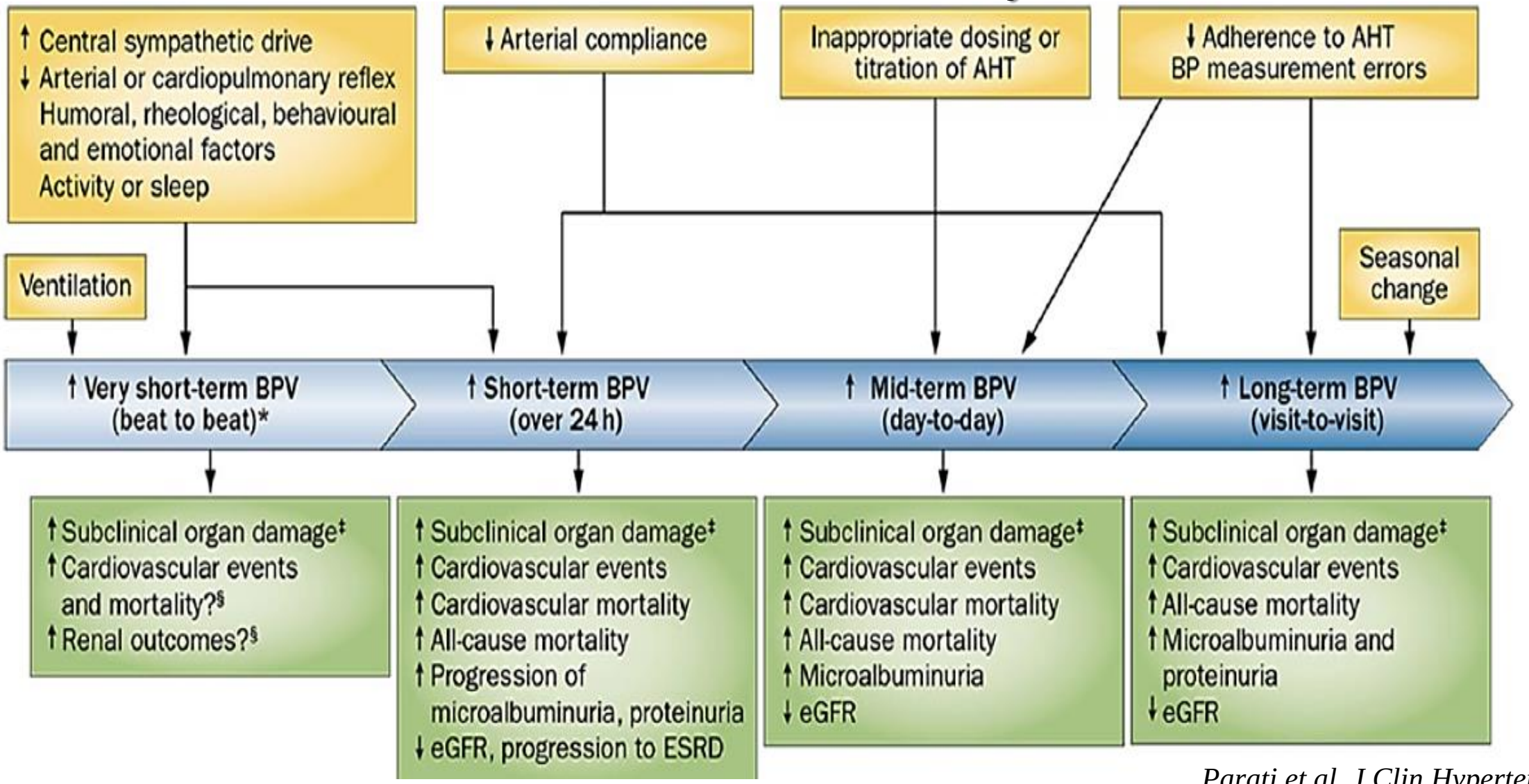


Braunwald's 11th



Harrison's 21st

Blood Pressure Variability



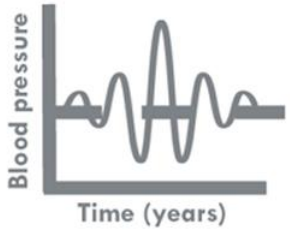
Parati et al. J Clin Hypertens., 2018

BPV and Health Outcomes

Health Outcome	*Findings*	*References*
Neurological and cardiovascular events	Higher systolic BPV represents strong predictor of stroke and vascular events/mortality, independent of mean systolic BP and baseline risk of cardiovascular events	Mehlum et al., 2018; Rothwell et al., 2010b; Tai et al., 2015
Structural heart changes	Left ventricular hypertrophy and systolic dysfunction are cardiac dysfunction typical of aging, associated with higher 24-h BPV	Irigoyen et al., 2016
Structural brain changes	Systolic BPV constitutes contributing factor to lower hippocampal volume, cerebral microbleeds, cortical infarcts and white matter hyperintensities,	Havlik et al., 2002; van Middelaar et al., 2019
Cognitive Impairment and Dementia	Low scores in cognitive tests have been found in older adults with high BPV, which is also related to increased risk of incident dementia. The latter is also increased by orthostatic hypotension and fluctuations in postural systolic BP	Alpérovitch et al., 2014; Ma et al., 2021; Rouch et al., 2020a, 2020b
Metabolic disorders	Systolic BPV accelerates development of pre-diabetes/diabetes in overweight or obese adults	Joshipura et al., 2018
Kidney disease	Subjects with higher systolic BPV show increased micro-albuminuria, progression of kidney disease and renal arteriosclerosis	Kawai et al., 2012
Sarcopenia	CV of systolic BP, rather than average systolic BP, is associated with sarcopenia in older patients with diabetes	Hashimoto et al., 2018
Hip fracture	CV of systolic BP constitutes a predictor of hip fracture in patients aged ≥ 50 years suffering from diabetes; VIM is independently associated with fracture incidence	Li et al., 2019; Yoo et al., 2021
Frailty	Higher visit-to-visit BPV is associated with risk of incident frailty in community dwelling patients aged ≥70 years	Rouch et al., 2021

Bencivenga et al. Ageing Res. Rev., 2022

BPV and Health Outcomes (2)



