Covid-19 effects on ARTErial StIffness and vascular AgiNg (CARTESIAN) study

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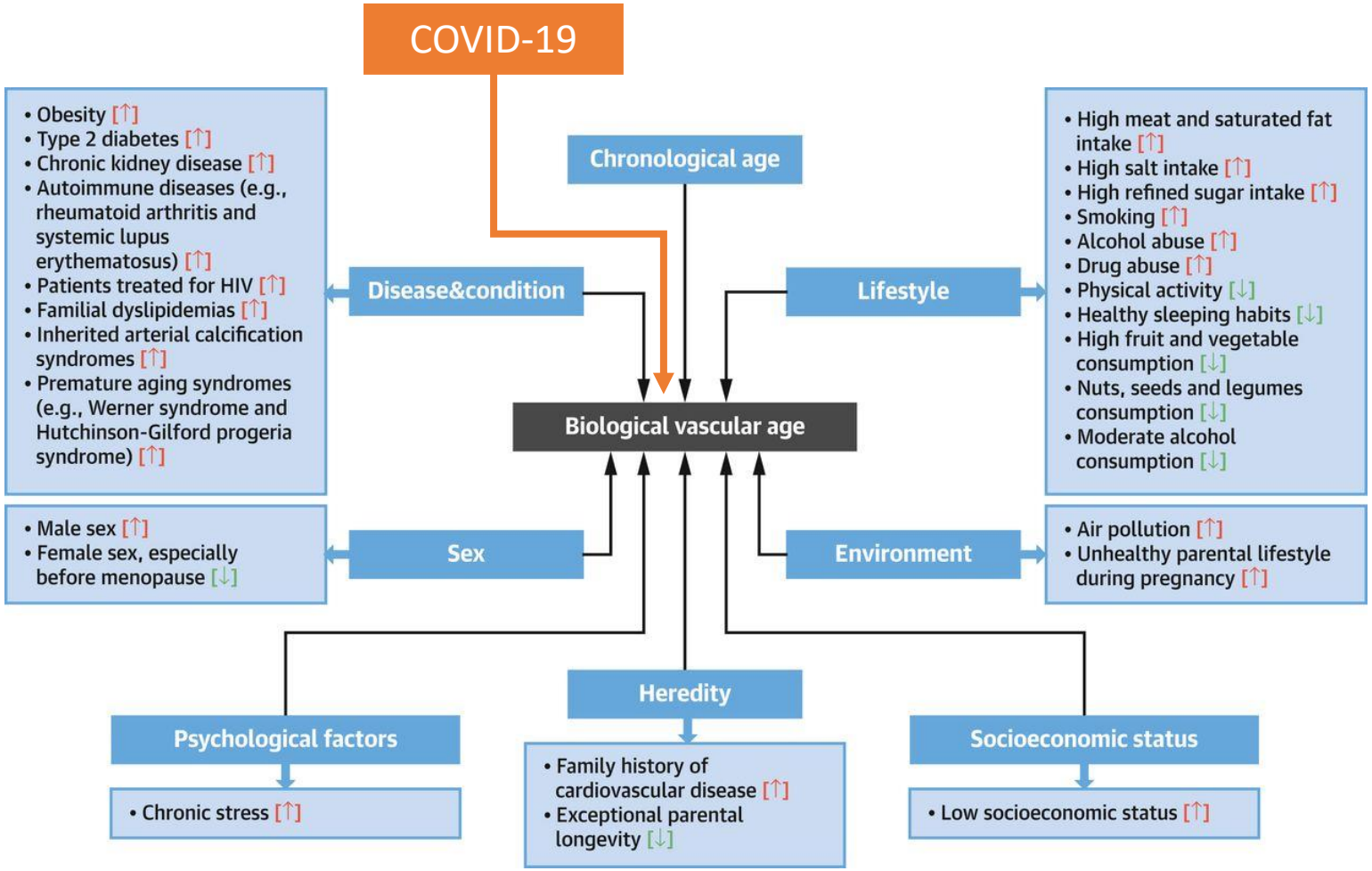
Study hypothesis:

