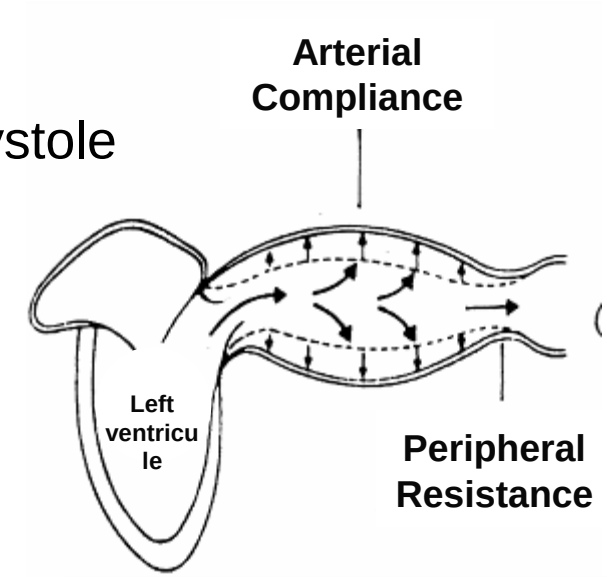
Pharmacologie spatiale: to the summit and beyond!

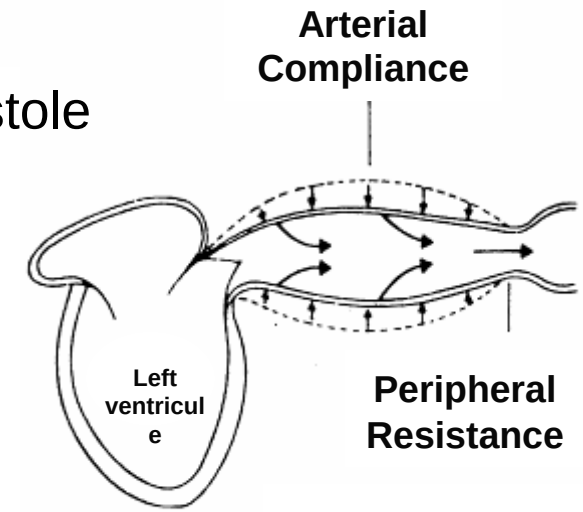
- Pr Pierre BOUTOUYRIE
- Université de Paris
- Hôpital Européen Georges Pompidou, APHP,
- INSERM U970, Paris, France

ARTERIAL STIFFNESS

Systole



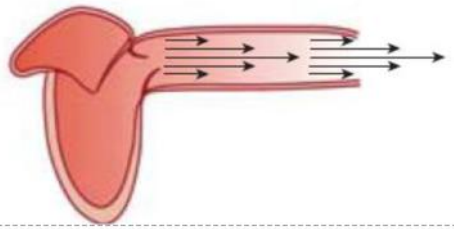
Diastole



Optimal stiffness of the aorta

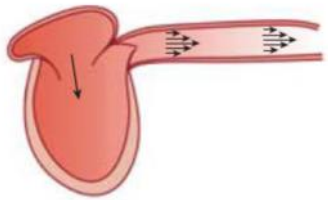
- Diastolic relay of heart contraction
- Limits pressure rise during systole
- Limits diastolic pressure decay
- Improves coronary (diastolic) perfiusion
- Limits peripheral pulsatility

Stiff arteries

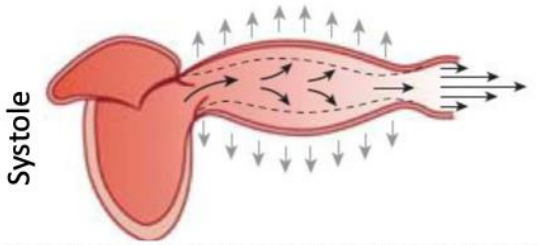


↗ systolic/pulse pressure

↘ diastolic flow

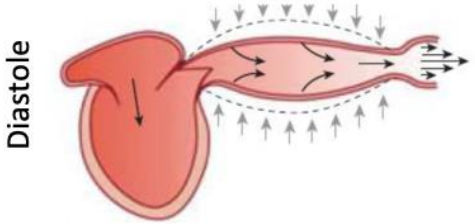


Elastic arteries



↘ systolic/pulse pressure

↗ diastolic flow



Arterial stiffness as a proxy of vascular aging

Easy to measure CV risk factors

- gender
- blood pressure
- lipids
- smoking
- diabetes …

Difficult to measure CV risk factors

- chronic low grade inflamm
- oxidative stress
- Autonomic ner
- DNA dam
- telo ning
- eight
- tics, epigenetics
- etal programming……

own CV risk actors

?

Closely correlated with cardiovascular events and death

al stiffness (cfPWV) is an lifetime integrator of risk factors

$$Stif = \int_{Birth}^{death} f(RF1, RF2 \ldots FR\infty)$$

Laurent S et al.. ATVB 1994, Hypertension 1994, Hypertension 2005, Hypertension 2012, Circ Res 2015

SUPERNOVA and EVA

SUPERNOVA

Robert Marchand, 1911-2021
« I am aged, not old! »

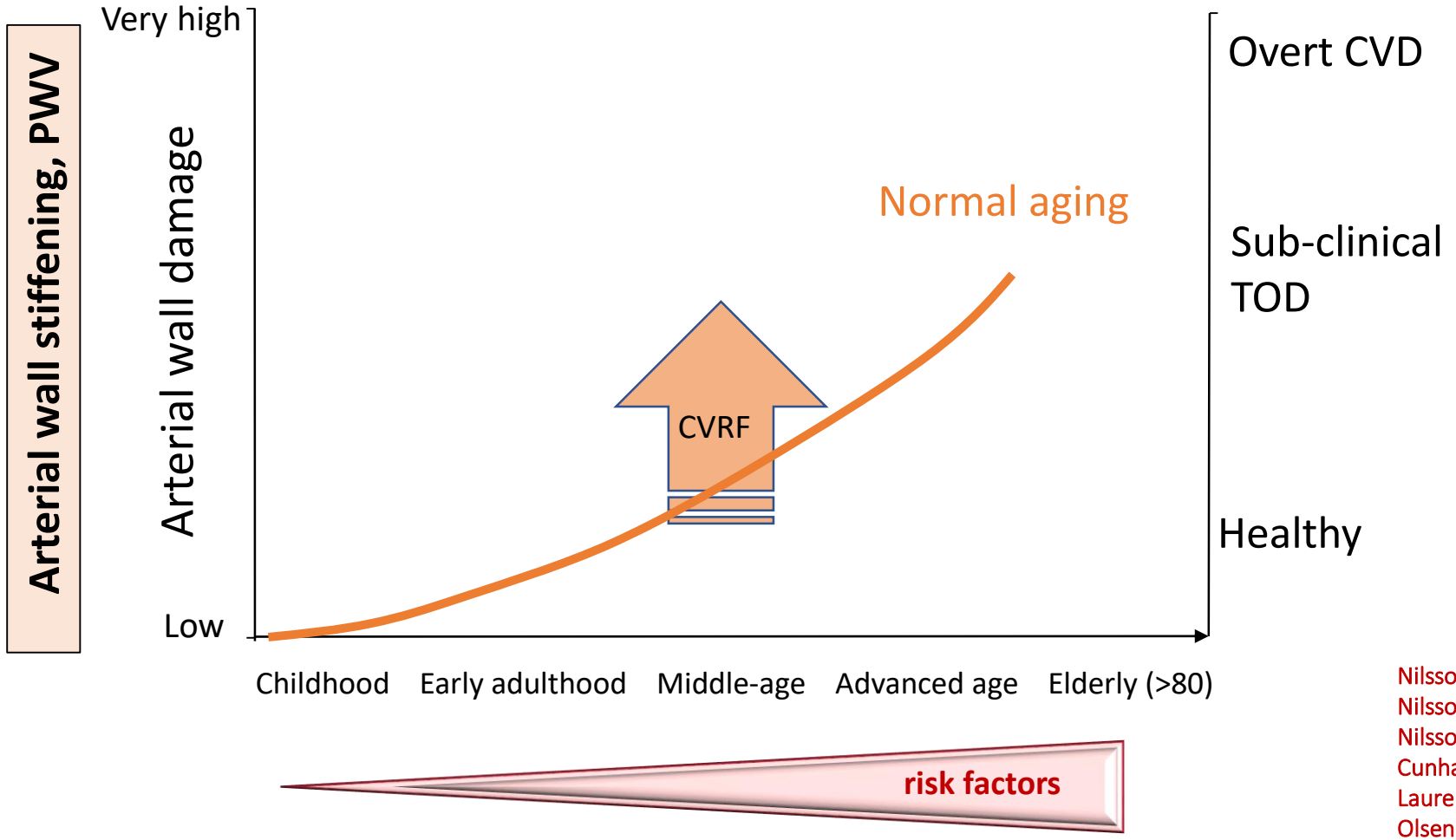
Established 1h record over 100 y (32,5 km)
over 105 y (22,8 km)

EVA

David Bowman
accelerated aging and rebirth
2001 a Space Odyssey, HG Clarkes, S Kubrick

EVA - Early Vascular Ageing

SUPERNOVA-supernormal vascular ageing



Nilsson P et al. J Hypertens 2008
Nilsson P et al. Hypertension 2009
Nilsson P et al. J Hypertens 2013
Cunha P et al. Curr Hypertens Rev 2017
Laurent S et al. Hypertension 2019
Olsen et al, Lancet 2016

EVA - Early Vascular Ageing

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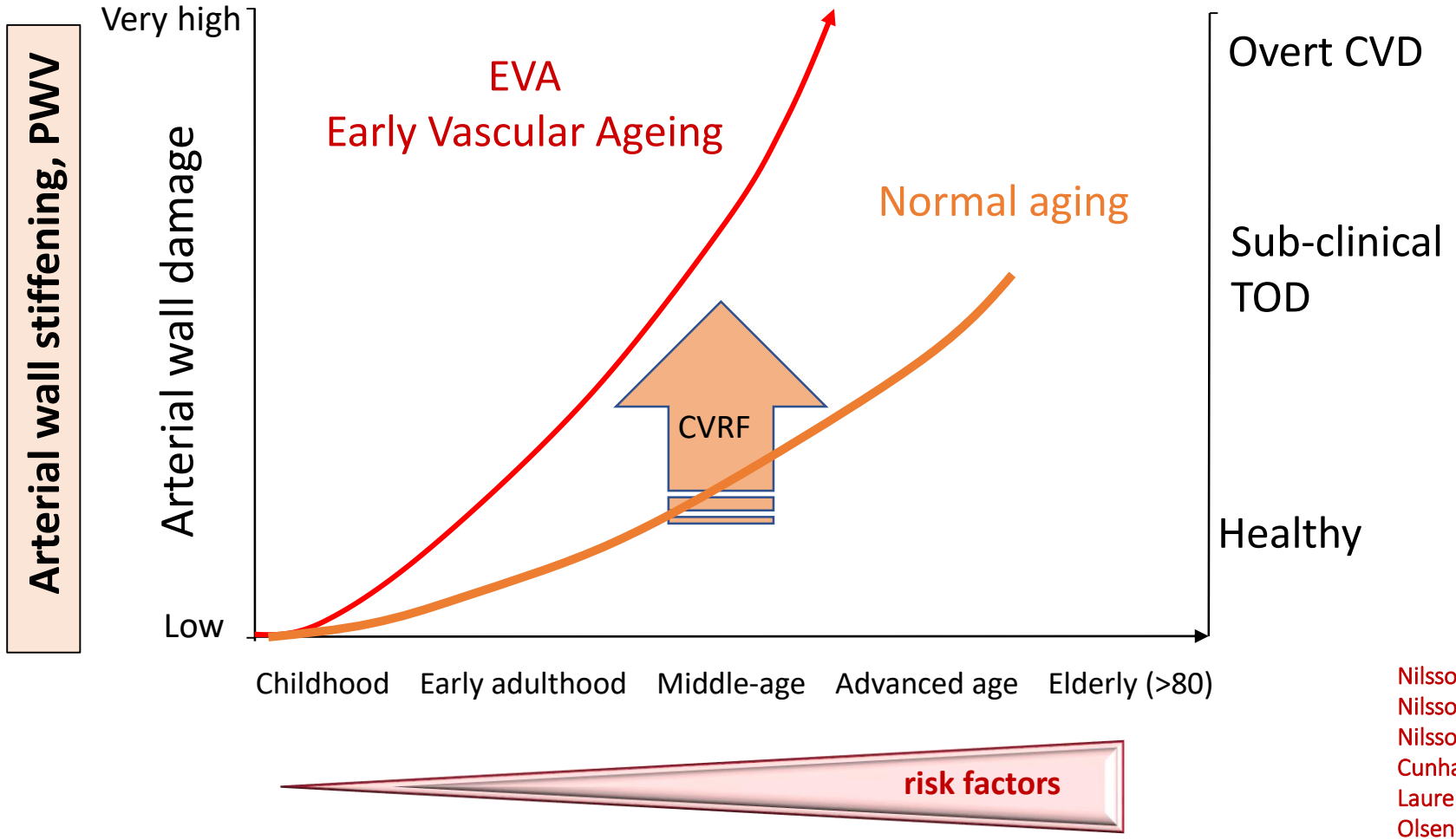