3319 non-institutionalized patients aged ≥ 65 from the S.AGES cohort

HIGHER visit-to-visit systolic, diastolic, mean arterial pressure VARIABILITY

BP measurements every 6 months for 3 years

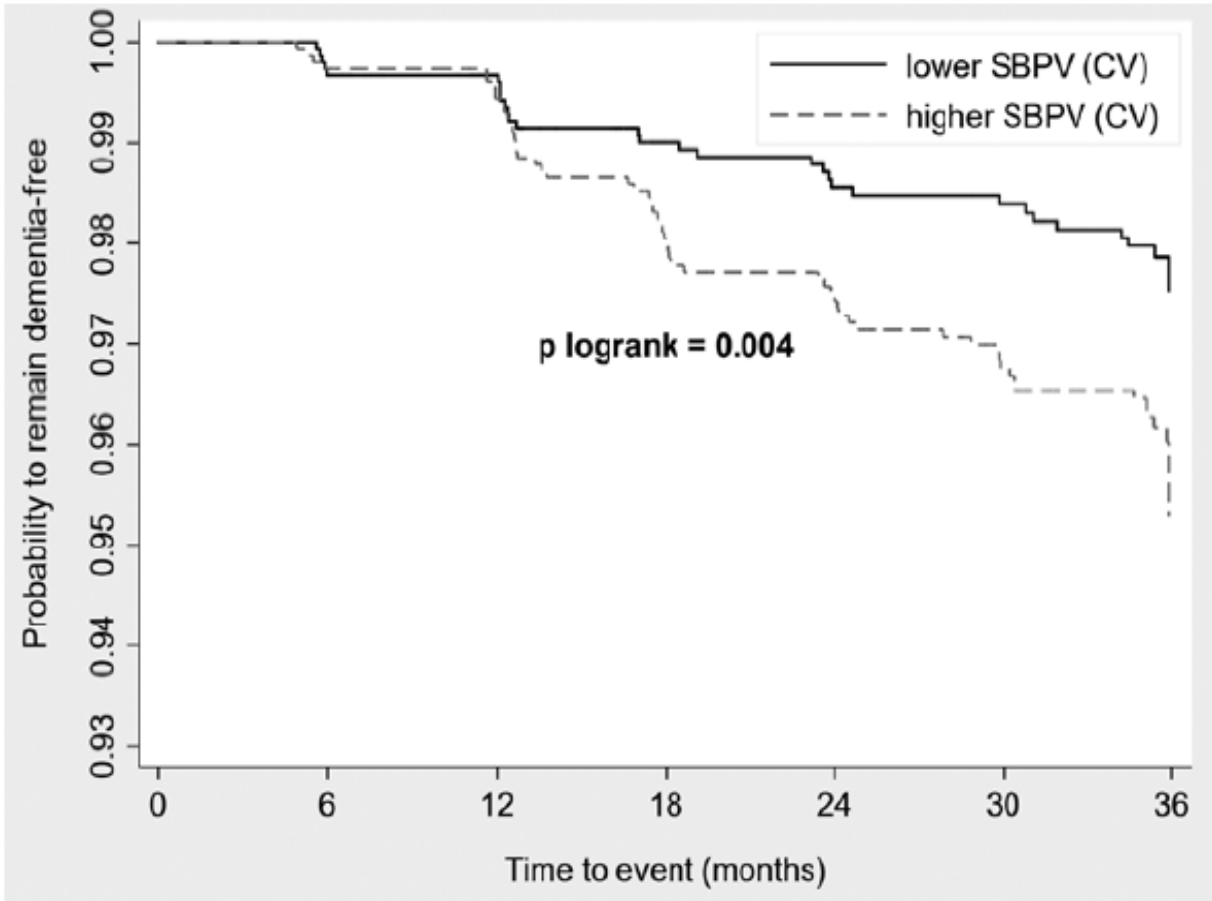
Independently of mean BP levels

POORER cognition (MMSE)

GREATER dementia risk (20-30%)

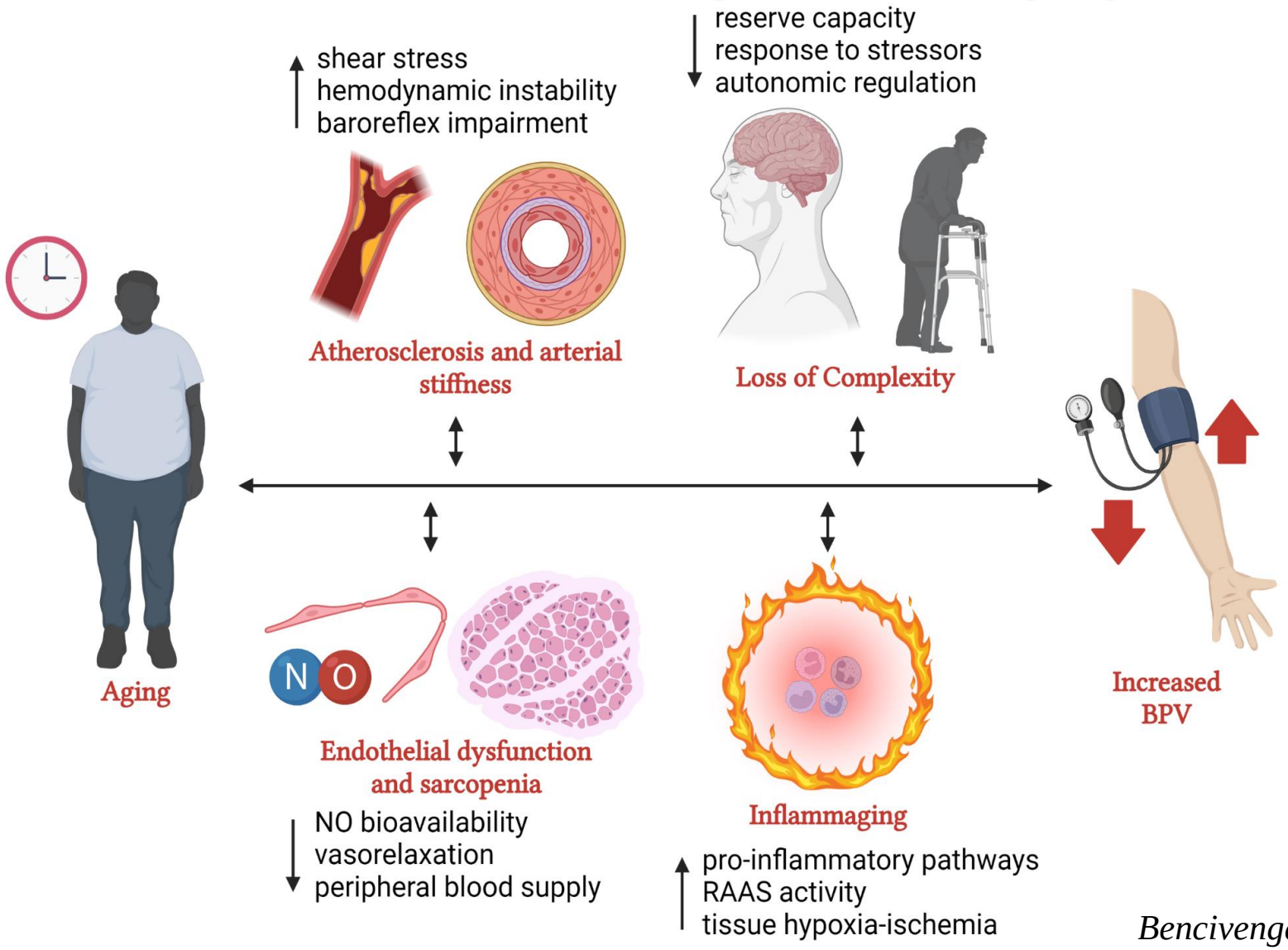
Beyond hypertension, higher BP variability is a major clinical predictor of cognitive impairment and dementia

Further studies are needed to assess whether controlling BP instability could be a promising interventional target in preserving cognition among older adults



Rouch et al. Hypertension, 2020

Mechanisms linking BPV and aging



Bencivenga et al. Ageing Res. Rev., 2022

Guidelines for the management of arterial hypertension

4.10 Blood pressure variability

Old studies on ambulatory intra-arterial BP monitoring have shown that BP is highly variable during the day and to a lesser extent during the night [175,176] due to the interplay between central factors, humoral influences, local vasoactive mechanisms and the buffering influences of the baroreflex [69]. This short-term BP variability was found to be quantitatively related to the BP levels, and thus greater in hypertension than in normotension [176], and to have an adverse effect on the genesis of HMOD [177]. These observations were confirmed by studies with noninvasive ambulatory monitoring, which also showed that 24 h or short-term BP variability is adversely related to the risk of CV outcomes, independently of the 24 h mean BP value [155,167,178,179]. However, although several studies have shown that treatment lowers 24 h BP variability, no study has ever addressed whether a treatment-related reduction of 24 h BP variability attenuates CV risk [155,167,178,179].