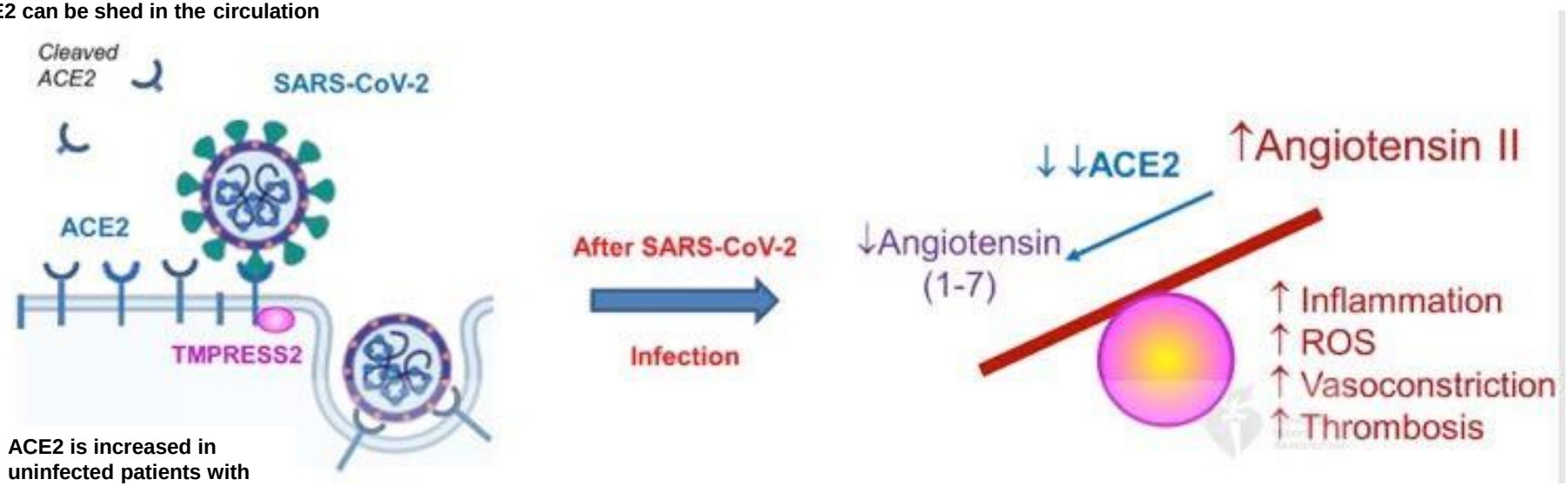
COVID-19 as a cause of early vascular aging (EVA): direct effects