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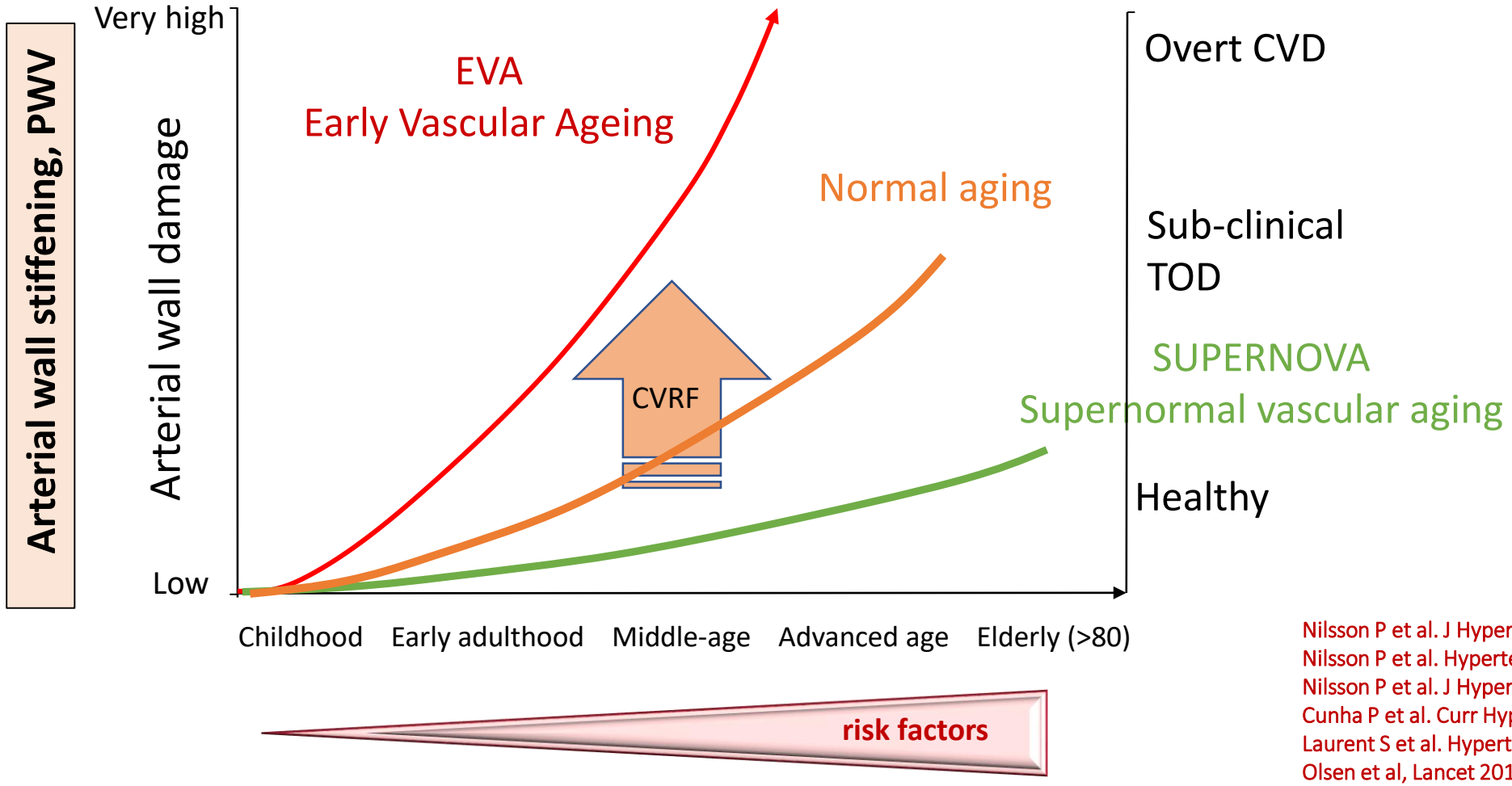

Nilsson P et al. J Hypertens 2008
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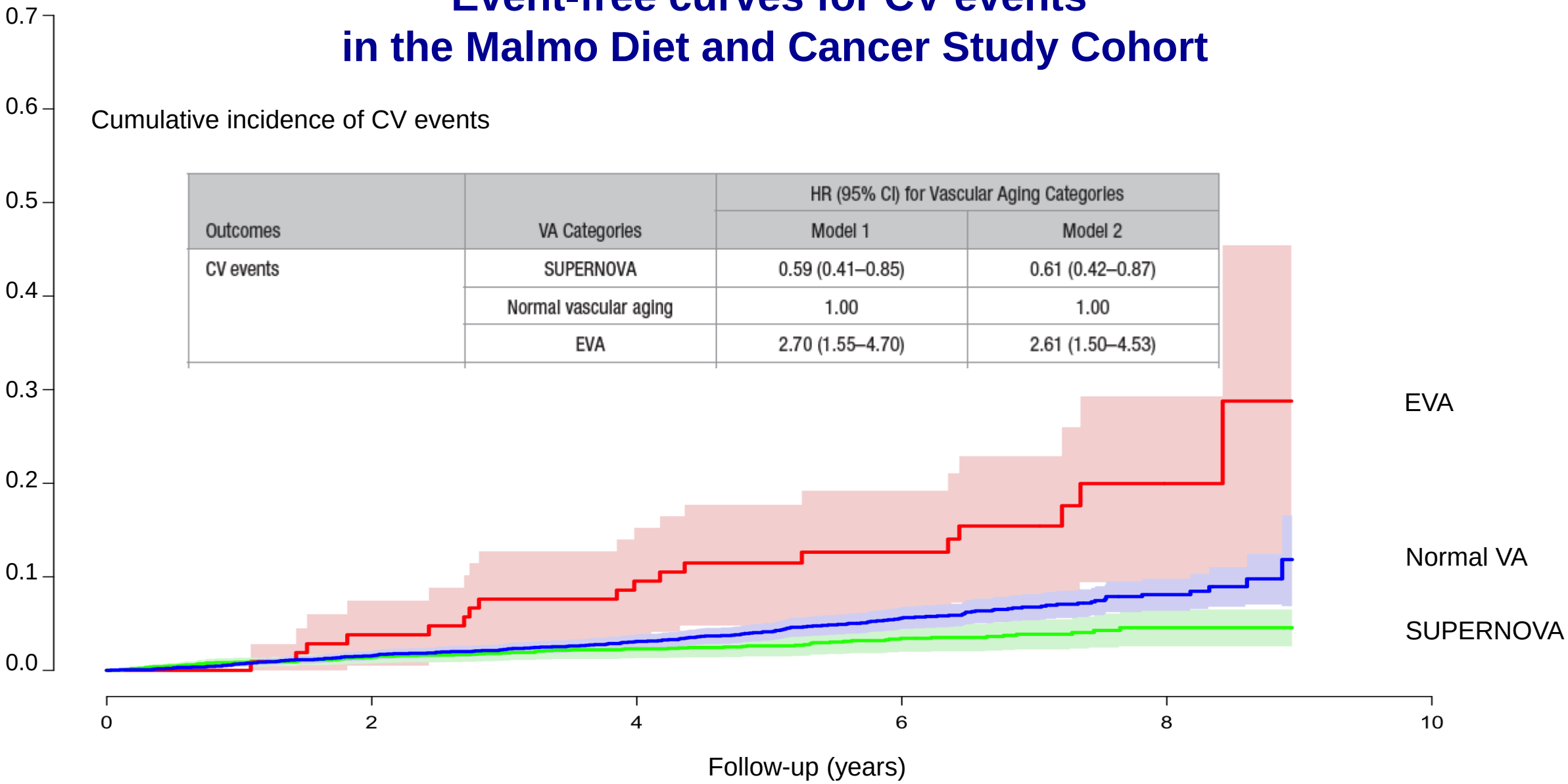
Nilsson P et al. J Hypertens 2013
Cunha P et al. Curr Hypertens Rev 2017
Laurent S et al. Hypertension 2019
Olsen et al, Lancet 2016

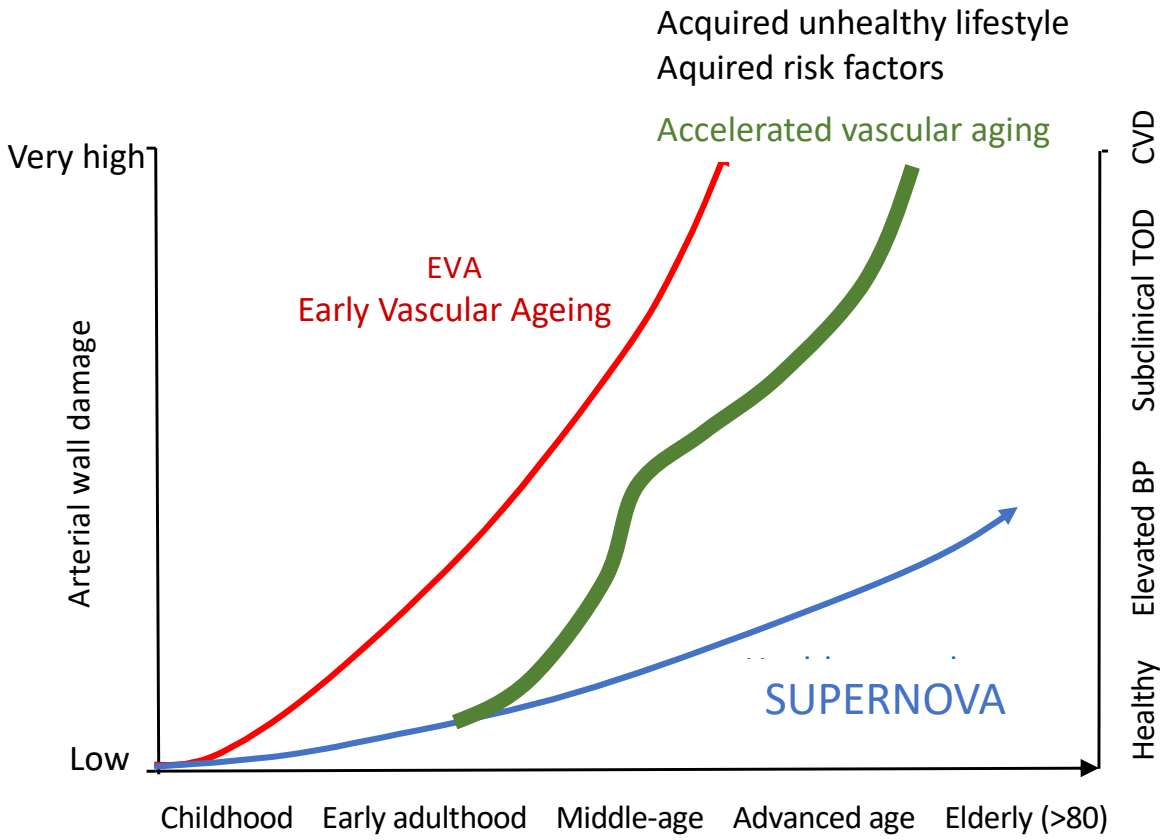
Event-free curves for CV events in the Malmo Diet and Cancer Study Cohort

Outcomes	VA Categories	HR (95% CI) for Vascular Aging Categories	
		Model 1	Model 2
CV events	SUPERNOVA	0.59 (0.41–0.85)	0.61 (0.42–0.87)
	Normal vascular aging	1.00	1.00
	EVA	2.70 (1.55–4.70)	2.61 (1.50–4.53)

