The Link of Heart Health and Brain Health

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June 13, 2020

Today's Agenda

- Heart vs Brain: a historical vignette
- Epidemiology and pathophysiology of AD
- Role of the vascular system in dementia
  - Blood brain barrier
  - Atherosclerosis and rarefraction
  - Amyloid angiopathy
- Unifying concept of neurologic & systemic amyloid
- Prevention of Alzheimer disease

Compare CAD and AD

1. **1913.** St. Petersburg, Russia. Nickolai Anichkov demonstrated that fatal heart attacks were caused by cholesterol build-up.
2. Western diet, lifestyle & tobacco make CAD the number one cause of death in the US.
3. **1948.** Framingham Study is launched, defines features of CAD and effective treatment emerges.
4. The incidence of heart disease has fallen since **1968.**

Alzheimer disease

1. **1906.** Alois Alzheimer described the case of Auguste Deter in Germany.
2. She had paranoia, delusions and memory loss for 4 years before dying at age 55.
3. Alzheimer dementia was felt to be a rare condition and was not recognized as a major cause of dementia in the elderly until **1970s**.
4. There is no effective treatment. The number of cases is rising and it is now the 5th most common cause of death in the US.

Treatment of CAD

- 1913. Discovery that cholesterol build-up causes heart attacks.
- Mid 1950s. Discovery that blood cholesterol was related to coronary atherosclerosis. Risk factors defined.
- November 30, 1967. First coronary bypass surgery.
- 1977. Andeas Gruntzig performed first coronary angioplasty.
  - (February 14, 1980. First angioplasty in Detroit, Dr. JC Rogers)
- First statin drug to reduce cholesterol, 1987. (Lovastatin.)

- ***And, the next breakthrough…***

Blockbuster trial!

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Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

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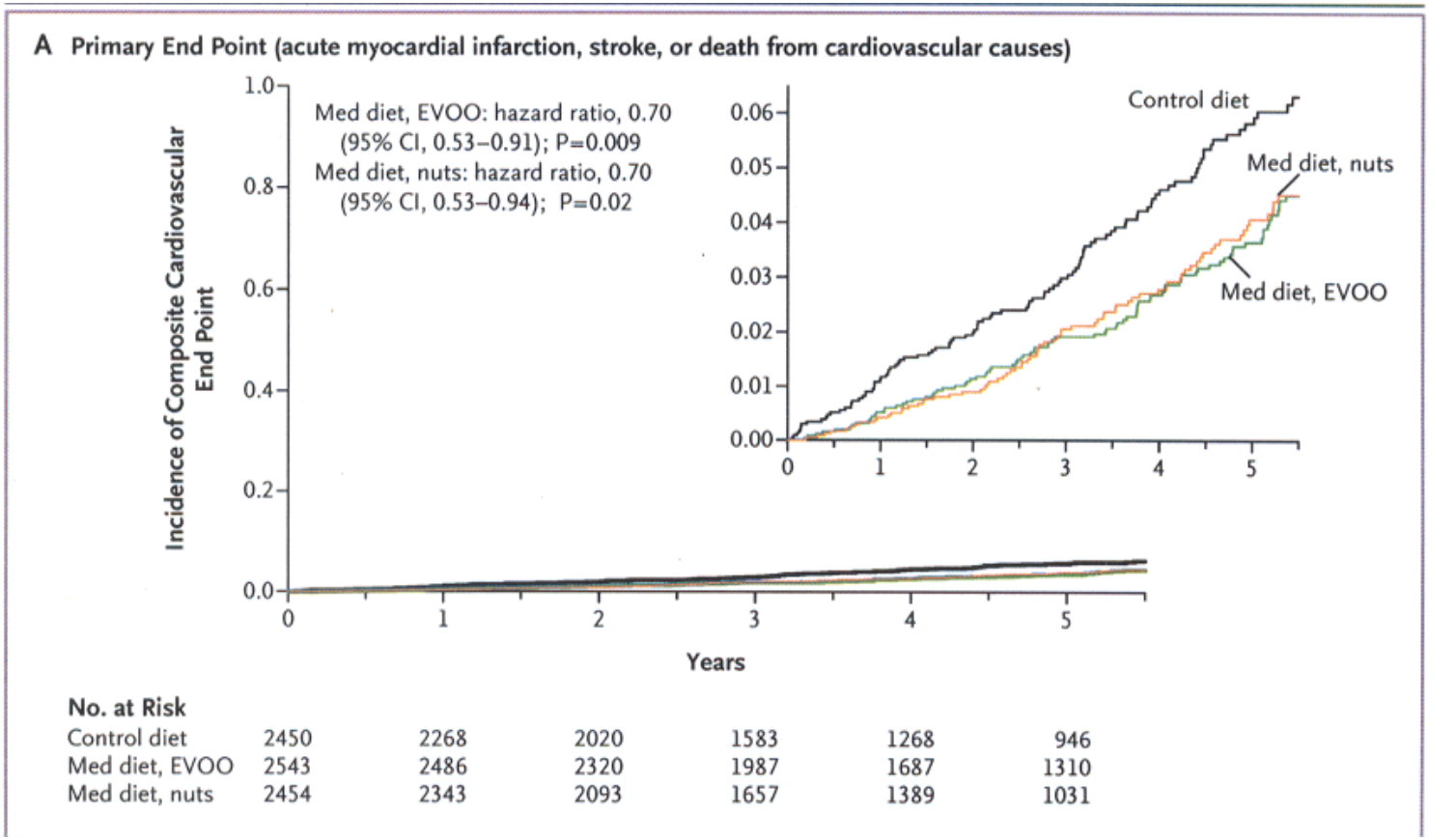
Results: primary endpoint