Adapted from Hamczyk M et al. J Am Coll Cardiol. 2020 Mar, 75 (8) 919-930

SARS-nCOV-2 is able to directly infect endothelial cells by binding ACE2

ACE2 can be shed in the circulation

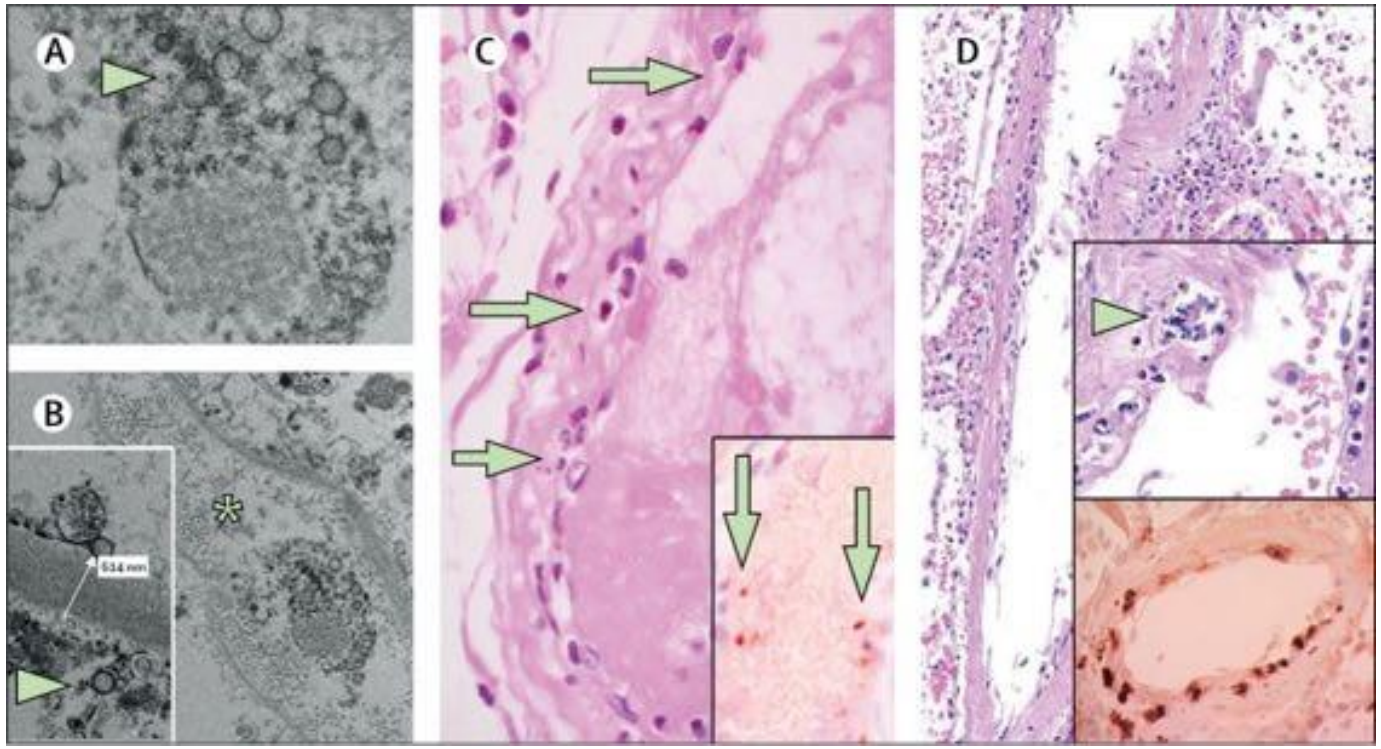


ACE2 is increased in uninfected patients with hypertension, heart failure, or diabetes

ACE2 internalized and down regulated with viral entry -> decrease in ACE2 function leads to dominant ANG II effects

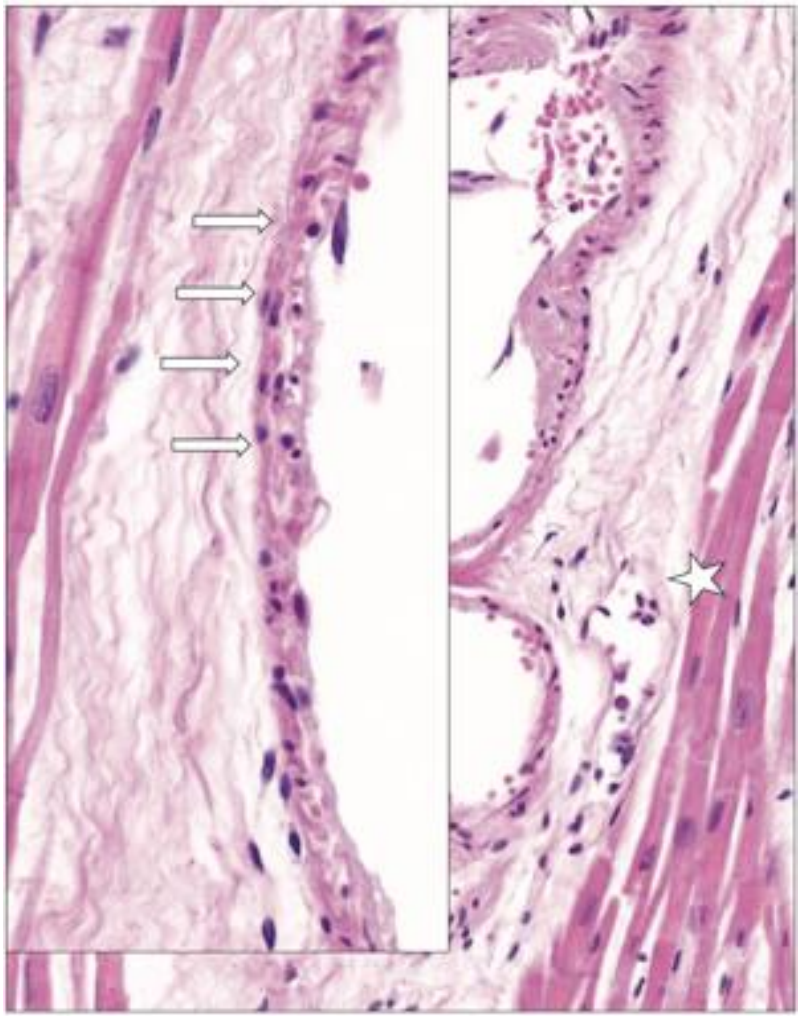
Liu P et al. Circulation 2020

Endothelial cell infection and endotheliitis in COVID-19



Viral inclusion structures in endothelial cells of glomerular capillary loops

Prominent endotheliitis of the submucosal vessels and apoptotic bodies (small intestine)