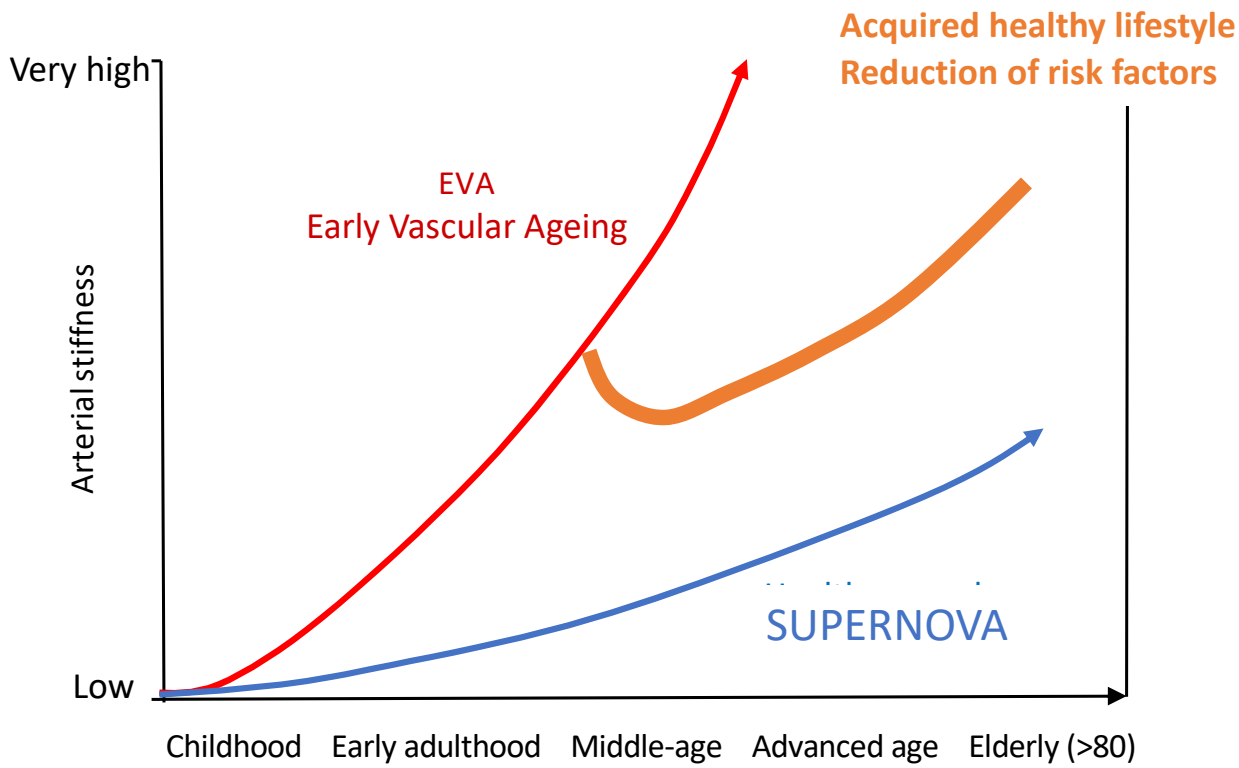


Bruno et al, Hypertension 2021

Progression of EVA



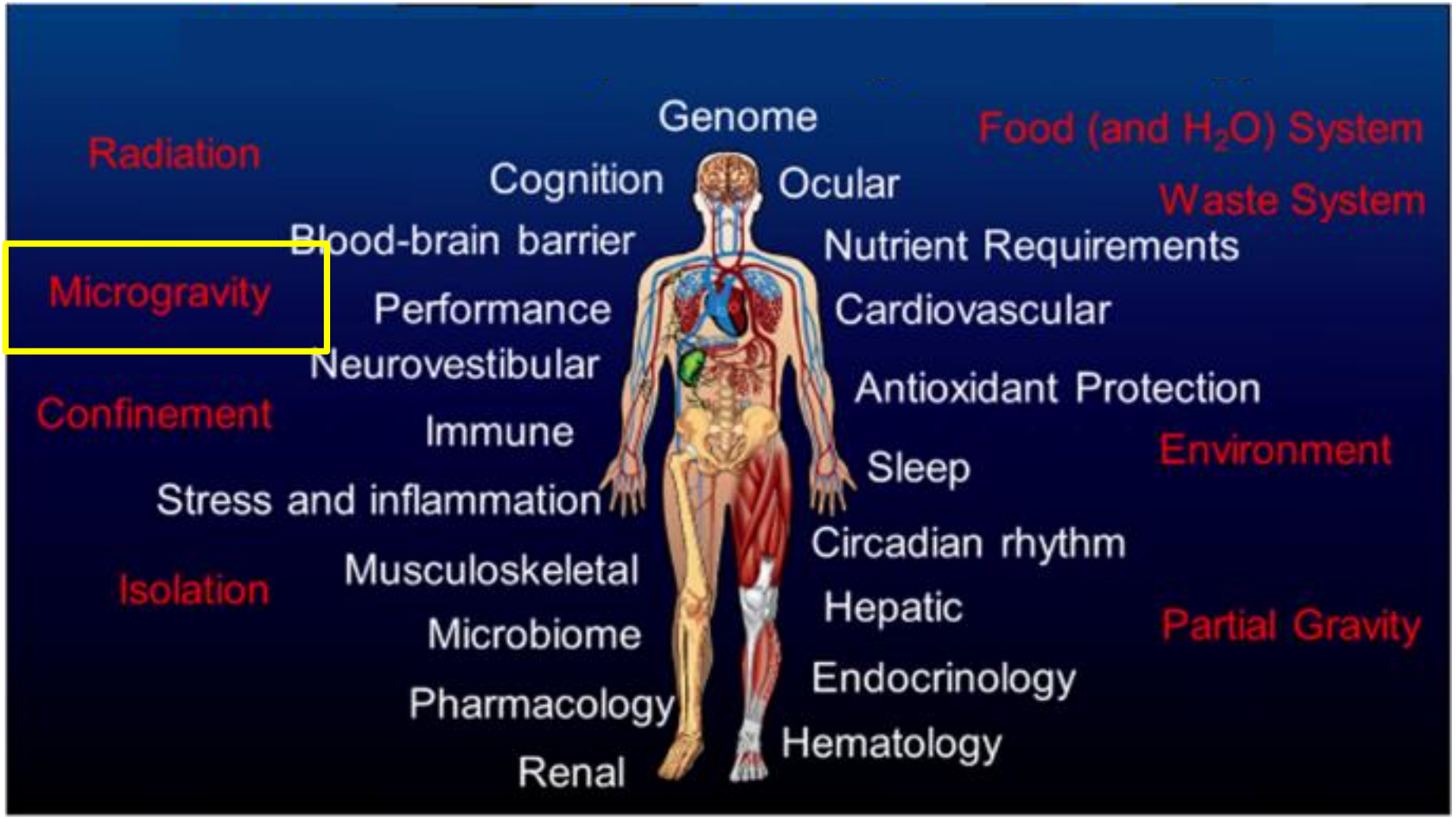
Reversibility of EVA



Nilsson P et al. Hypertension 2009

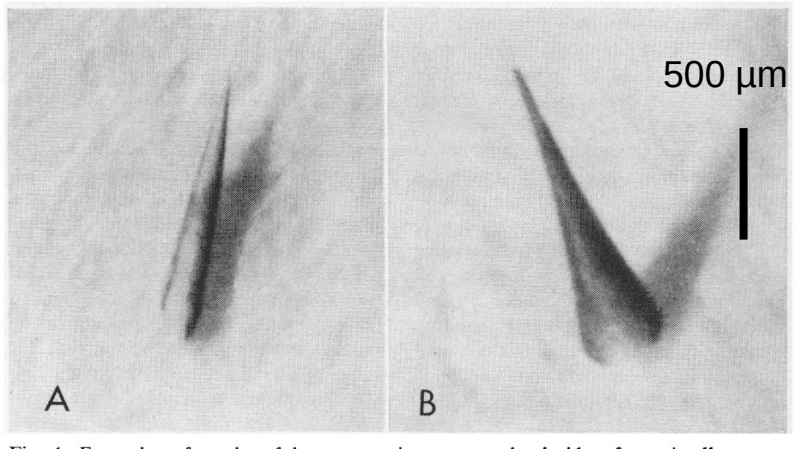

Context
Spaceligths,
Microgravity and early
cardiovascular aging
Space pharmacology
challenges
PK/PD studies in space
Pharmacological
countermeasures

Health hazards during spaceflight



Patel et al, Microgravity 2020

Effects of cosmic high energy radiations on the brain



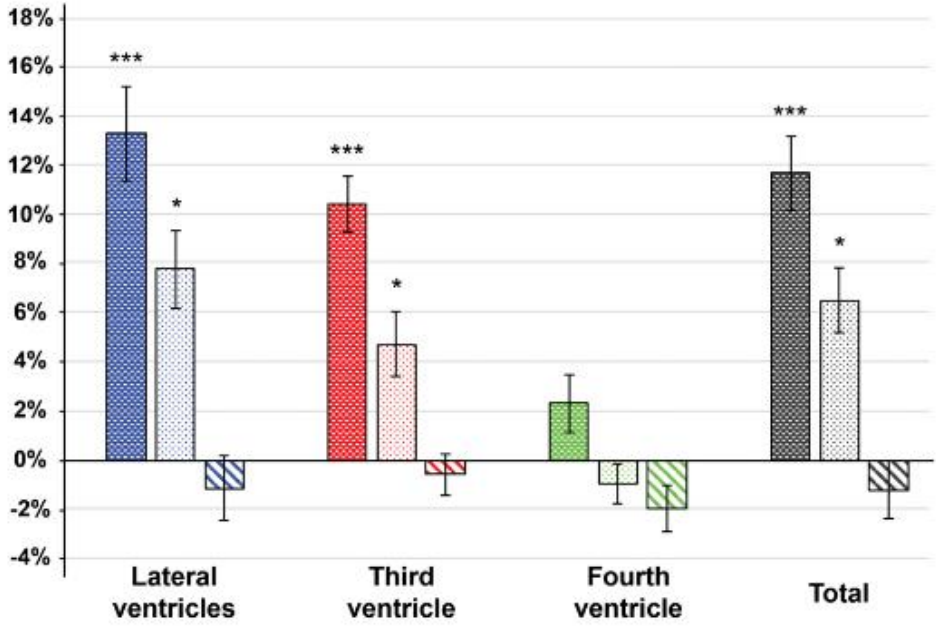
Entry hole Exit hole

Table 2. Estimates of cell loss fractions for Apollo 12 flight and hypothetical 2-year flight.

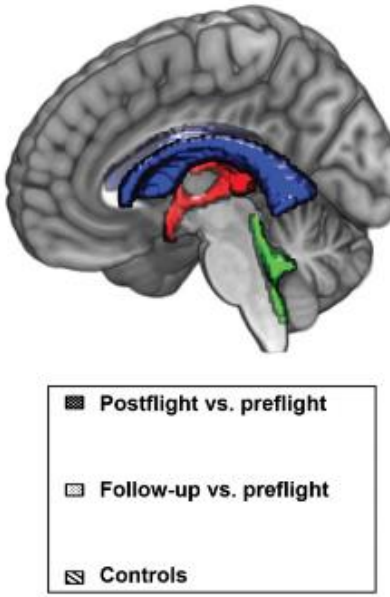
Cells	Cell diameter (µm)	Nuclear diameter (µm)	Fraction lost (parts per million)	
			Apollo 12 flight	2-Year flight*
Granular layer cerebellum	4	3.6	0.50–0.65	40–50
Light receptors	6 × 20	4	0.64–5.7	50–500
Cerebrum	19	4	2–14	16–120
Giant Betz	45	18	13–83	1,050–6,600
Anterior horn	70	25	26–200	2,000–16,000

* The flux was assumed to be the same as during the Apollo 12 flight.