A number of studies have also focused on other types of BP variability. Conflicting results have been reported on the prognostic value of within-visit BP variations [180], whereas some studies have reported an association between day-to-day BP variability as assessed by HBPM and the risk of CV outcomes [166,181]. However, the largest body of available evidence relates to what is known as visit-to-visit or long-term BP variability. Post hoc analyses of antihypertensive treatment trials have shown that long-term BP variability such as that measurable as BP differences between visits spaced by 6 or 12 months apart, is associated with CV risk in treated hypertensive patients. In posthoc analyses of three trials, an increase in the number of medical visits in which office BP was reduced to the recommended control value was accompanied by a proportional reduction in the risk of CV outcomes and mortality, independently of the mean office BP reached during the treatment period [182–184]. Furthermore, in trials or treated cohorts of patients with different demographic and clinical characteristics, between-visit office BP variations were found to be associated with the risk of CV and kidney outcomes, also independently of the mean BP values reached during the years of treatment [185–187]. In one study, combined use of on-treatment mean BP and visit-to-visit BP variability identified more accurately the CV risk of treated hypertensive patients than either measure alone [188]. This suggests that in treated patients, protection depends also on time spent under BP control, as more recently confirmed by the relationship between CV events and calculated TTR (time on therapeutic BP range) or BP load (ratio between BP values at BP target and all values during the treatment period) in renal denervated patients and treated diabetic patients, respectively [189,190]. From a practical perspective, this justifies the recommendation to pay attention to consistency of BP control in treated patients, because absence of control at a given visit probably does not represent a fleeting innocent BP elevation but a prolonged period with high BP in the preceding months. Evidence from the ELSA trial shows that an inconsistent BP control is common in treated hypertensive patients [191].

ESH/ERA/ISH Guidelines, 2023

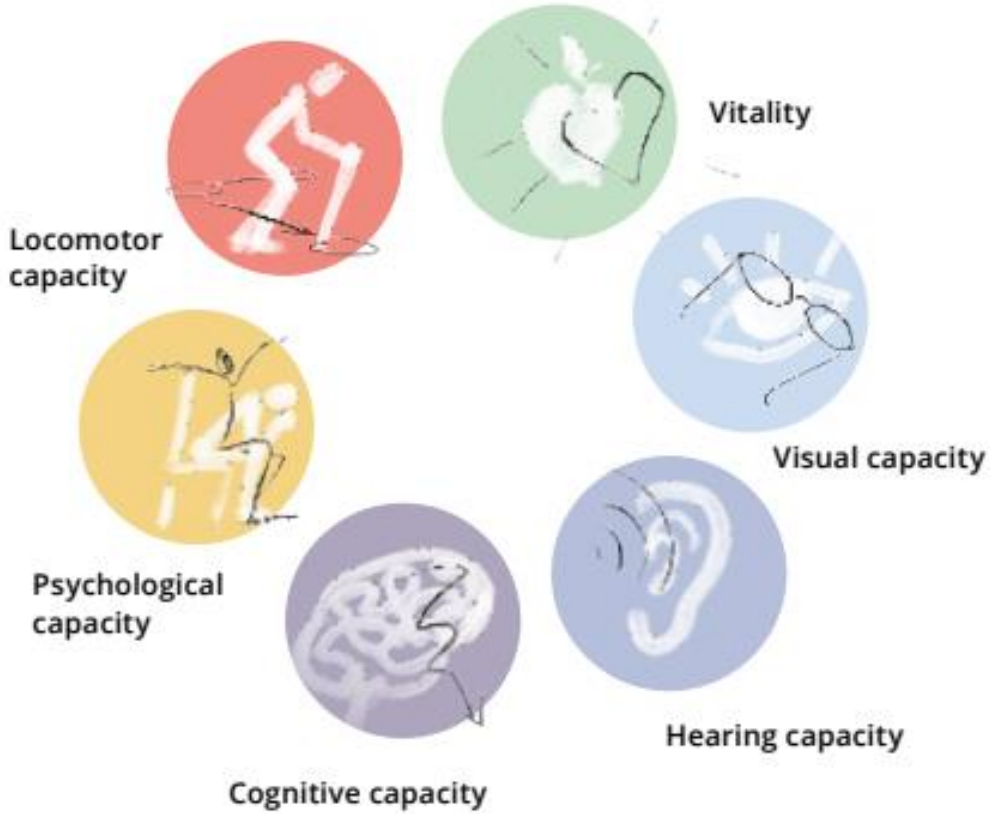
Other BP measures and indices (pulse pressure, BP variability, exercise BP, and central BP) may be considered but are not often used for routine clinical use at present. They may provide useful additional information in some circumstances and are valuable tools for research.	IIb	C