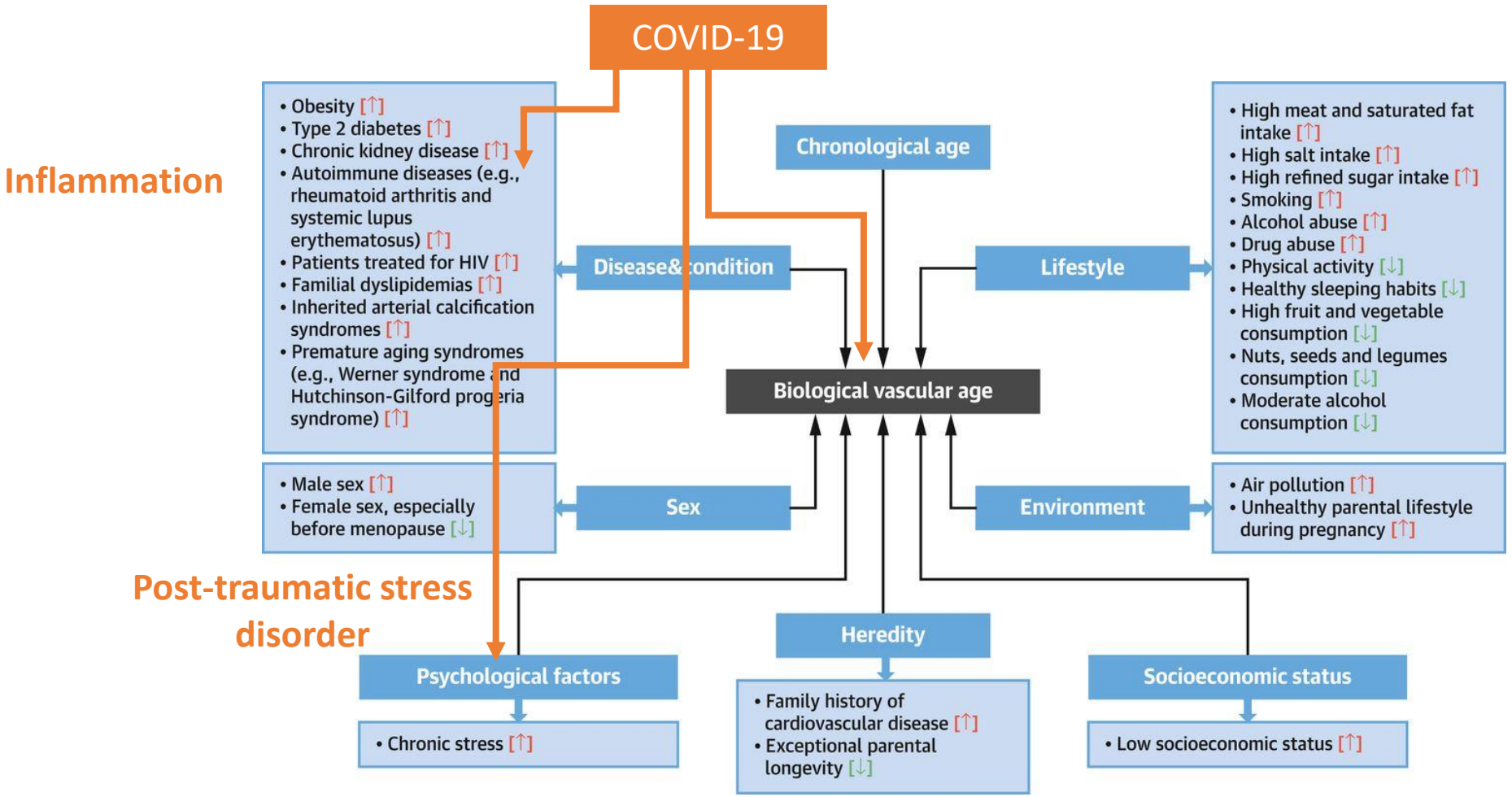


Endotheliitis and apoptosis in the lung

Presence of **vascular changes without lymphocytic myocarditis**

Varga Z et al, Lancet 2020

COVID-19 as a cause of early vascular aging (EVA)