Comstock et al, Science 1971

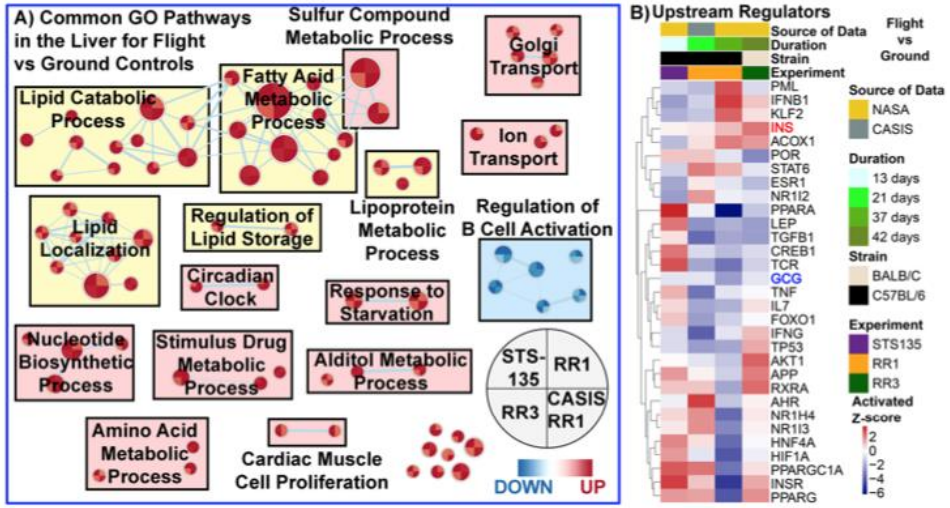


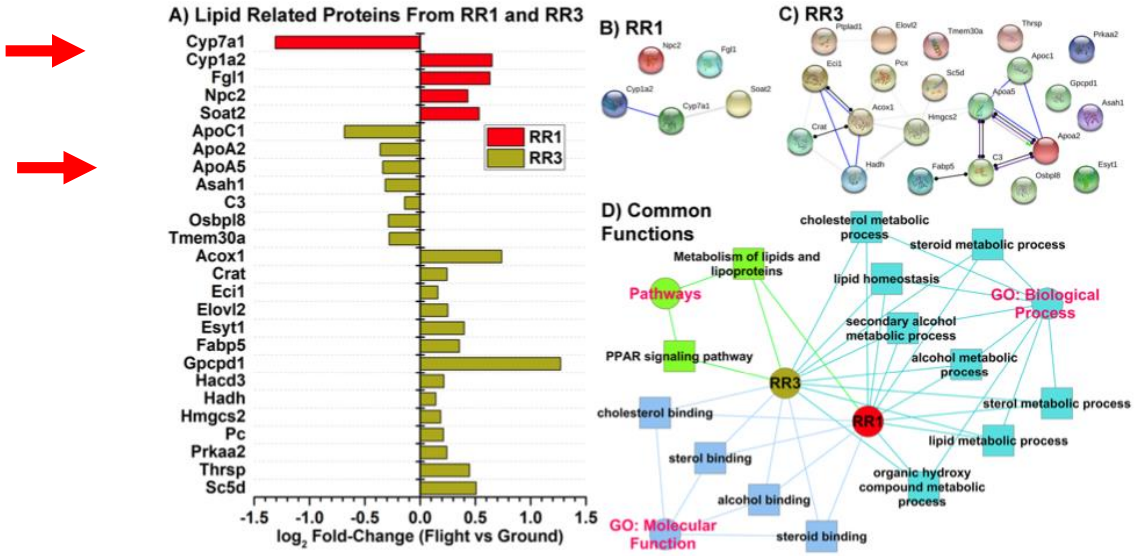
Van Ombergen 2021



Liver function of long-term spaceflight in mice

Multiomic approach
Mice flying 11 to 40 days

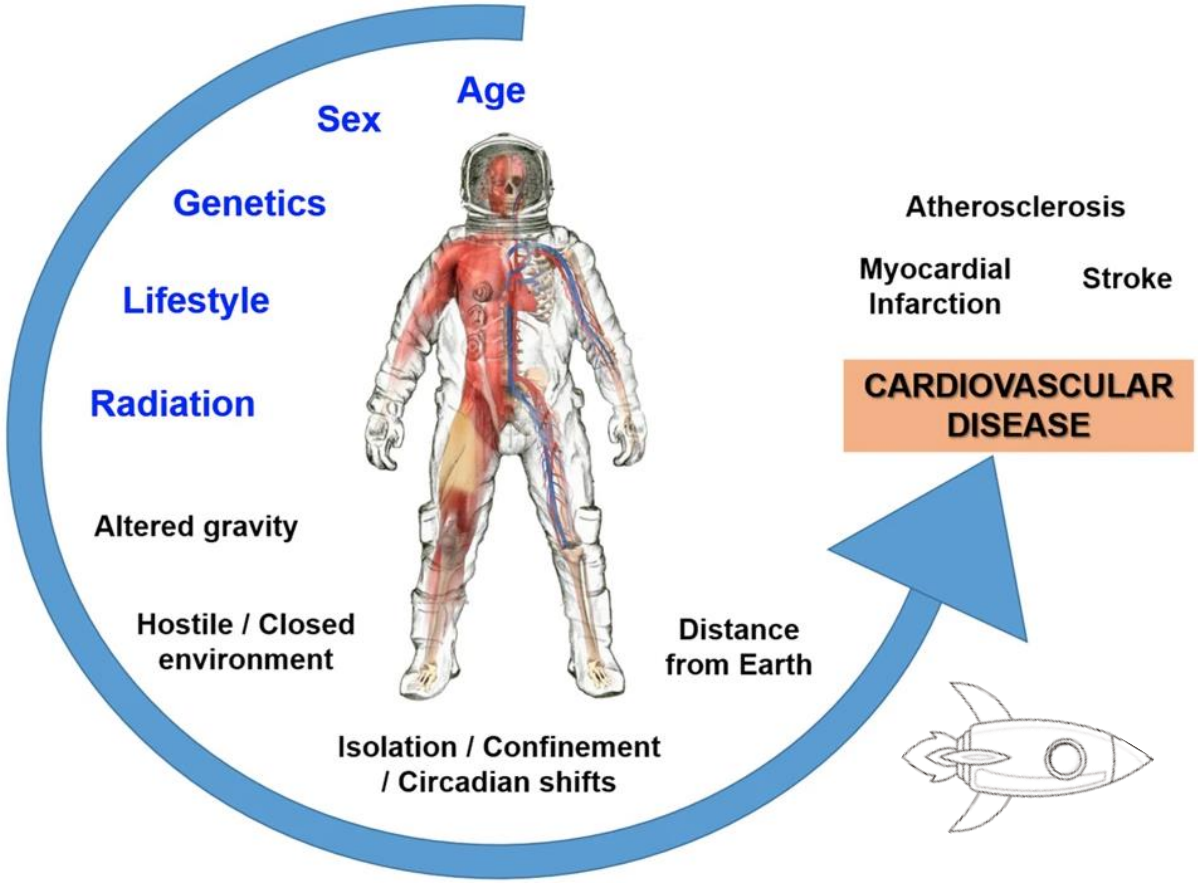




- Upregulation of CYP1A2, 2C29 and 2E2
- Non alcoholic liver Fatty disease
- Improper metabolism of lipids and glucide
- Forseen modification of drug metabolism

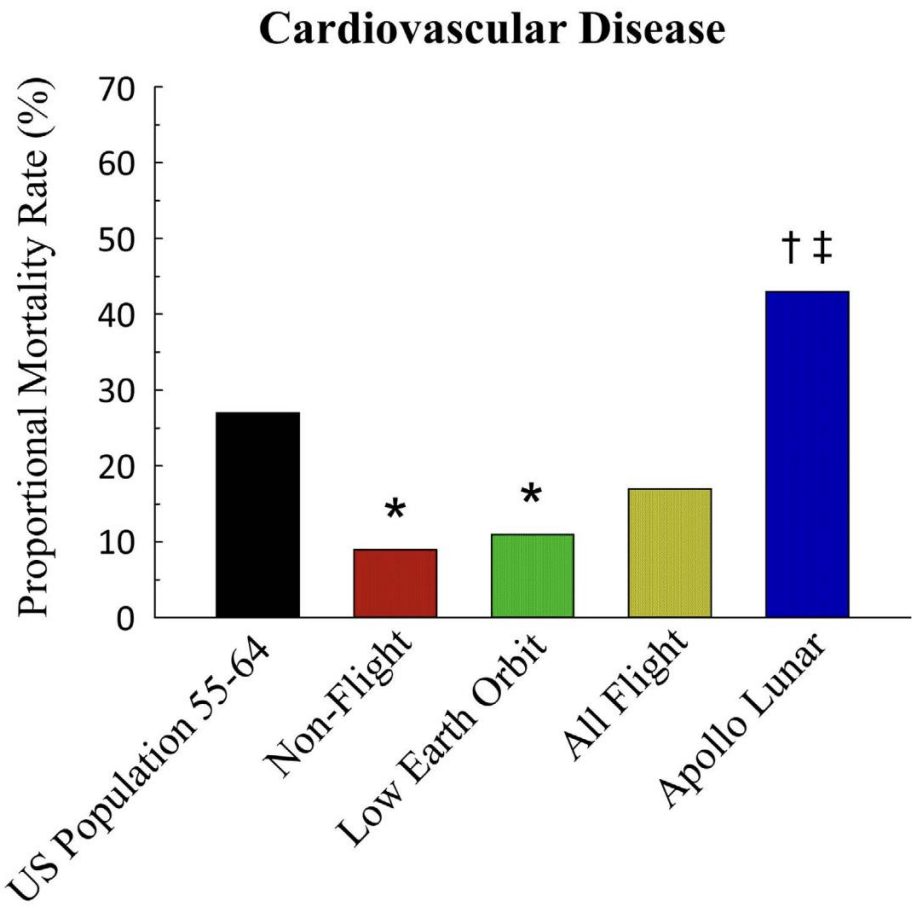
Moskaleva et al, 2015
Beheshti et al 2019
Winken et al 2022

Spaceflight induced Cardiovascular deconditioning



Inflammation/immunity

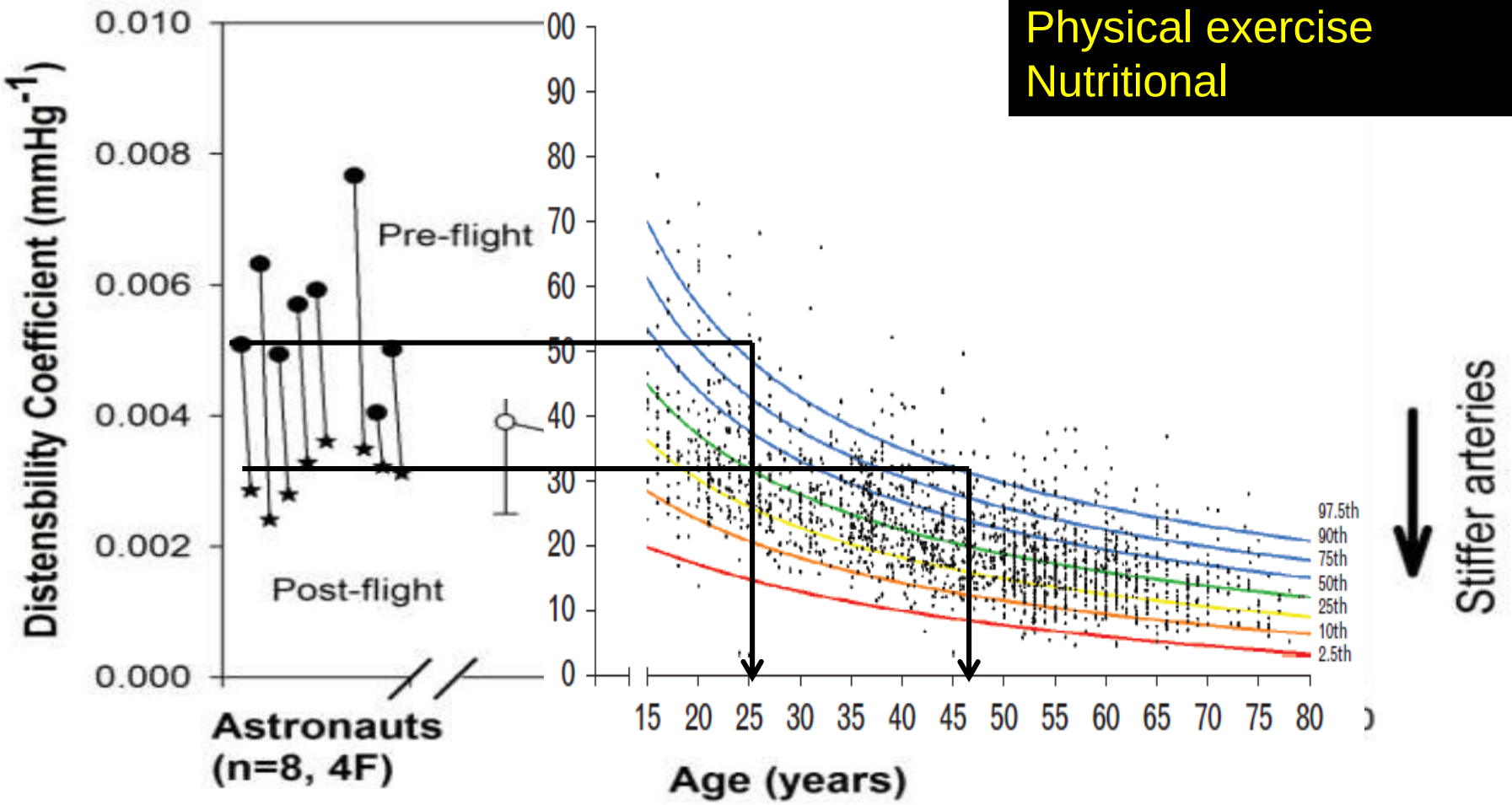
Early Vascular Aging?



Delp et al, Scient Rep 2016

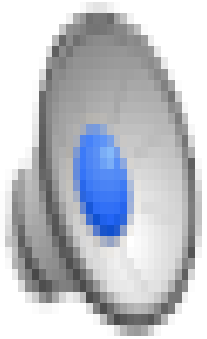
Effect of long-term spatial conditions on carotid distensibility

Despite countermeasures
Physical exercise
Nutritional

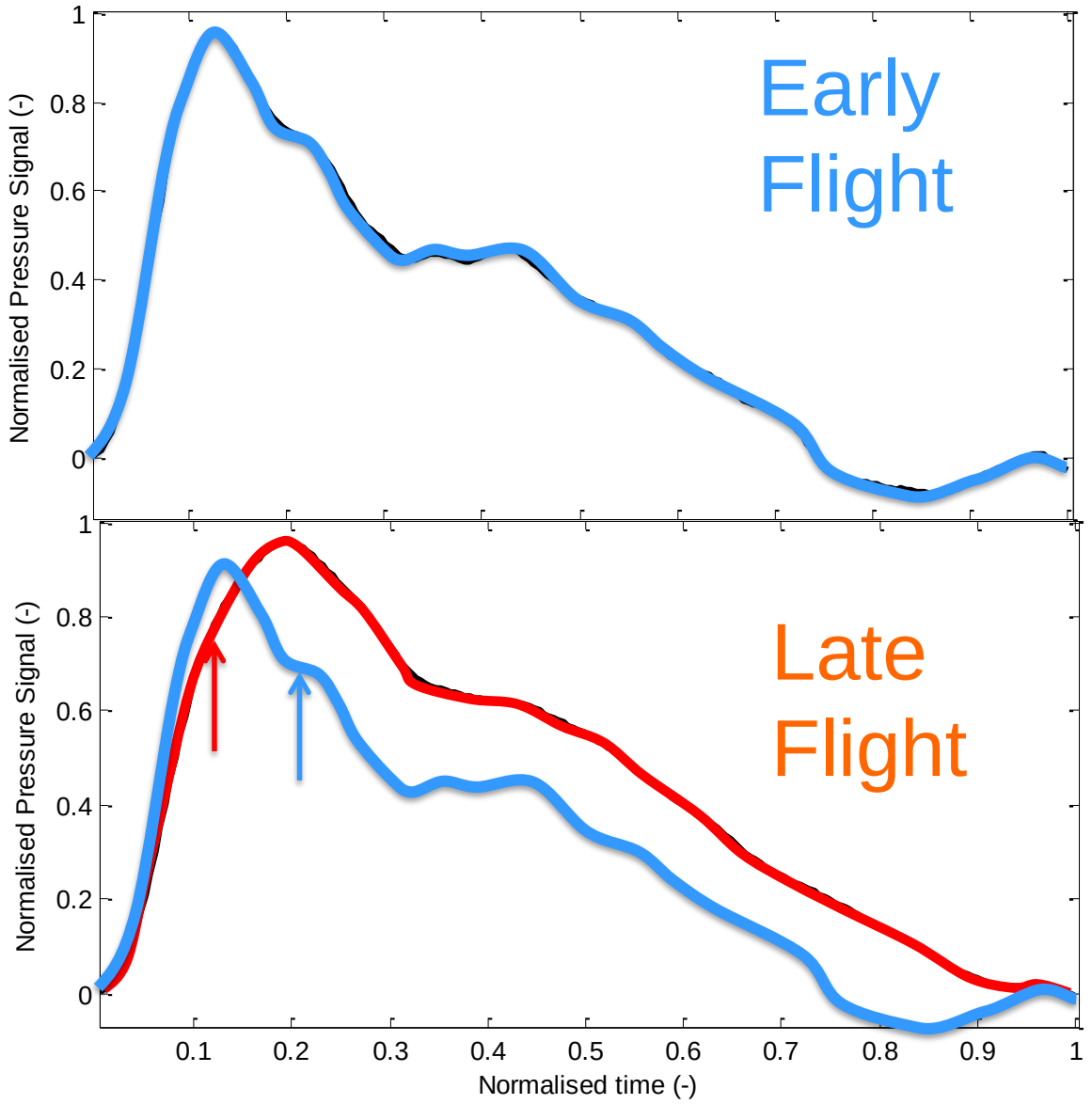


Hugton et al, Am J Physiol Heart Circ Physiol. 2016
Engelen et al, J Hypertens 2015