©ESC/ESH 2018

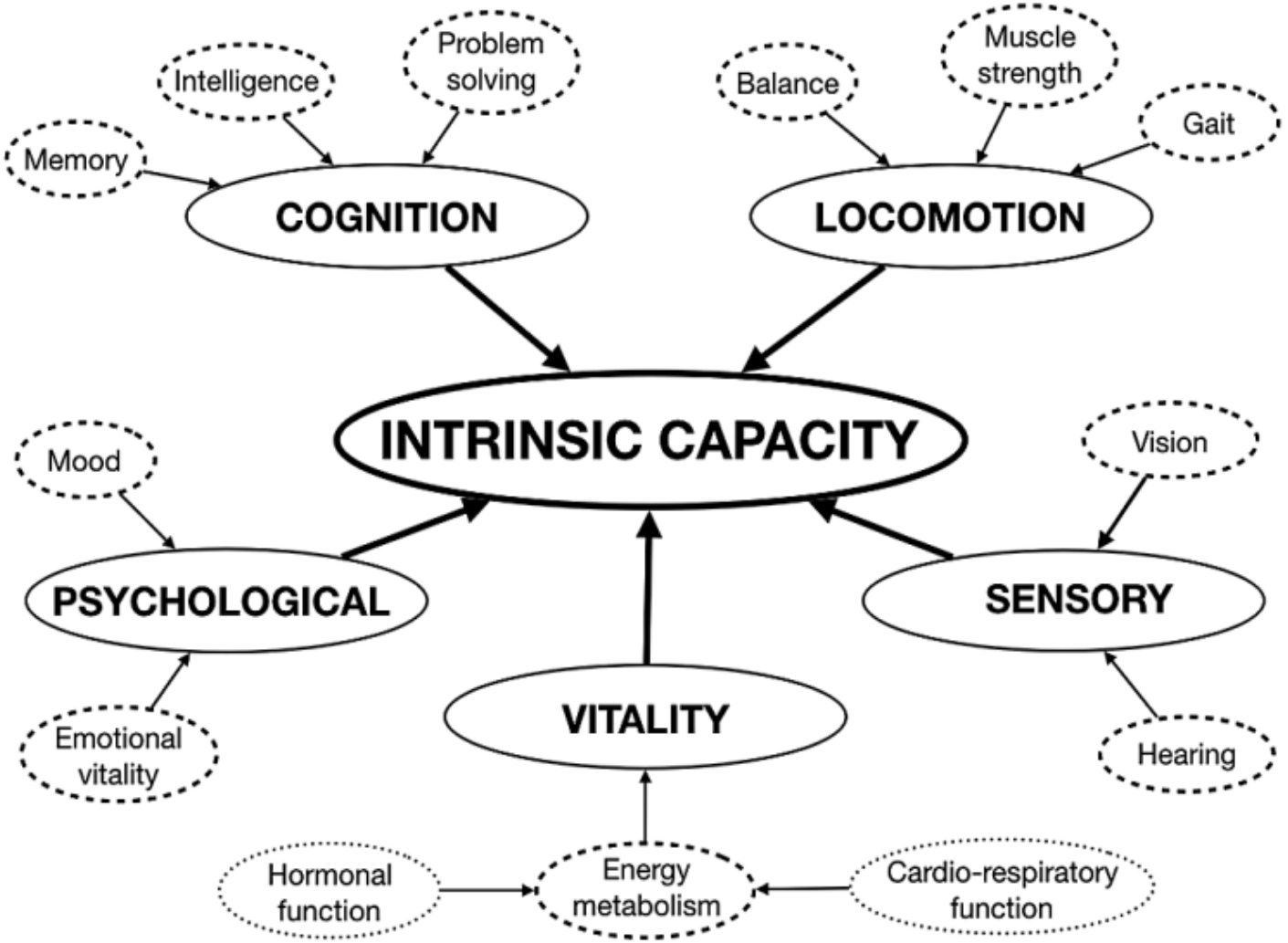
ESC/ESH Guidelines, 2018

Intrinsic capacity

"the composite of all the physical and mental capacities of an individual"



WHO Clinical Consortium on Healthy Ageing 2017



Cesari et al. J Gerontol A Biol Sci Med Sci., 2018

Intrinsic capacity (2)

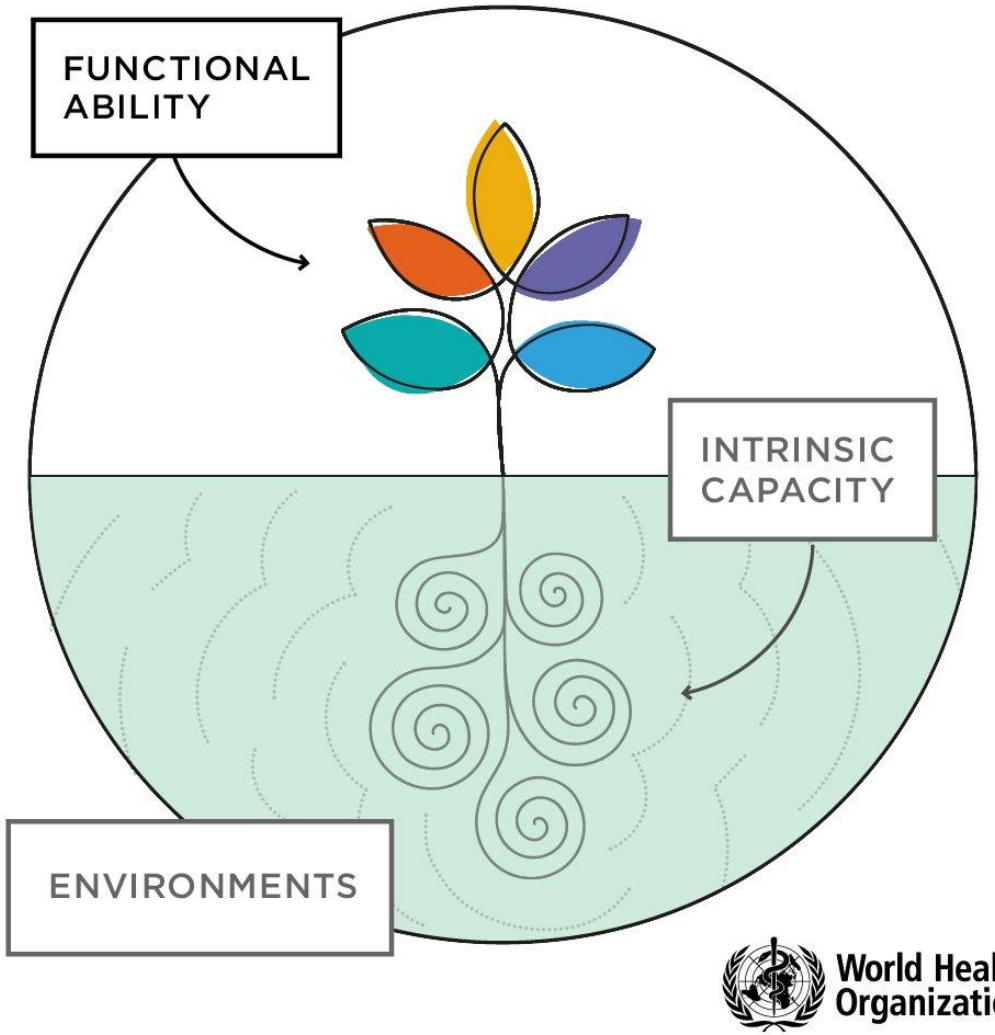


TABLE 2 | Comparison between frailty and intrinsic capacity.