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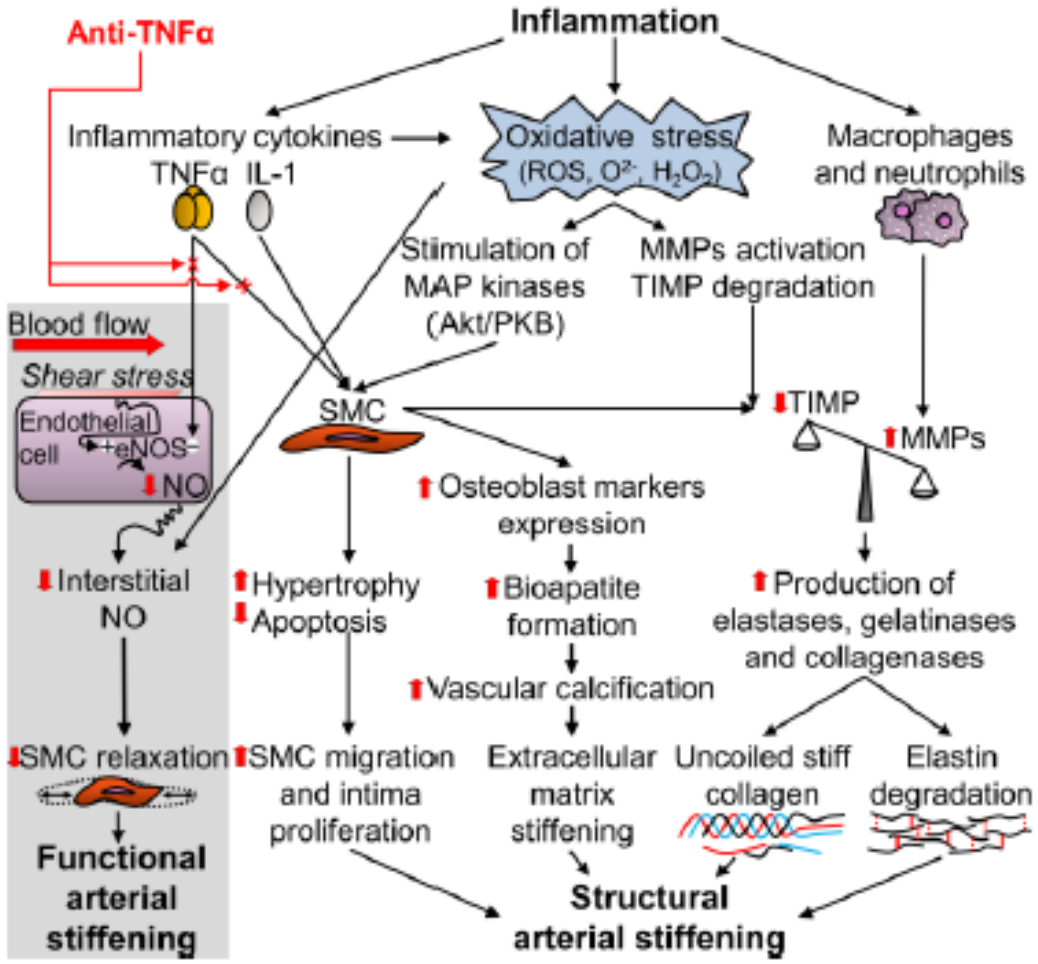
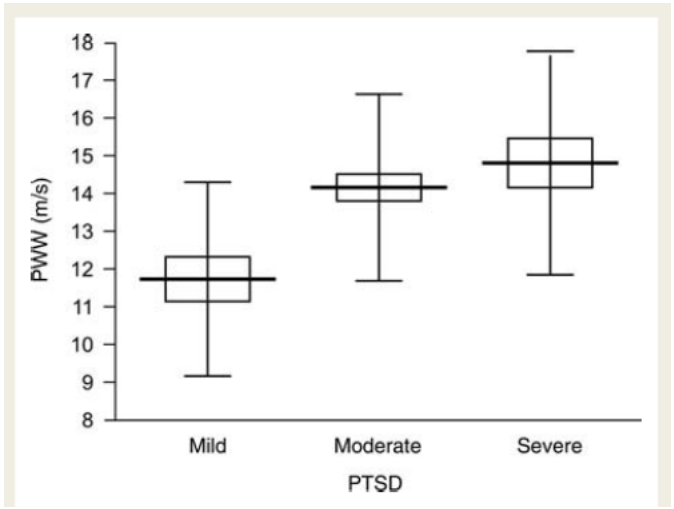
EVA and inflammation