EVERYWARE mission



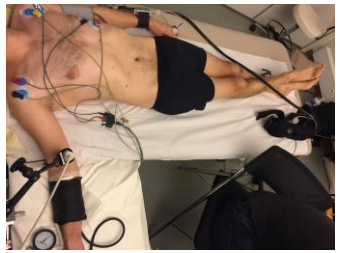
Carotid pulse waveform



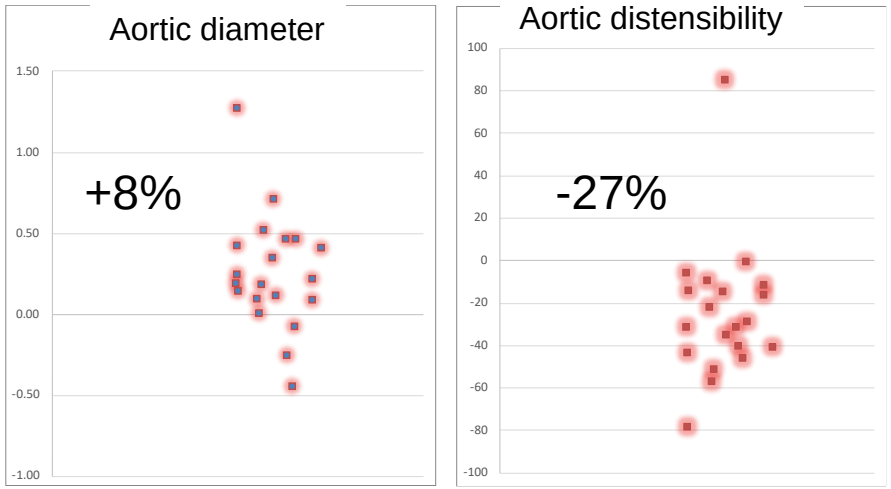
Time-changes in vascular age during and after **60 days head down bedrest**

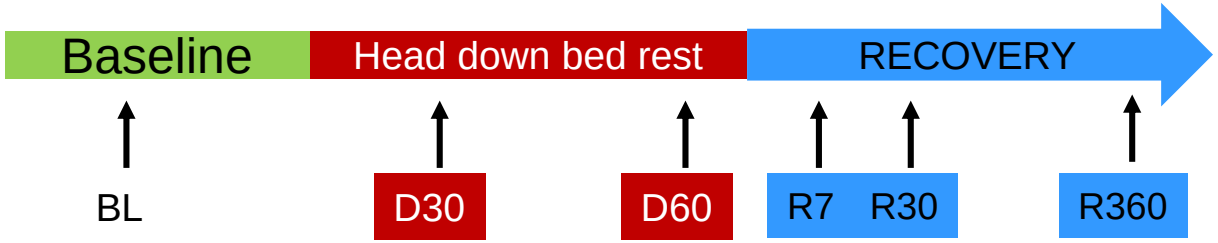
20 healthy males

- Age 32
- Vascular age lower than calendar age at baseline

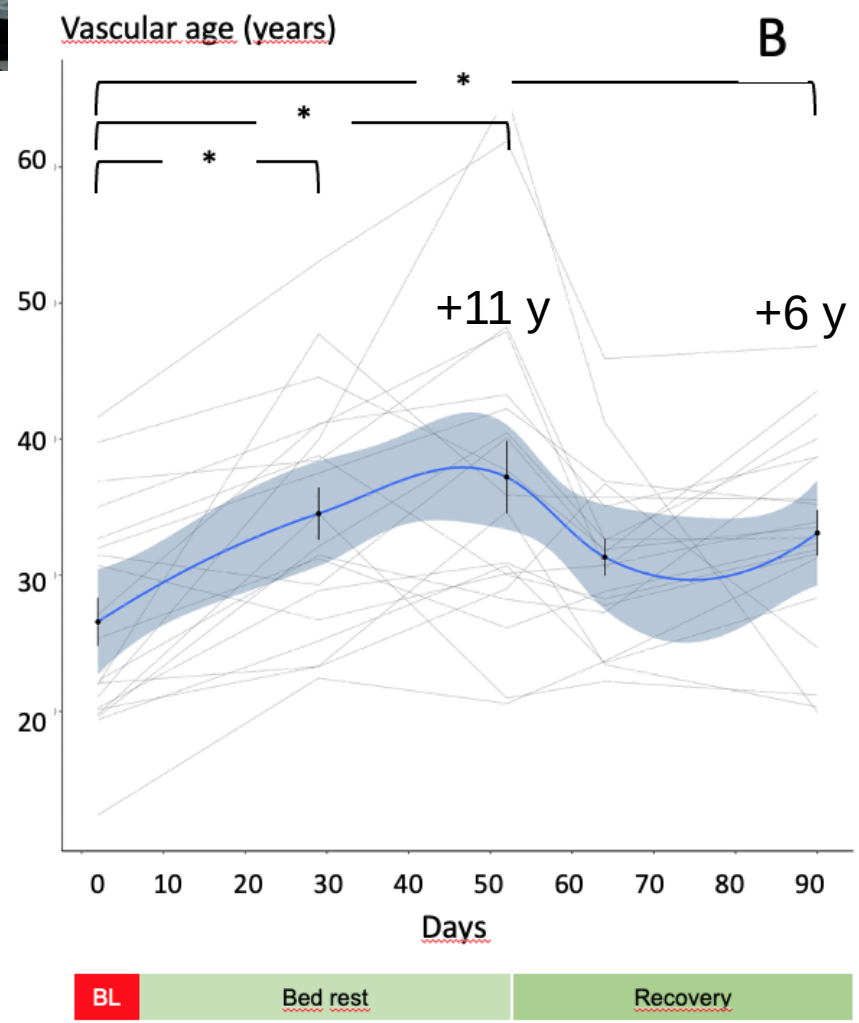


MRI





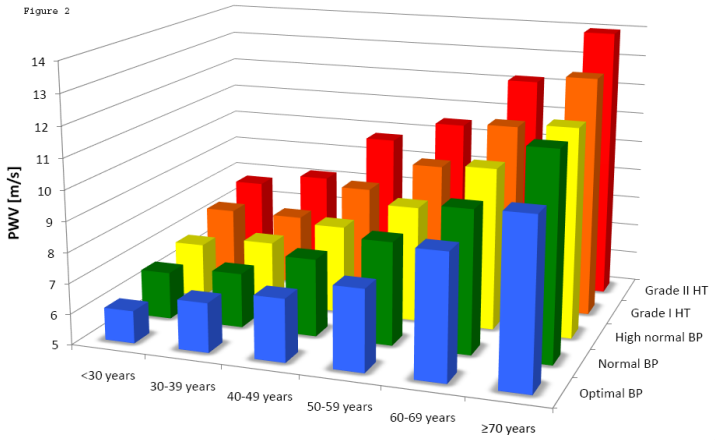
Echotracking, tonometry, MRI



Boutouyrie et al, J Hypertens 2022

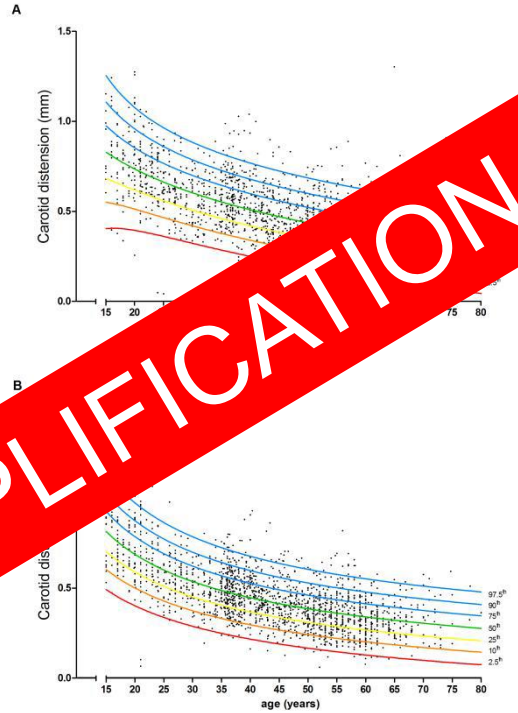
Reference Methods

- Carotid-femoral PWV by tonometry



Boutouy
Eur 10

- Carotid stiffness vascular ultrasound



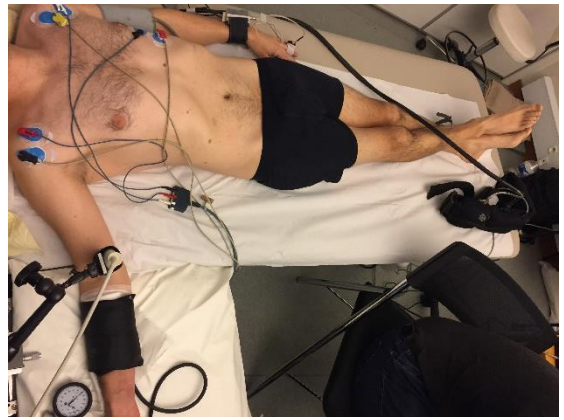
Engelen et al, Bossuyt et al, J Hypertens 2015

Vascular Lab

Nor nconfortable

onsuming+++

impossible to generalize



NEED FOR SIMPLIFICATION FOR WIDER USE

Pharmacology in space

Why is it needed ?

- Inefficiency of actual countermeasures
- Profound modification of body in space affecting drug PK/PD
- Very limited knowledge of PK/PD
- Documented failure of treatments
- No pharmacological countermeasures yet proposed for space related health issues including early vascular ageing
- Older less selected astronauts ➔ potential health issues
- Long term flights → increased risk

Why is it missing ?

- Obstacles for pharmacological studies

- Logistical and technical constraints of sample biologics fluid
  - Venous puncture by non-professionals in microgravity
  - Risk of free-floating biomaterials
  - Sample storage (energy cost of -80° C)
  - Very limited lab facilities on board
  - Cost of sample retrieval

➔ practically impossible to perform

Pharmacological countermeasures 2022 PSK

Microgravity and dry matrix spots

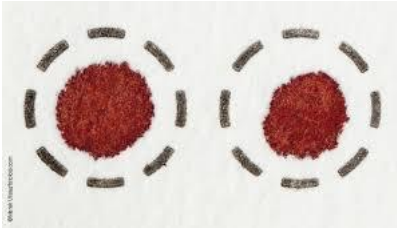
Dried Matrix Spot

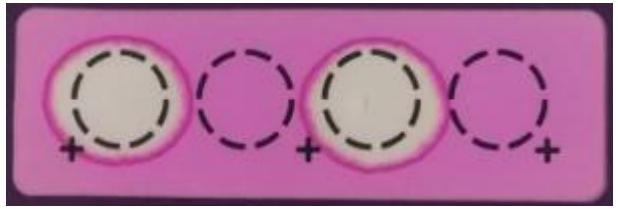
Advan

Transfer of blood/urine drops in microgravity

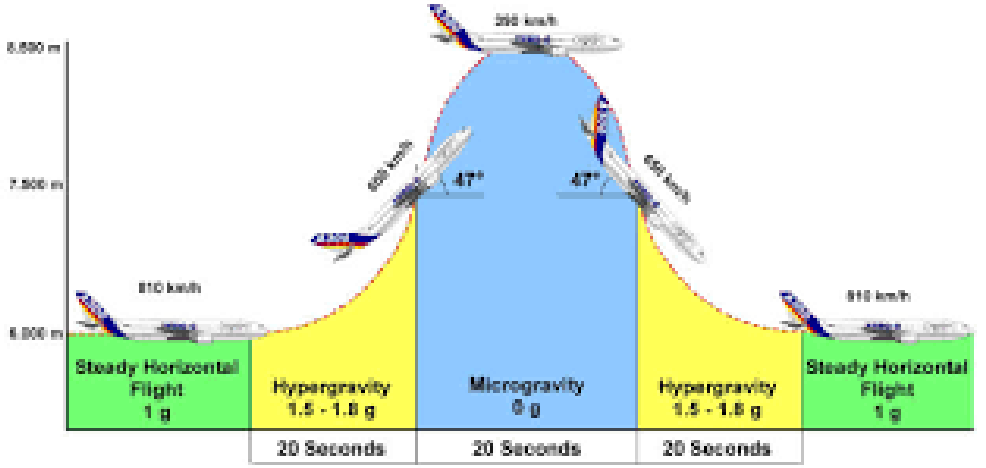
- Easy and fast collection by non-professionals
- Multiple possible dosages (infectious disease, genetics, etc)
- Safe, very low risk of biohazard
- light (< 3 grams/sample)
- Easy to store (room temp. or +4°C)
- Very small volume 50 µL
- Adapted to repeated biological fluid sampling
- Very low cost
- Applicable to extreme situations