	Frailty	Intrinsic capacity (IC)
Definition	Progressive decline of physiological systems conferring increased vulnerability to stressors and exposing to the risk of adverse health outcomes	Composite of all mental and physical capacities
When	Geriatric condition	After the age corresponding to the median of the local life expectancy at birth
Time dimension	Cross-sectional assessment	Longitudinal assessment for tracking trajectories
Characteristics	Defined by deficits and abnormalities	Defined by reserves and residual capacities
Original purpose	Developed for addressing the unmet clinical needs of the older person	Developed to inform about public health strategies in the promotion of healthy ageing
Interventions	Comprehensive geriatric assessment, possibly within a network of integrated care	Comprehensive intervention based on integration of care and social services

Belloni et al. Frontiers in Medicine, 2019

Hypothesis

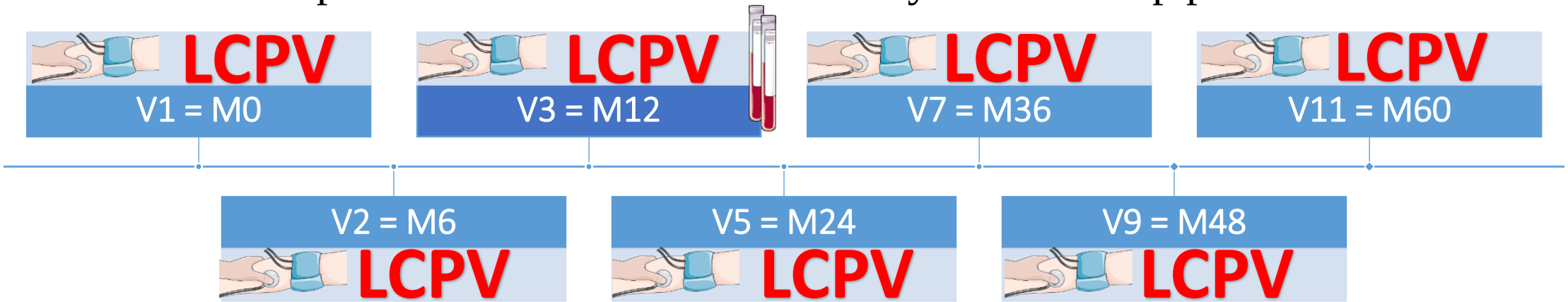
Higher BPV, as plausible epiphenomenon of less successful aging process, is associated with IC decline over time

Study design

Secondary analyses from the Multidomain Alzheimer Preventive Trial (MAPT)

Population

Non-frail community-dwelling volunteers aged ≥70 years
Repeated clinical controls over a 5-year follow-up period



L, Locomotion; C, Cognition; P, Psychology; V, Vitality; S, Sensory

Visit-to-visit BPV parameters

- Standard Deviation: global measure around the mean value, independent of the order $\sqrt{\frac{\sum_{i=1}^{n}(x_i-\bar{x})^2}{(n-1)}}$
- Coefficient of Variation: corrects for correlations between mean levels and SD $100 \times SD/\bar{x}$
- Variation Independent of Mean: SD irrespective of mean BP levels $k \times SD/\bar{x}^m$
- Residual Standard Deviation: takes account of trend over time in order to avoid over-estimation of BPV $\sqrt{\frac{\sum_{i=1}^{n}(x_i-\hat{x}_i)^2}{(n-2)}}$
- Average Real Variability: takes into account the order of individual BP measurements $\frac{1}{n-1}\sum_{i=1}^{n-1}|x_{i+1}-x_i|$
- Successive Variation: similar to ARV, more influenced by discrepancies between successive measurements $\sqrt{\frac{1}{n-1}\sum_{i=1}^{n-1}(x_{i+1}-x_i)^2}$

Rouch L. et al. Hypertension, 2020

Intrinsic Capacity

- **4 domains**, without sensory
- From V0 to V11
- 5 years follow-up
- 7 IC and BP assessments

1. Cognition: MMSE < 25
2. Psychological: GDS > 4
3. Locomotion: SPPB < 10
4. Vitality: handgrip < 27 m, < 16 f

Two outcomes

Global IC performance → IC Z-score

(Unadjusted and multivariable-adjusted linear mixed models to explore the relation with BPV over time)

Incident IC impairment → Incidence of ≥ 1 additional impaired domain than baseline

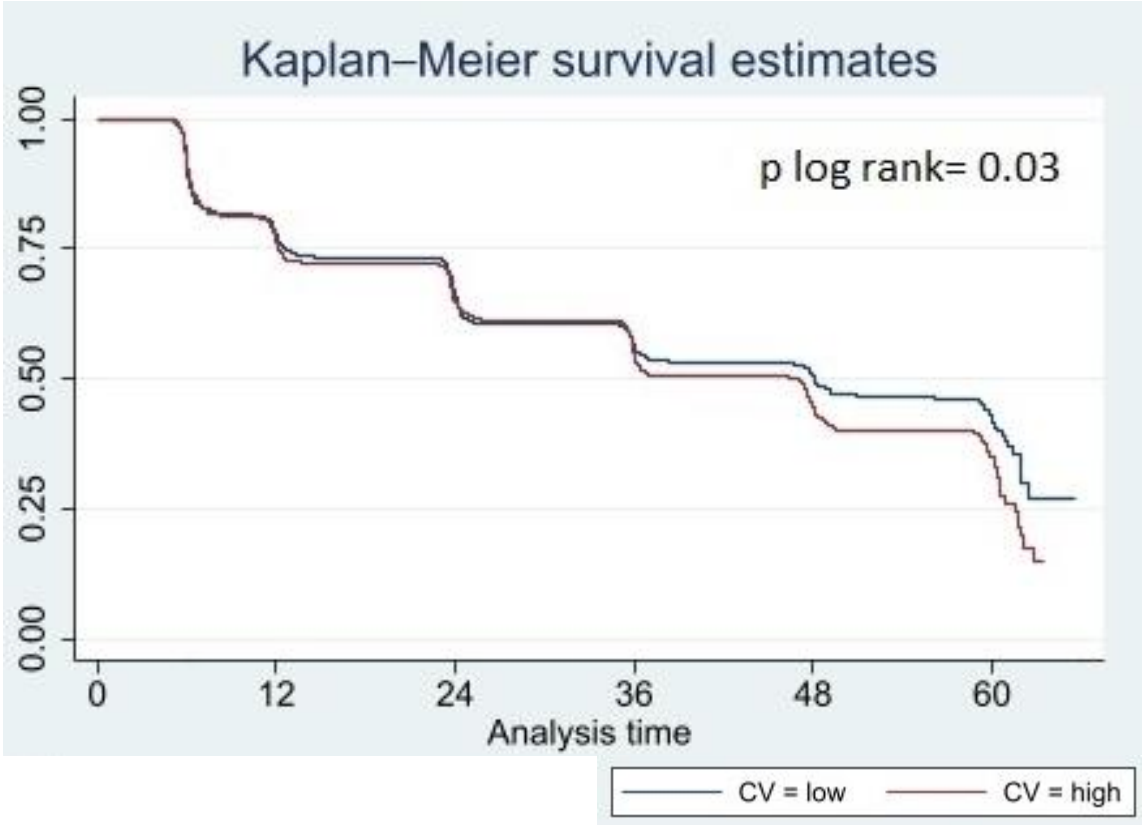
(Survival analisys: Cox proportional hazard models and Kaplan-Meier curves for BPV)