Zanoli L et al, J Hypert 2020, in press

EVA and PTSD



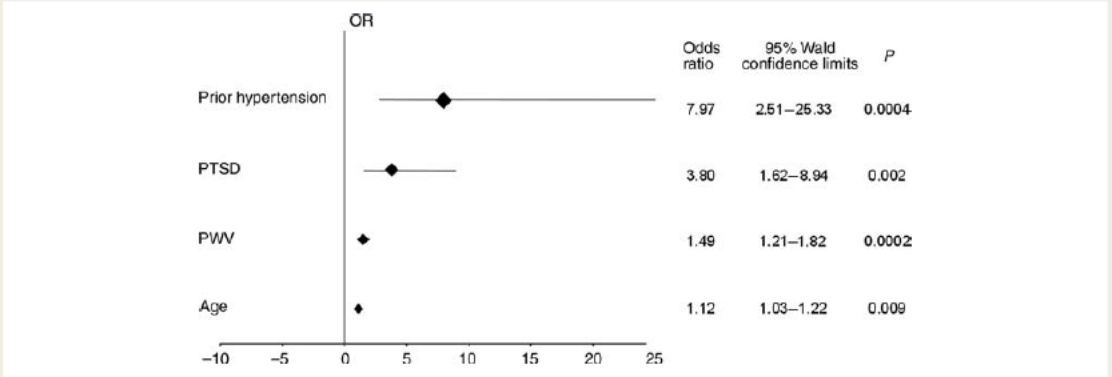
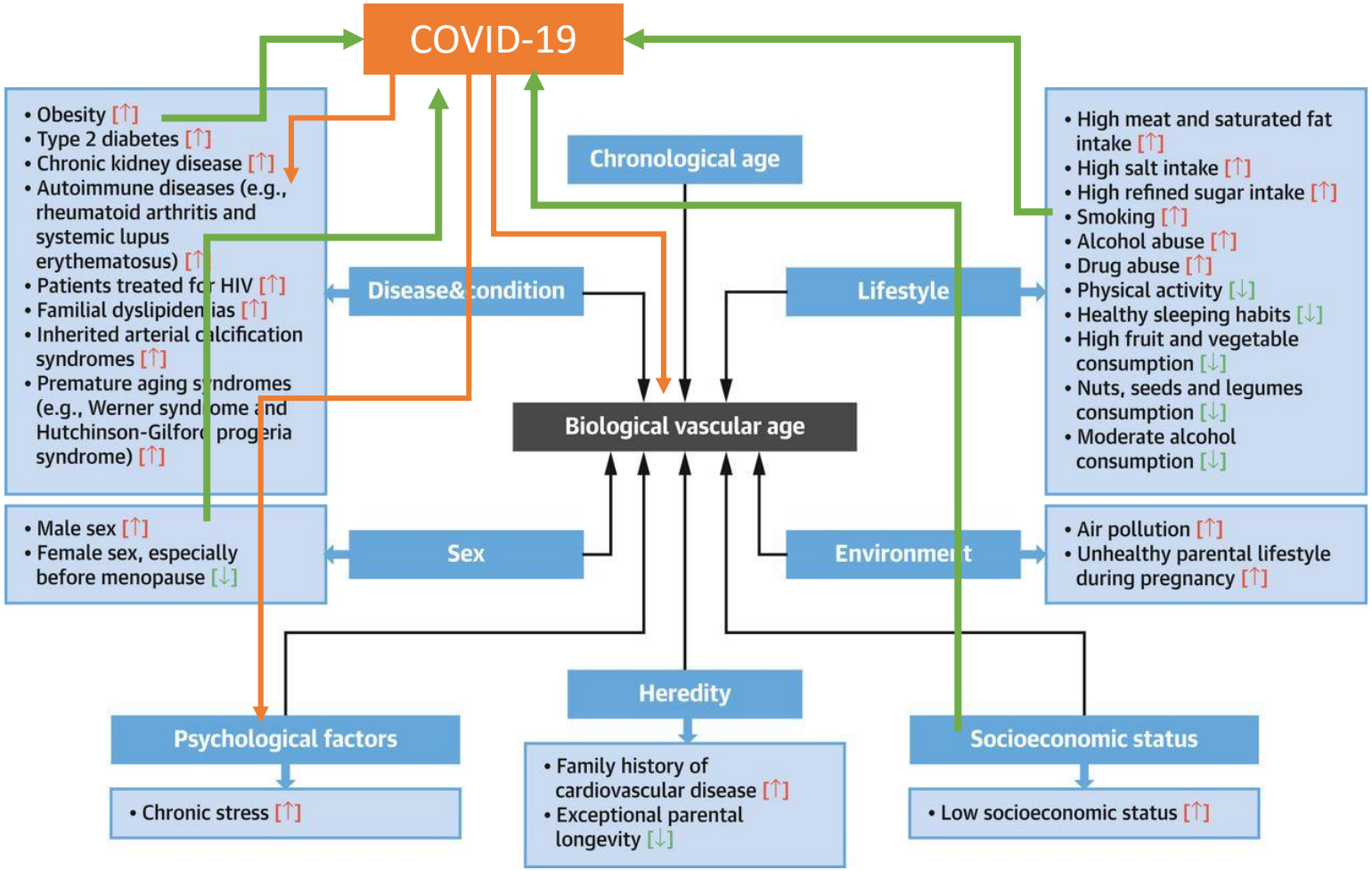


Figure 2 Characteristics associated with the history of coronary heart disease in stepwise logistic regression analysis. Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 12.58$, df = 8, $P = 0.127$.