- Not all drugs are detectable (according to their chemical properties)
- Lesser control on fluid volume ➔ lesser precision





Parabolic flight validation

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Results

- After 90 parabols
  - 127/128 drop transfers
  - No free flying drop or material
- Precision whithin specs compared to 1g conditions

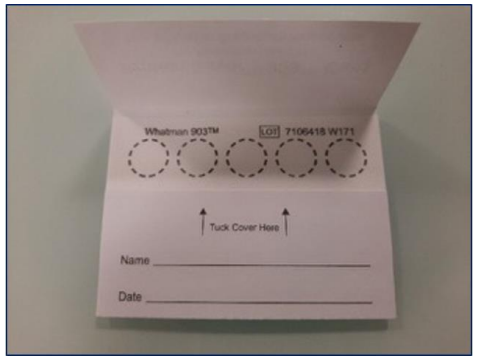
2023 Pharmacology Space Kit- PSK

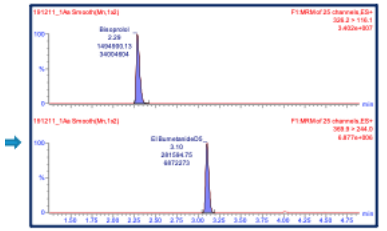
Validation of self-sampling of capillary blood and transfer to blotting paper in microgravity for caffeine dosage

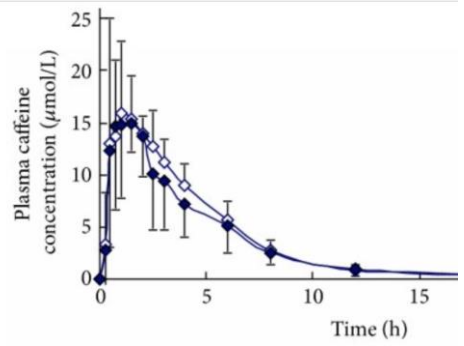
- **Blood :** Caffeine as a proof of concept and probe for CYP 1A2
- Primary endpoint: feasibility of self-sampling
- 30 healthy participants

Parabolic flights

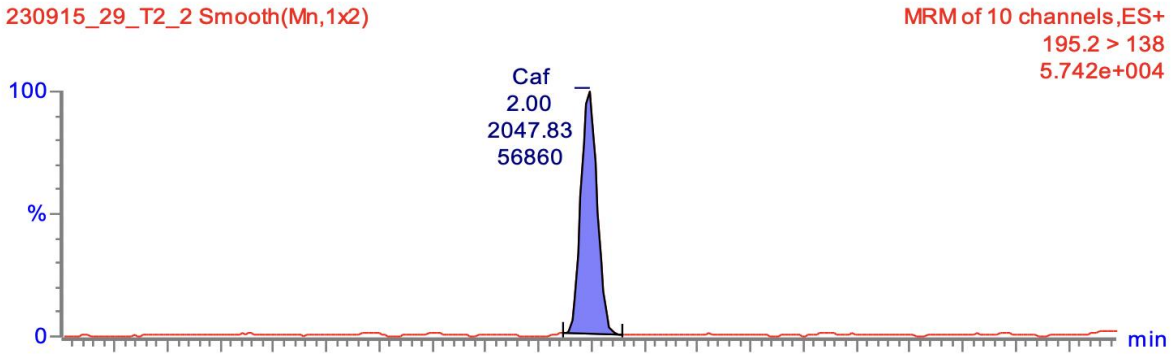
Baseline	Parabole x	Ground 1	Ground 2	LAB
7:30	PX	13:00	15:00	







1OO% of exploitable deposits



TRANSATLANTIC MDRS CREW 261
MISSION SUMMARY

JAMES BURK

ALINE DECADI

CECILE RENAUD

JULIEN VILLA-MASSONE

KRIS DAVIDSON

ERIN KENNEDY

AUDREY DEROBERTMASURE

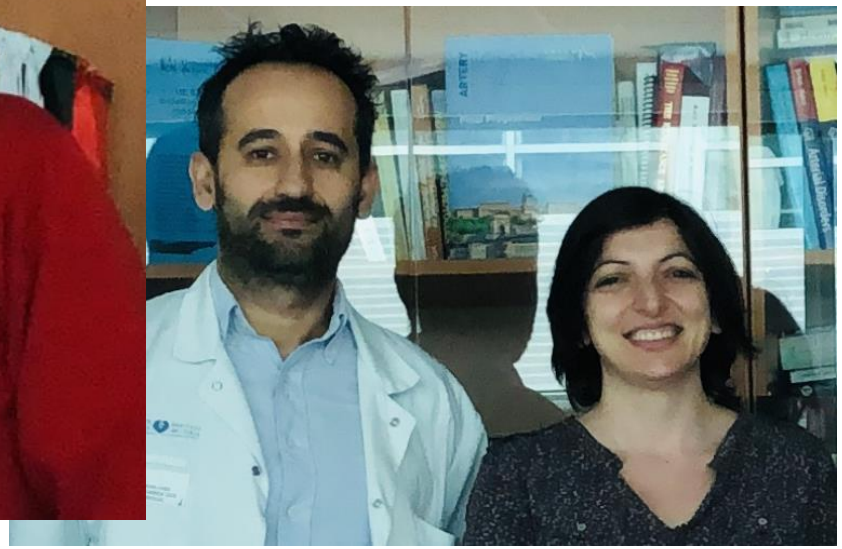
Crew Commander : James Burk
Executive Officer and Safety Officer : Aline Decadi
Crew Engineer : Julien Villa-Massone
GreenHab Officer : Cécile Renaud
Crew Journalist : Kris Davidson
Crew Robotic : Erin Kennedy
Medical Officer : Audrey Derobertmasure

PARIS TEAM: LOGISTIC AND MEDICAL SUPPORT

Liamine Kafi

Audrey Derobertmasure

Pierre Boutouyrie



Hakim Khettab

Rosa Maria Bruno

COSMOS

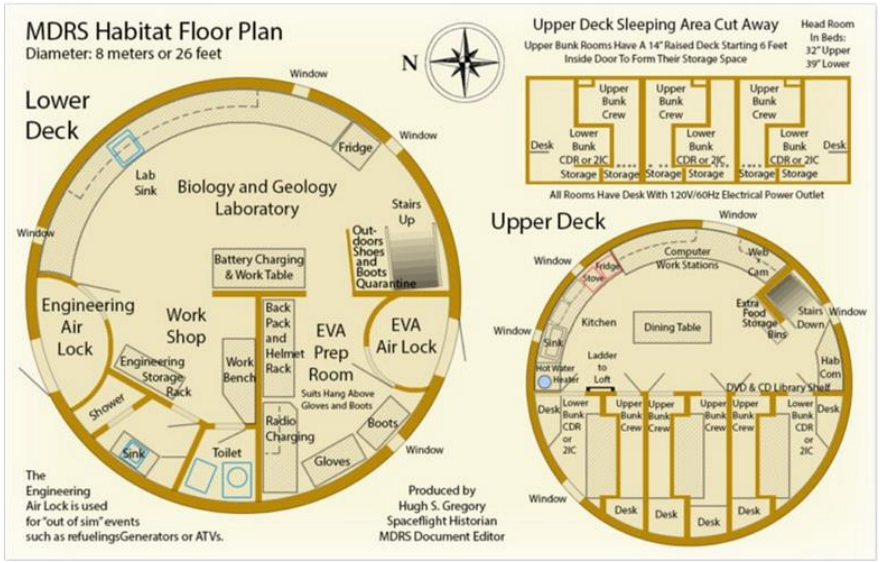
PI: AUDREY DEROBERTMASURE

Cardiovascular Monitoring and pharmacology on mars:

- **MAEVA - Mars Early Vascular Ageing monitoring**
  Daily cardiovascular monitoring and body composition

- **PASKAL- Pharmacology Space Kit – Analysis**
  Self-management of biological samples in isolation

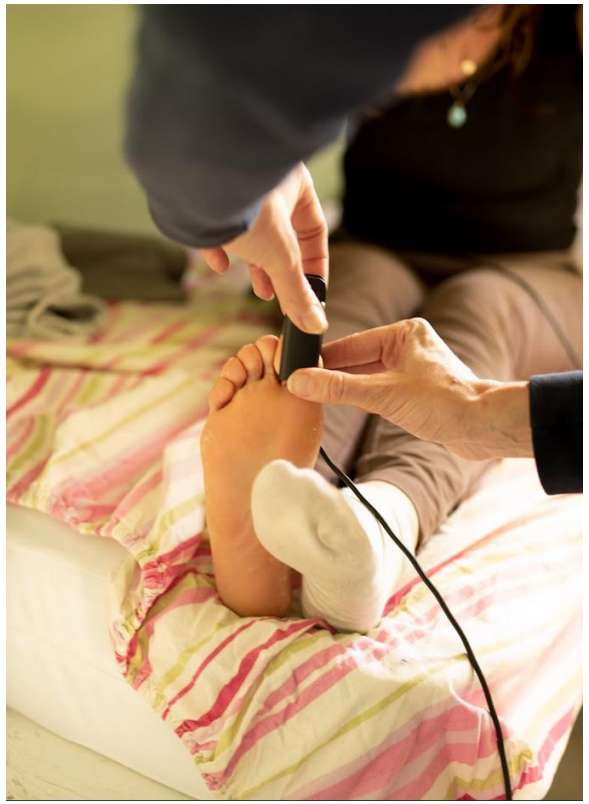
The HAB

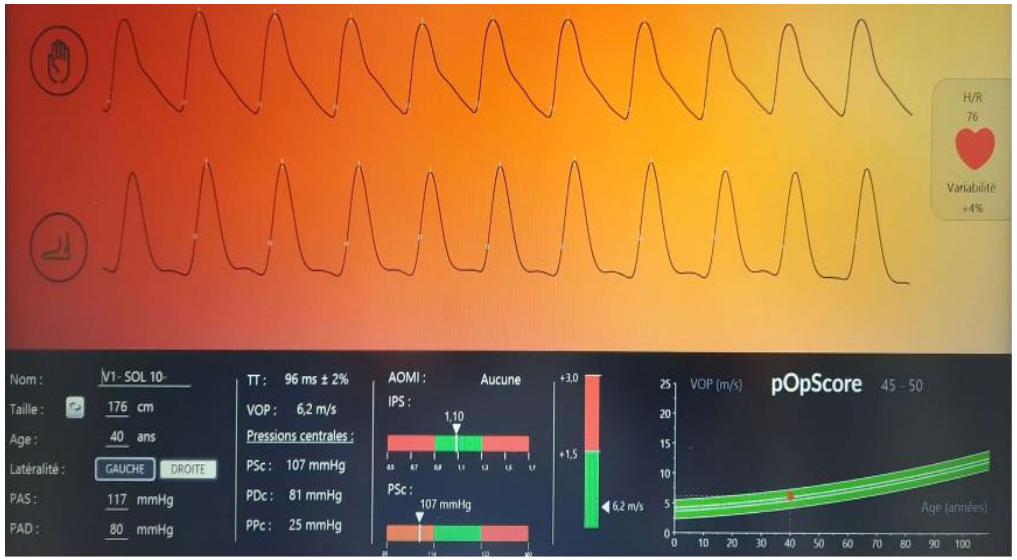

MDRS Habitat Floor Plan
Diameter: 8 meters or 26 feet
N
Lower Deck
Window
Fridge
Lab Sink
Biology and Geology Laboratory
Stairs Up
Out-doors Shoes and Boots Quarantine
Battery Charging & Work Table
Engineering Air Lock
Work Shop
Back Pack and Helmet Rack
EVA Prep Room
Suits Hang Above Gloves and Boots
EVA Air Lock
Engineering Storage Rack
Work Bench
Shower
Radio Charging
Boots
Sink
Toilet
Gloves
The Engineering Air Lock is used for "out of sim" events such as refuelingsGenerators or ATVs.
Produced by Hugh S. Gregory Spaceflight Historian MDRS Document Editor
Upper Deck Sleeping Area Cut Away
Upper Bunk Rooms Have A 14" Raised Deck Starting 6 Feet Inside Door To Form Their Storage Space
Head Room In Beds: 32" Upper 39" Lower
Upper Bunk Crew
Lower Bunk CDR or 2IC
Desk
Storage
All Rooms Have Desk With 120V/60Hz Electrical Power Outlet
Upper Deck
Computer Work Stations
Web Cam
Extra Food Storage Bins
Stairs Down
Kitchen
Dining Table
Sink
Stove
Fridge
Ladder to Loft
Hot Water Heater
DVD & CD Library Shelf
Hab Com