Findings

Over 1400 non frail community dwelling older adults

1. Is BPV associated with IC Z-score decline over time? YES

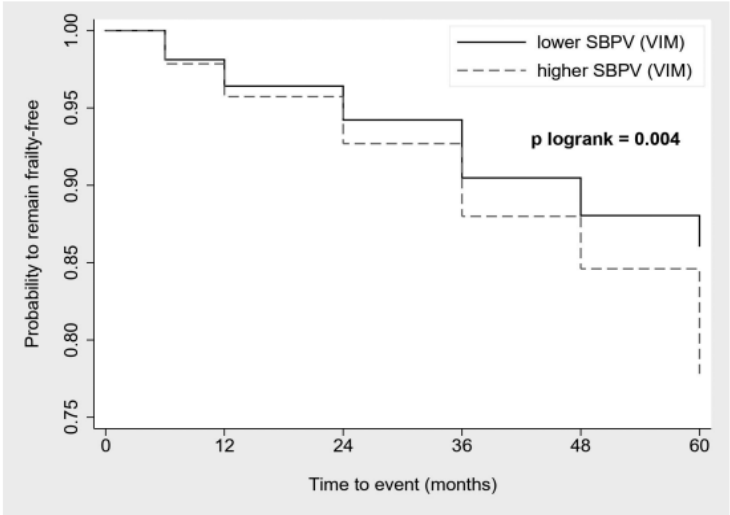
2. Is BPV associated with incidence of additional IC domain impairment? YES

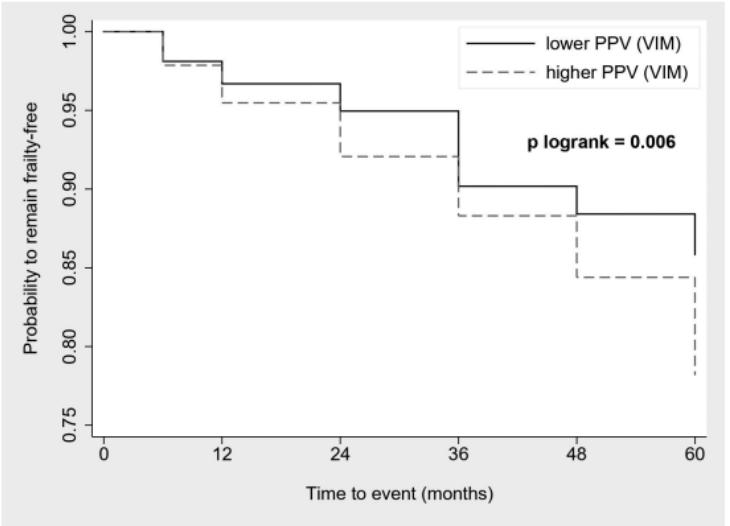


Visit-to-visit BPV and incident frailty in older adults

Visit-to-Visit BPV (per 1-*SD* increase)	Incident Frailty							
	SBP Model				DBP Model			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
SD	1.24 (1.08–1.43)	<.01	1.20 (1.03–1.39)	.02	1.12 (0.97–1.30)	.13	1.06 (0.91–1.22)	.47
CV	1.24 (1.07–1.43)	<.01	1.18 (1.02–1.36)	.03	1.14 (0.98–1.32)	.08	1.04 (0.89–1.20)	.64
VIM	1.23 (1.07–1.42)	<.01	1.17 (1.01–1.35)	.03	1.13 (0.98–1.31)	.10	1.05 (0.90–1.21)	.55
RSD	1.17 (1.02–1.35)	.02	1.12 (0.96–1.31)	.14	1.09 (0.95–1.26)	.22	1.03 (0.89–1.19)	.70
ARV	1.32 (1.15–1.51)	<.001	1.21 (1.05–1.39)	<.01	1.22 (1.06–1.40)	<.01	1.11 (0.97–1.28)	.13
SV	1.27 (1.11–1.46)	<.01	1.19 (1.03–1.37)	.02	1.15 (1.00–1.33)	.05	1.08 (0.93–1.24)	.30

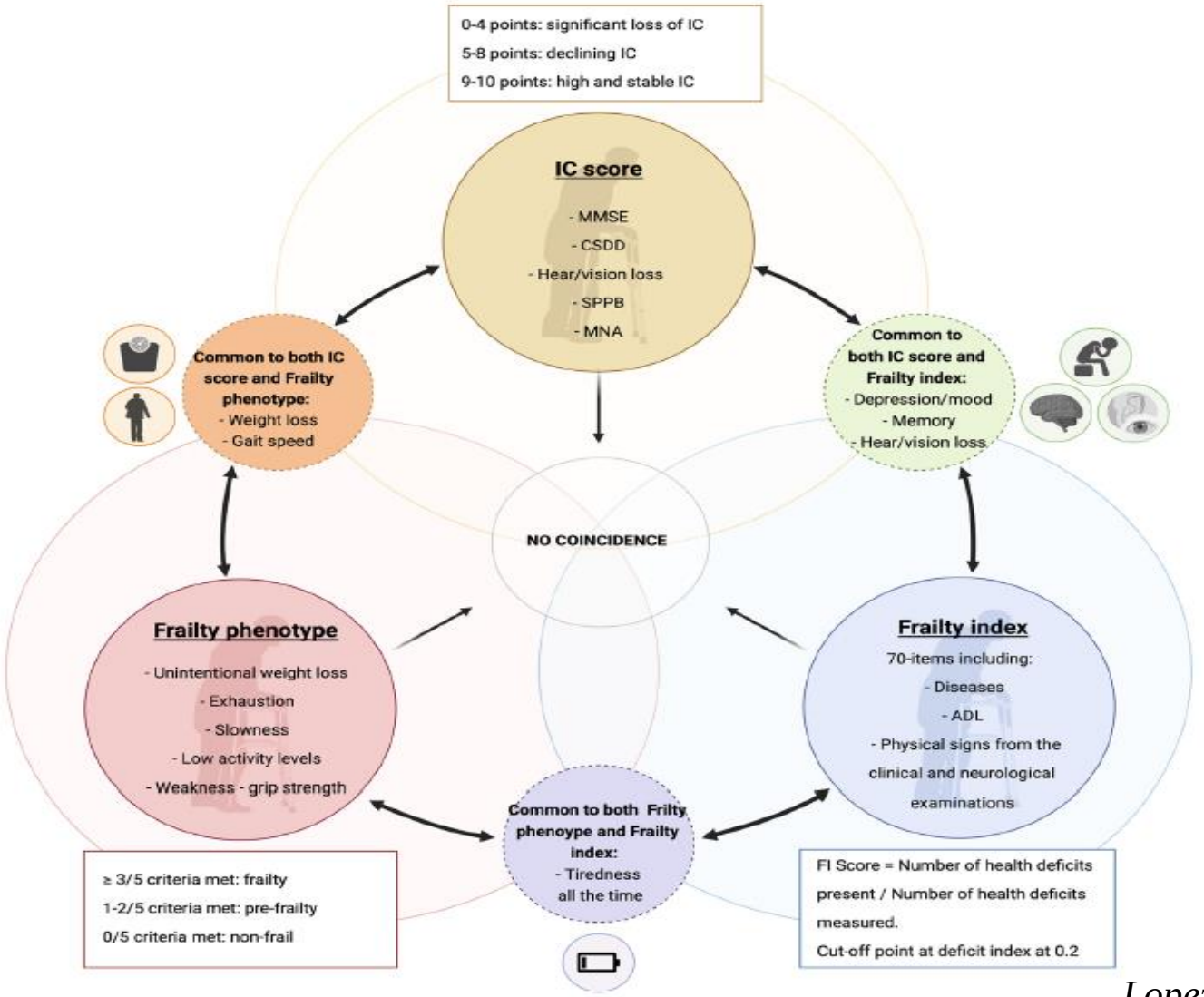
Visit-to-Visit BPV (per 1-*SD* increase)	Incident Frailty							
	MAP Model				PP Model			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
SD	1.16 (1.01–1.34)	.04	1.11 (0.95–1.29)	.18	1.27 (1.10–1.47)	<.01	1.16 (1.00–1.34)	.04
CV	1.16 (1.01–1.35)	.04	1.09 (0.94–1.26)	.27	1.24 (1.07–1.43)	<.01	1.17 (1.01–1.35)	.03
VIM	1.16 (1.01–1.34)	.04	1.08 (0.93–1.26)	.28	1.26 (1.09–1.46)	<.01	1.17 (1.01–1.35)	.03
RSD	1.11 (0.97–1.28)	.13	1.07 (0.93–1.24)	.34	1.27 (1.11–1.44)	<.001	1.16 (0.99–1.35)	.06
ARV	1.29 (1.12–1.48)	<.001	1.18 (1.02–1.36)	.02	1.28 (1.12–1.47)	<.001	1.17 (1.01–1.34)	.03
SV	1.20 (1.05–1.39)	<.01	1.13 (0.98–1.30)	.10	1.26 (1.10–1.45)	<.01	1.16 (1.00–1.34)	.04