Walczewska J et al, Eur Heart J 2011

Early vascular aging (EVA) as a prognostic factor for COVID-19



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Cardiovascular comorbidities are associated with worse COVID-19 prognosis

		Non-severe	severe	Presence of endpoint	
Any	261 (23.7)	194 (21.0)	67 (38.7)	39 (58.2)	222 (21.5)
Chronic obstructive pulmonary disease	12 (1.1)	6 (0.6)	6 (3.5)	7 (10.4)	5 (0.5)
Diabetes	81 (7.4)	53 (5.7)	28 (16.2)	18 (26.9)	63 (6.1)
Hypertension	165 (15.0)	124 (13.4)	41 (23.7)	24 (35.8)	141 (13.7)
Coronary heart disease	27 (2.5)	17 (1.8)	10 (5.8)	6 (9.0)	21 (2.0)
Cerebrovascular disease	15 (1.4)	11 (1.2)	4 (2.3)	4 (6.0)	11 (1.1)
Hepatitis B infection¶	23 (2.1)	22 (2.4)	1 (0.6)	1 (1.5)	22 (2.1)
Cancer‖	10 (0.9)	7 (0.8)	3 (1.7)	1 (1.5)	9 (0.9)
Chronic renal disease	8 (0.7)	5 (0.5)	3 (1.7)	2 (3.0)	6 (0.6)
Immunodeficiency	2 (0.2)	2 (0.2)	0	0	2 (0.2)

Guan W et al, NEJM 2020

	Total (n=191)	Non-survivor (n=54)	Survivor (n=137)	p value
Demographics and clinical characteristics				
Age, years	56·0 (46·0–67·0)	69·0 (63·0–76·0)	52·0 (45·0–58·0)	<0·0001
Sex	..	..	..	0·15
Female	72 (38%)	16 (30%)	56 (41%)	..
Male	119 (62%)	38 (70%)	81 (59%)	..
Exposure history	73 (38%)	14 (26%)	59 (43%)	0·028
Current smoker	11 (6%)	5 (9%)	6 (4%)	0·21
Comorbidity	91 (48%)	36 (67%)	55 (40%)	0·0010
Hypertension	58 (30%)	26 (48%)	32 (23%)	0·0008
Diabetes	36 (19%)	17 (31%)	19 (14%)	0·0051
Coronary heart disease	15 (8%)	13 (24%)	2 (1%)	<0·0001
Chronic obstructive lung disease	6 (3%)	4 (7%)	2 (1%)	0·047
Carcinoma	2 (1%)	0	2 (1%)	0·37
Chronic kidney disease	2 (1%)	2 (4%)	0	0·024
Other	22 (12%)	11 (20%)	11 (8%)	0·016

Zhou et al, Lancet 2020

Aim of the study

- The main objective of the study is to evaluate the presence of EVA 3-6 months and 12-15 months after COVID-19 infection
- The primary endpoint will be **carotid-femoral pulse wave velocity (PWV)**, an established biomarker of EVA.
- **Secondary endpoint variables**:
  - Central hemodynamics + wave separation / wave intensity analysis
  - Flow mediated dilation in the brachial artery (in equipped centers)
  - 24h- brachial and central blood pressure (in equipped centers)
  - Geometry and distensibility in the common carotid artery by ultrasound (in equipped centers)
  - Geometry and distensibility in the radial and digital arteries by ultrahigh-frequency ultrasound (in equipped centers)
  - Cardiac dysfunction by cardiac ultrasound (in equipped centers)
  - Thoracic aorta calcifications by CT (retrospective)

Research questions

- Is EVA dependent of COVID-19 severity?
- Which role for psychosocial factors (PTSD, socio-economic status) in COVID-19-induced EVA?
- Which role for previous chronic or acute treatments ?
- Which role for pre-existing cardiometabolic disease?