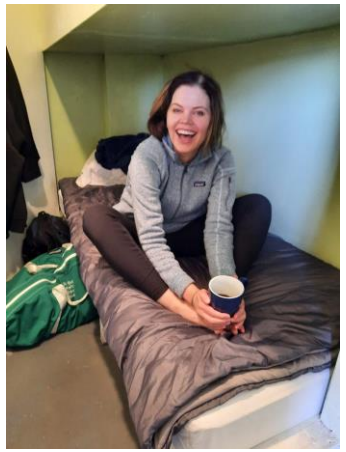
Food on Mars

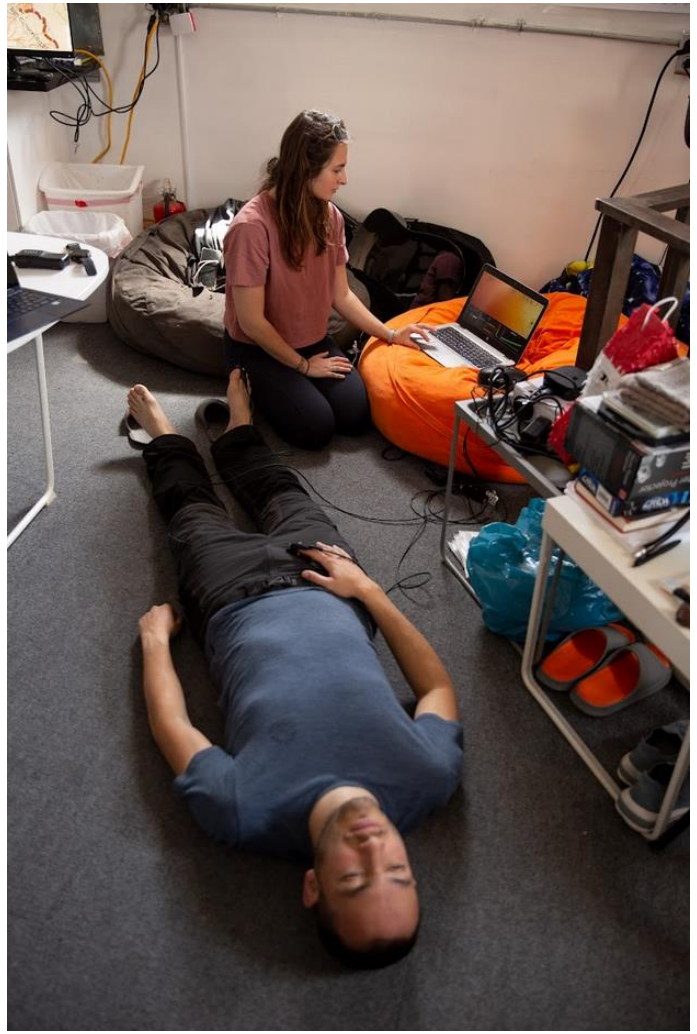
MAEVA – Blood pressure monitoring (Withings)

MAEVA – Pulse Wave Velocity measurements (pOpmètre)



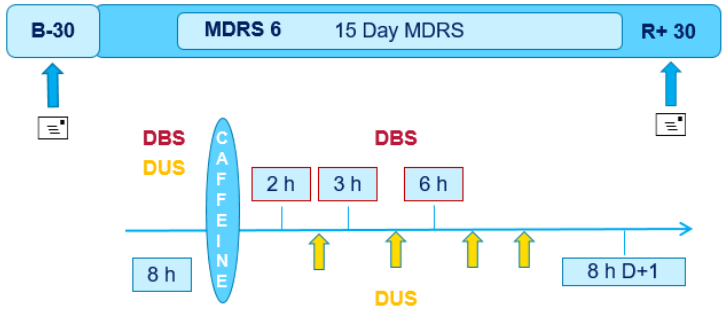






MAEVA – Body composition (Withings: fat, muscle, bone and water mass (+ Heart Rate,VOP)

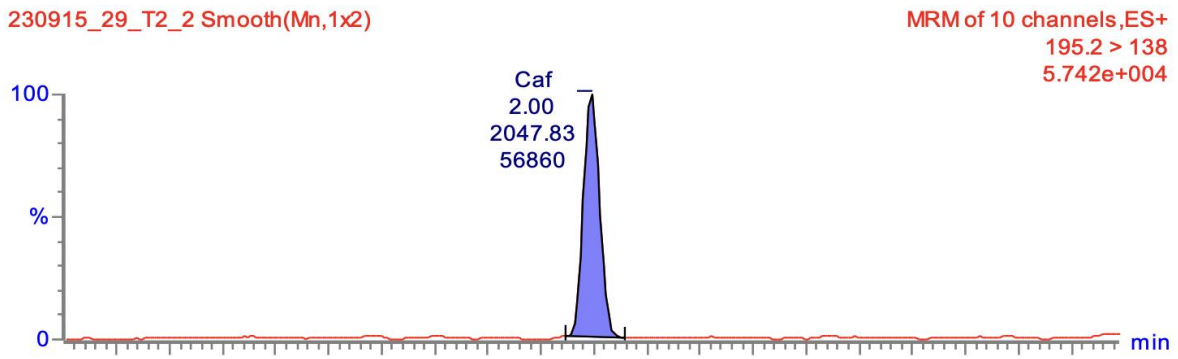
PASKAL – A pharmacokinetic study of caffeine and paraxanthine in blood and urine with dried matrices sampling methods

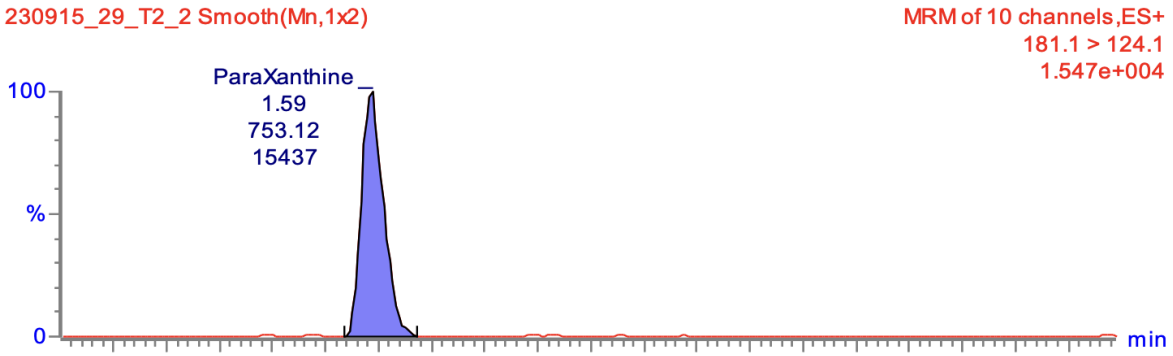


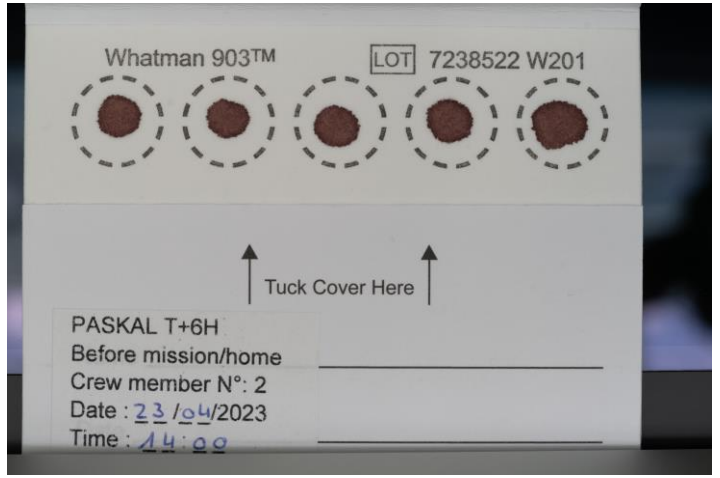
FEASIBILITY : PHARMACOKINETICS OF CAFFEINE (PASKAL)

- Pharmacokinetics of caffeine
  - 100% of samples were analyzed
  - Peaks of caffeine and metabolites (paraxanthine) easily detected
  - Expected pharmacokinetics obtained (results pending)
  - Modification linked to MRDS pending

FEASIBILITY : PHARMACOKINETICS OF CAFFEINE (PASKAL)



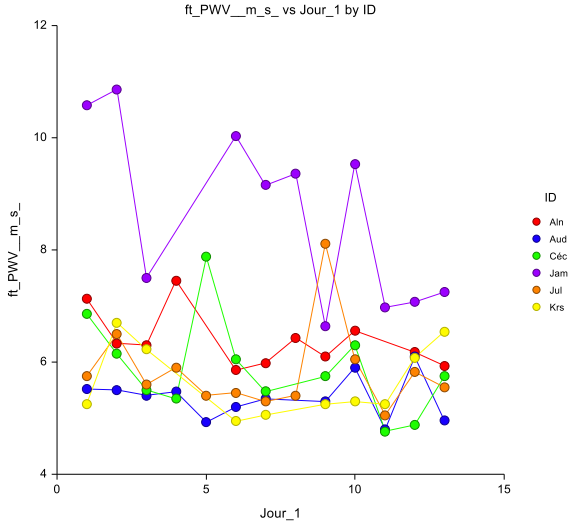




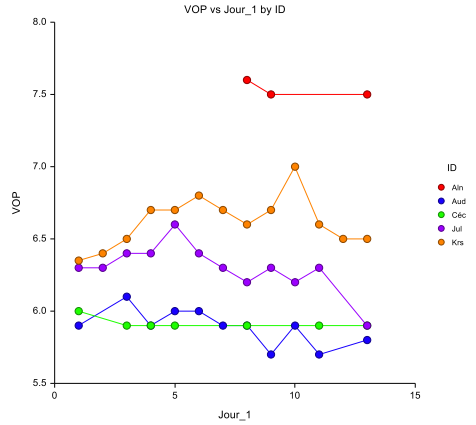
- 6 months storage,
- room temperature
- 50 microliters of blood

FEASIBILITY VASCULAR MEASUREMENTS (MAEVA)

- Measurement of finger toe pulse wave velocity (popmetre)
  - 95% of valid measurements
  - 5% failure caused by cold habitat and Raynaud Syndrome



- Measurements of body weight and body composition
  - 100% of valid measurement for weight
  - 95% of valid measurement for body composition
- Measurement of pulse wave velocity
  - 30% of valid measurements, measurement failures caused by cold feet and insufficient blood flow for impedancemetry