Rouch et al ,J Gerontol A Bio Sci Med Sci., 2021

Intrinsic capacity vs. frailty



Lopez-Ortiz et al.Ageing Res Rev., 2022

Intrinsic capacity vs. frailty (2)

	Intrinsic capacity	Frailty	Physical resilience
Concept	A composite of all mental and physical capacities.	A clinical syndrome that reflects a state of increased vulnerability to multiple adverse outcomes.	An ability to recover from physically or psychologically traumatic events.
Characteristic	Positive attributes	Negative effects	Positive attributes
Context	Healthy aging	Opposite of successful aging	Successful aging
Trajectory	Throughout the lifespan	Later phase of life during the downhill trajectory before disability occurs	Throughout the lifespan but a response after external stressors
Indicators/ Measurement Approaches	**Mobility:** balance, chair stand, gait speed **Cognition:** time orientation, three-word recall **Vitality:** grip strength, BMI **Psychological:** low energy/fatigue, depression **Sensory:** vision, hearing	**Biological factors:** individual factors, nutrition, medical conditions, physical abilities **Psychological factors:** cognition, depression, emotional regulation, motivation, stress appraisal **Social factors:** community, social status, social connections, family/friend support	**Phenotypes:** frailty, robustness, fatigability **Age discrepancy:** biological vs. chronological age **Trajectory:** after prior or experimental stressors

Abbreviations: BMI, body mass index.

Yaru Zhou et al. Aging and Disease, 2022

ORIGINAL ARTICLE

Biomarkers of mitochondrial dysfunction and inflammaging in older adults and blood pressure variability

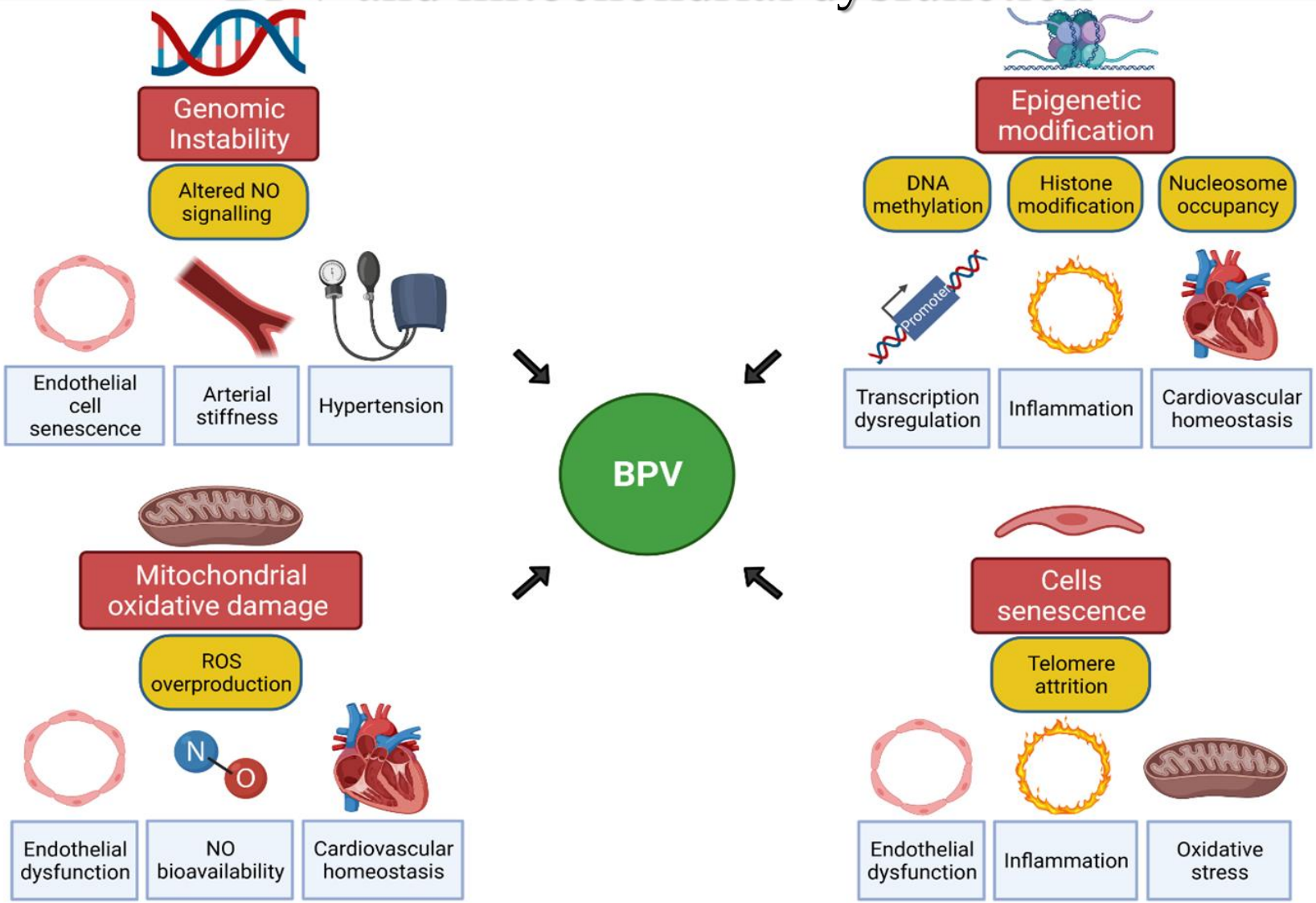
Leonardo Bencivenga · Mathilde Strumia · Yves Rolland · Laurent Martinez · Philippe Cestac · Sophie Guyonnet · Sandrine Andrieu · Angelo Parini · Alexandre Lucas · Bruno Vellas · Philipe De Souto Barreto · Laure Rouch · for the MAPT/D. S. A. group

Higher values of GDF-15 are significantly associated with increased SBPV.