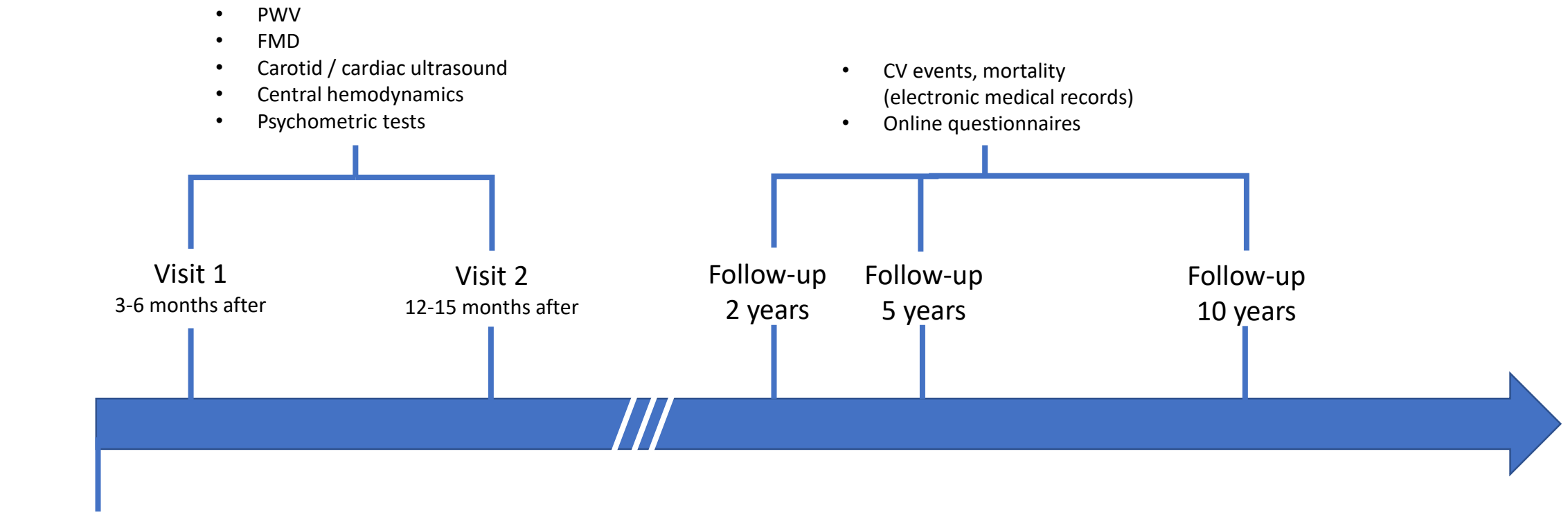
- 10-year follow-up: is COVID-19-induced EVA associated with increased CV morbidity and mortality?

Study population

- The study will include 4 groups :
  - Patients with recent (<6 months) confirmed infection by SARS-Cov-2, requiring a **hospitalization in intensive care unit**
  - Patients with recent (<6 months) confirmed infection by SARS-Cov-2, requiring a **hospitalization in a medicine unit**
  - Patients with recent (<6 months) confirmed infection by SARS-Cov-2, **not requiring hospitalization**
  - Individuals presenting at the Emergency department for suspected COVID19, but resulted to be **negative**

Study design

- Case-control, longitudinal, multicenter study



CARTESIAN Consortium structure

- **PIs:** Rosa Maria Bruno, Pierre Boutouyrie
- **Scientific Committee:** responsible of scientific contents and publications, management of future analysis requests
- **National Study Coordinators** (1 for each Country) **-** Consortium of national studies with identical protocol
- **Centralized electronic CRF** on RedCap
- **Centralized raw data analysis**
- Publication policy: **all researchers are authors**

CARTESIAN study: state of the art

- The protocol started the submission process to the Ethical committee in France and Italy
- >30 interested centers in 12 countries, >2000 patients
- 3 companies in the VascAgeNet offered devices/softwares to centers for the study duration
- The Artery Society offers a seeding budget for each center (up to 5000 Euro, depends on number of participating centers and recruitment volume)
- Application to national grants is encouraged (ongoing in France – ANR and UK – BHF)

Thank you for the attention!

Join the CARTESIAN study:
http://www.arterysociety.org/our-activities/cartesian-2/

Background and rationale

- SARS-nCOV-2 is able to directly infect endothelial cells by binding ACE2, inducing marked endothelial damage, vasculitis and endotheliitis
- COVID-19-associated systemic severe inflammation may induce immune-mediated damage to the vasculature, thus increasing long-term risk of CV events, as already demonstrated for hospitalized pneumonia
- SARS-nCOV survivors have altered glucose and lipid metabolism twelve years after infection
- Having survived COVID-19 might be a cause of post-traumatic stress disorder (PTSD), especially if the patient needed intensive care. A direct correlation between PTSD symptoms and EVA has been demonstrated.
- Previous chronic treatments (i.e. renin-angiotensin system blockers) or treatments administered in the acute phase may have direct consequences on vascular ageing in COVID-19 patients; either protective or deleterious
- Cardiometabolic disorders, notably hypertension, obesity and diabetes, are important contributors to the severity of COVID-19.