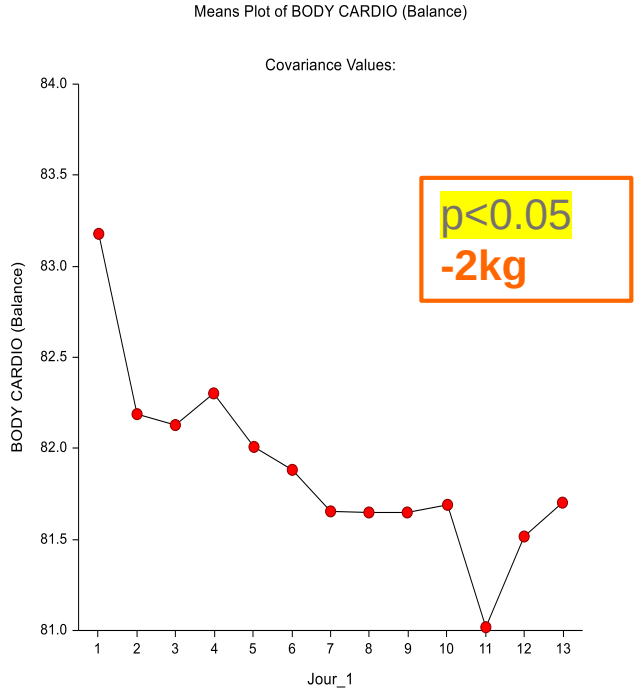


Results – Body Composition

Global Mass

Term-by-Term Hypothesis Test Results

Model Term	F-Value	Num DF	Denom DF	Prob Level
Jour_1	5.3533	12	53.0	0.000008

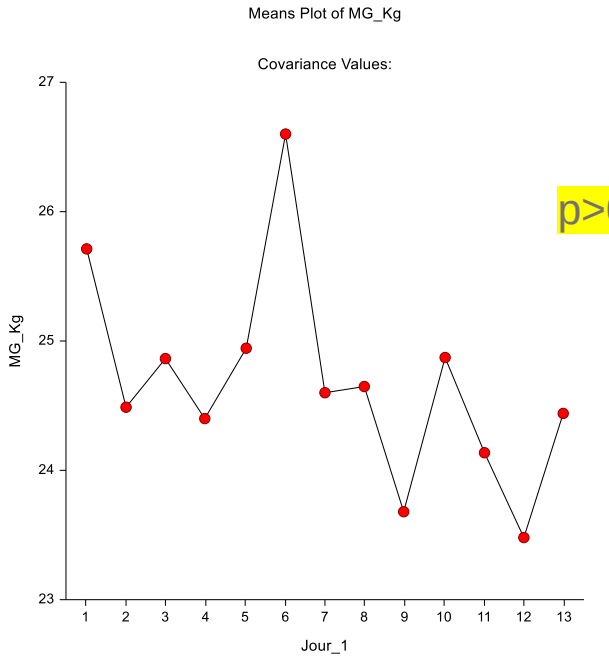


p<0.05
-2kg

Fatty Mass

Term-by-Term Hypothesis Test Results

Model Term	F-Value	Num DF	Denom DF	Prob Level
Jour_1	1.3361	12	46.0	0.231793

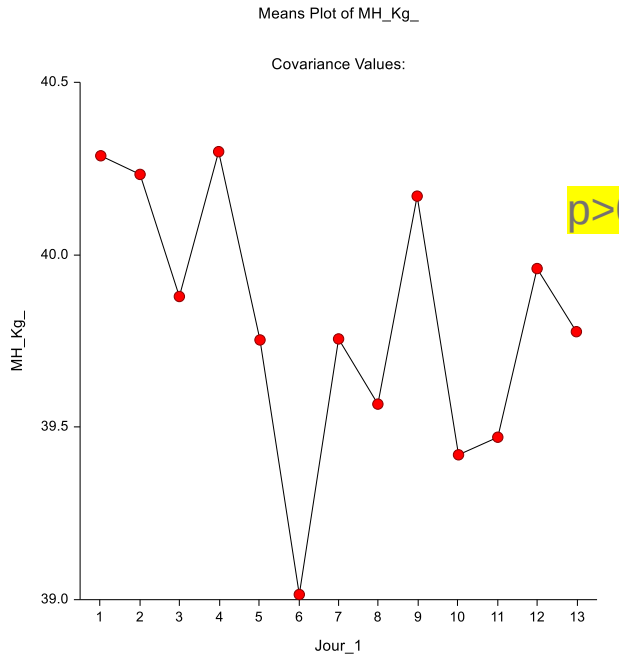


p>0.05

Water Mass

Term-by-Term Hypothesis Test Results

Model Term	F-Value	Num DF	Denom DF	Prob Level
Jour_1	1.6699	12	46.0	0.105596

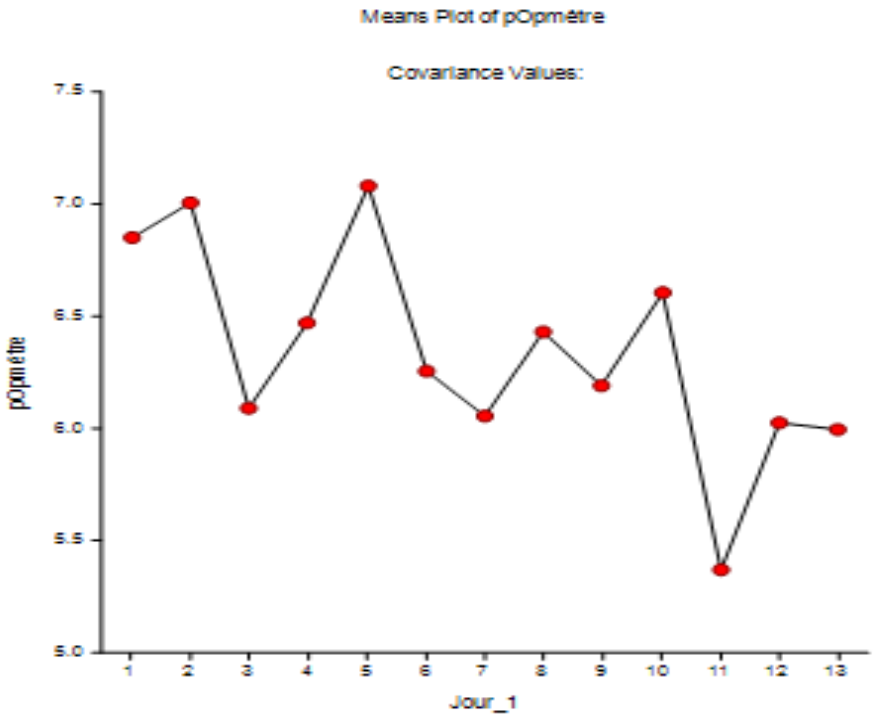


p>0.05

No statistical significance in the reduction of fat and water mass, but a statistically significant decrease in overall weight

MAEVA – Preliminary results

- Variation of the Pulse Wave Velocity (PWV) over time (p=0.152)



- Non-significant statistical significance of systolic blood pressure (SBP) variations

Filter	Condition = "Usuel";"usuel"
Response	BPM Connect (tensiométre)
Subject	ID
Repeated	Jour_1

Term-by-Term Hypothesis Test Results

Model Term	F-Value	Num DF	Denom DF	Prob Level
Jour_1	1.1596	12	60.0	0.332357

Progressive decrease over time in PWV, without statistical significance

MAEVA – Arterial stiffness reduction is dependent on weight reduction

Filter Condition = "Usuel"
Response pOpmétre
Subject ID
Repeated Jour_1

Term-by-Term Hypothesis Test Results

Model Term	F-Value	Num DF	Denom DF	Prob Level
BODY CARDIO (Balance)	0.8289	1	21.9	0.372518
Jour_1	1.4104	12	33.7	0.209393
BODY CARDIO (Balance)*Jour_1	1.9206	12	33.6	0.067649

Interaction of PWV variables from the pOpmetre with weight over time.

CONCLUSIONS OF MRDS PASKAL AND MAEVA

- Performing a full pharmacokinetic profile is feasible
  - in total autonomy by trained non-medical staff
- Performing longitudinal monitoring of cardiovascular health is feasible
  - In total autonomy by trained non-medical staff
  - Based on finger to toe pulse wave velocity
  - Attention must be paid to details, including adequate warming of hands and feet
- The benefic effects of caloric restriction, physical exercise explain weight loss and improvement of PWV, and overcome the possible deleterious effects of stress, confinement and exhaustion

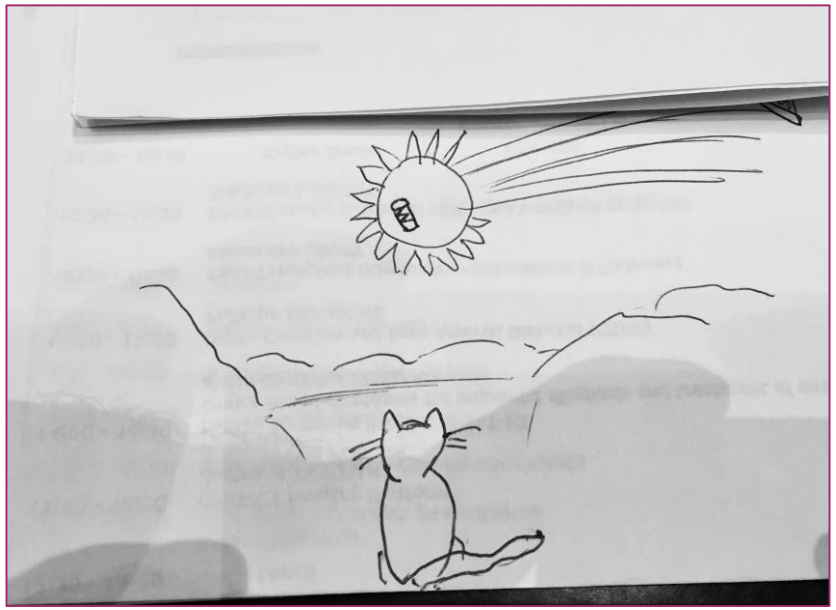


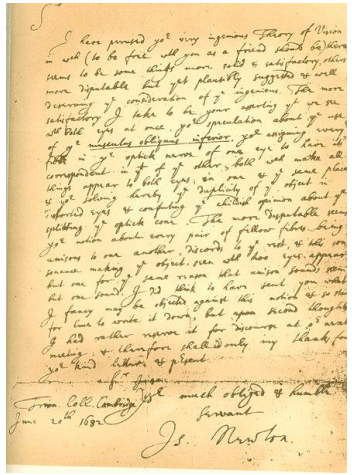
Photo credit: Kris Davidson

Vascular age by Body Cardio from Withings

Ballistocardiography (BCG)

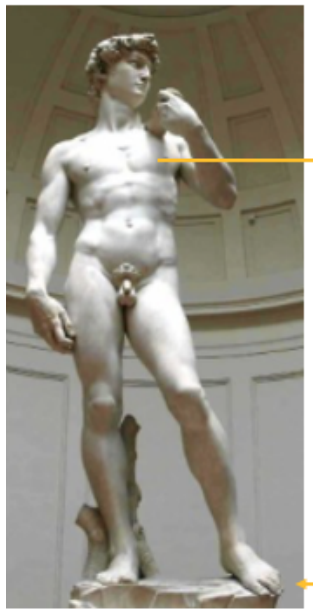
- Newton's second law: action-reaction
  - Human heart ejects 150 g of blood at 2 m/s
  - The kinetic energy of blood dissipates in small vessels
  - The kinetic energy is transfered to the body, which oscillates until next beat

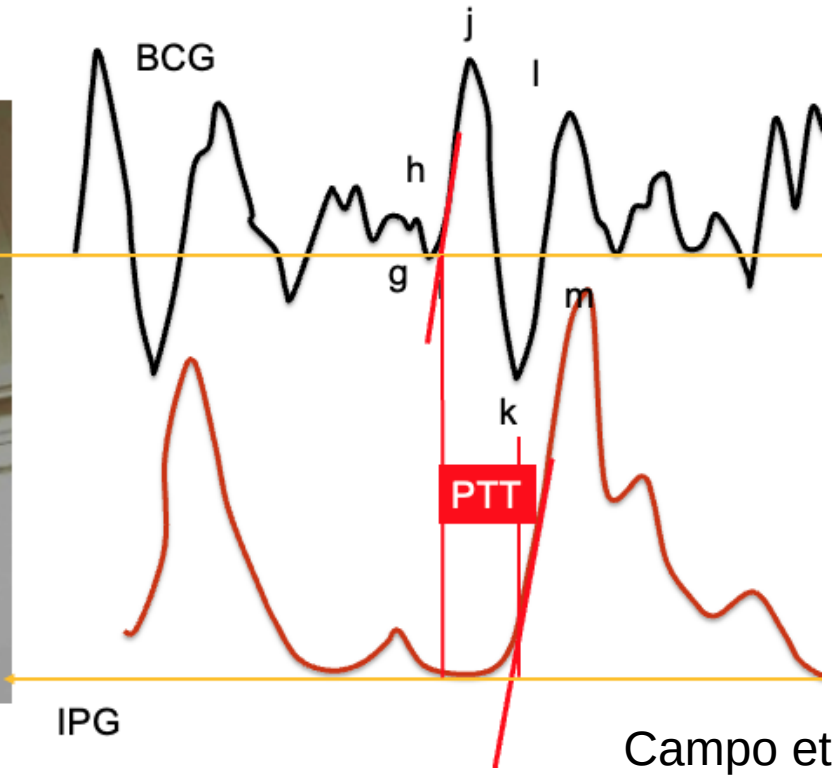
Starr, Am J Physiol 1939
Elliot, Circulation 1954
Pinheiro OBEJ 2010



Impedance plethysmography

- Ohm's law
  - Changes in electric impedance of a body segment due to blood flow

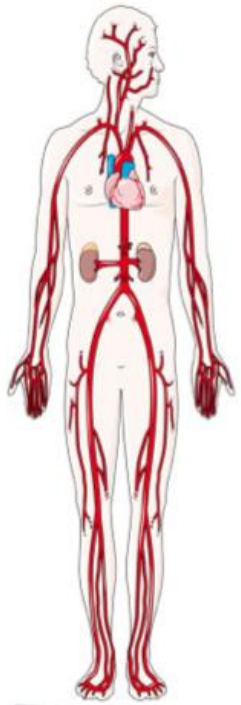




Campo et al, 2017

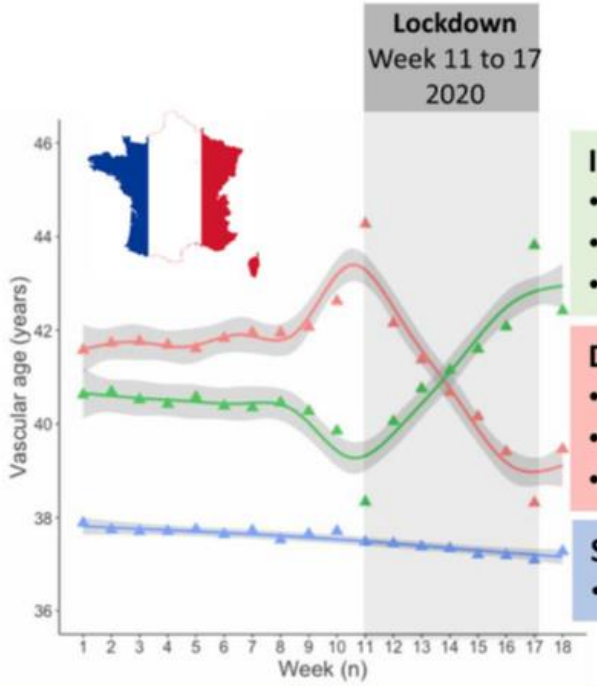
WITHINGS BODYSCAN applications for research: effect of lockdown during COVID pandemics

PWV recordings by smart bathroom scales between Jan 1st and Apr 30th 2020 → N=4,953,817



Total lockdown
N=26,196
Vascular age -22.4 weeks during lockdown

Partial lockdown
N= 26,847
Vascular age -8.4 weeks during lockdown



Increasing vascular age cluster (18.2%):
- High baseline vascular age
- Men
- Living alone

Decreasing vascular age cluster (21.1%):
- High baseline vascular age
- Men
- Lost weight during lockdown

Stable vascular age cluster (60.7%):
- Low baseline vascular age

Bruno et al, Eur Hear J Dig Health 2022