Visit-to-visit BPV over a 4-year period	*SBPV*				*DBPV*			
	Unadjusted		*Adjusted*		*Unadjusted*		*Adjusted*	
	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
SD	0.11 (0.03)	<0.001	0.07 (0.03)	0.03	0.04 (0.03)	0.12	-0.00 (0.03)	0.88
CV%	0.09 (0.03)	<0.01	0.07 (0.03)	0.04	0.05 (0.03)	0.06	-0.00 (0.03)	0.98
VIM	0.08 (0.03)	<0.01	0.07 (0.03)	0.04	0.05 (0.03)	0.08	-0.00 (0.03)	0.93
RSD	0.14 (0.03)	<0.001	0.10 (0.03)	<0.01	0.08 (0.03)	<0.01	0.01 (0.03)	0.59
ARV	0.10 (0.03)	<0.001	0.07 (0.03)	0.02	0.03 (0.03)	0.22	-0.01 (0.03)	0.66
SV	0.09 (0.03)	<0.001	0.07 (0.03)	0.04	0.04 (0.03)	0.18	-0.00 (0.03)	0.95

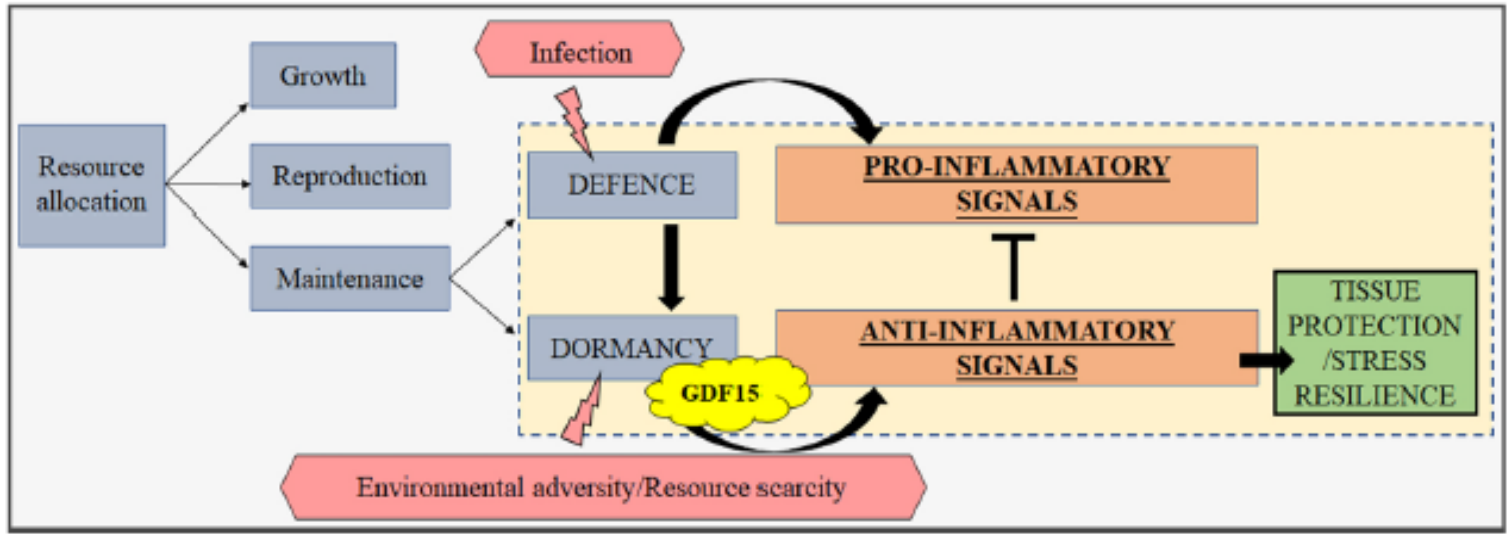
Bencivenga et al. Geroscience, 2022

BPV and mitochondrial dysfunction



Bencivenga et al. Ageing Res. Rev., 2022

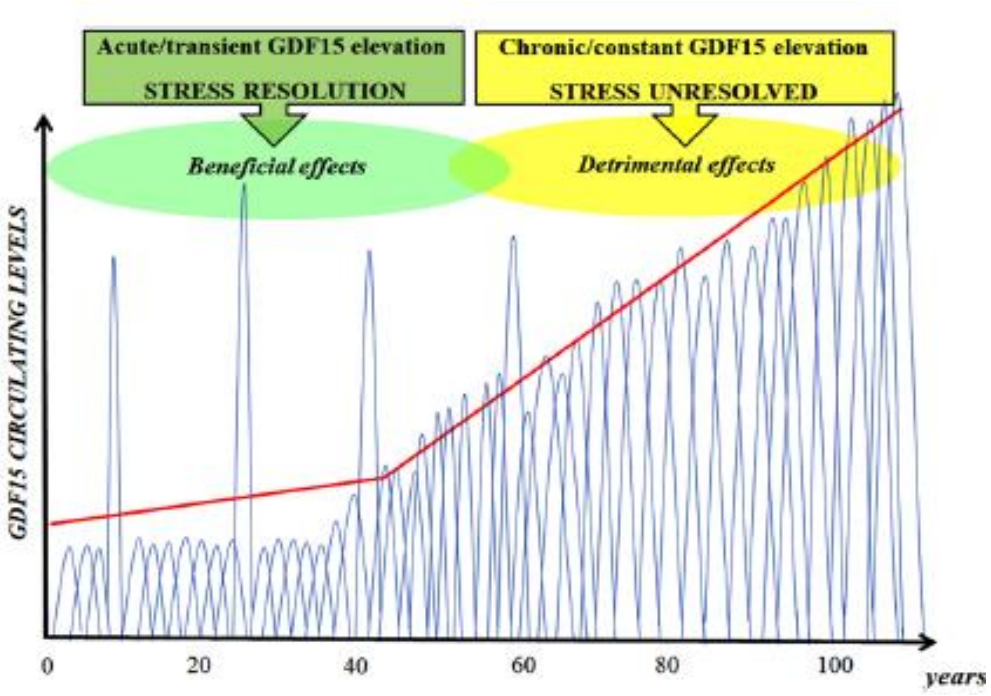
BPV as "early" marker of IC decline, preceding frailty



"mitochondrial dysfunction" is an antagonistic hallmark: opposite activity depending on intensity and duration

BPV, as epiphenomenon of the homeostatic alterations, may anticipate the onset of systemic reactions such as inflammation

BPV can contribute to the decline of global functions, anticipating frailty in older healthy people



Conte et al. Ageing Res. Rev., 2022

Strengths

Association between a clinical variable and a measure of global function

Over 1400 community dwelling older adults

5-year follow-up period (up to 7 visit-to-visit measurements to BPV)

IC assessed through 2 complementary scores

6 different BPV parameters

Limits

Secondary analysis from MAPT

No data on specific antihypertensive drugs

Non frail population as inclusion criteria

No assesment of sensory domain