At Last

- Cardiology – an equal footing for
  - Prevention
  - Treatment

- What about brain health?
  - Prevention
  - Treatment

Alzheimer Disease

- Described by Alois Alzheimer Nov 3, 1906.
  - Patient: Auguste Deter
  - Symptoms: delusional jealousy, paranoia, memory loss began at age 51
  - Death at age 55
  - Autopsy by Alzheimer
    - Amyloid plaques
    - Neurofibrillary tangles
    - Arteriosclerotic changes

Basic mechanism of Alzheimer disease

- Amyloid, a protein produced in the brain in response to inflammation, can build up to toxic levels, and then
  - cause damage to brain cells,
  - which then produces more inflammation,
  - leading to more nerve damage and memory loss.
- This vicious cycle becomes relentless.

So, we should block amyloid, right?

- Nope. Every research study on medications that block amyloid protein shows no benefit

Let's back up a step…

- Maybe the problem is not just the production of amyloid, but the body's ability to remove the amyloid protein.
- The first problem is that the aging process weakens the blood vessels that protect the brain from undesirable agents.
- In addition, the body's natural methods of clearing out this amyloid protein become damaged and the amyloid builds up rapidly.

The time course of dementia

- This accumulation of beta amyloid begins silently and slowly. It may take 10 or 15 years before the disease becomes obvious.
- By then, it’s too late for there to be any benefit from using medications that might lower amyloid levels.

Epidemiology of AD

- Early onset
  - Amyloid precursor protein (APP); > 30 mutations; involved in synaptic transmission; accounts for 10-15% early onset AD
  - Presenillin 1; 50% of early-onset familial AD; early age of onset (43 years)
  - Trisomy 21 (Down syndrome); extra copy of APP
- These genetic cases account for just 1% of AD

Genetics of Late Onset AD (LOAD)

- Most firmly established genetic risk factor for late-onset AD is apolipoprotein E (*APOE*)
  - Located on chromosome 19
- The *APOE* epsilon 4 allele is a risk factor for AD and possibly vascular dementia as well
- Allele frequency

Whites	15%
African	25 (8-41%)
Asians	7-24%

APOE and Strength of Association

- I allele confers 2 to 3- fold increased risk of AD
- 2 copies (homozygous) confers 8- to 12-fold risk compared to non-carriers

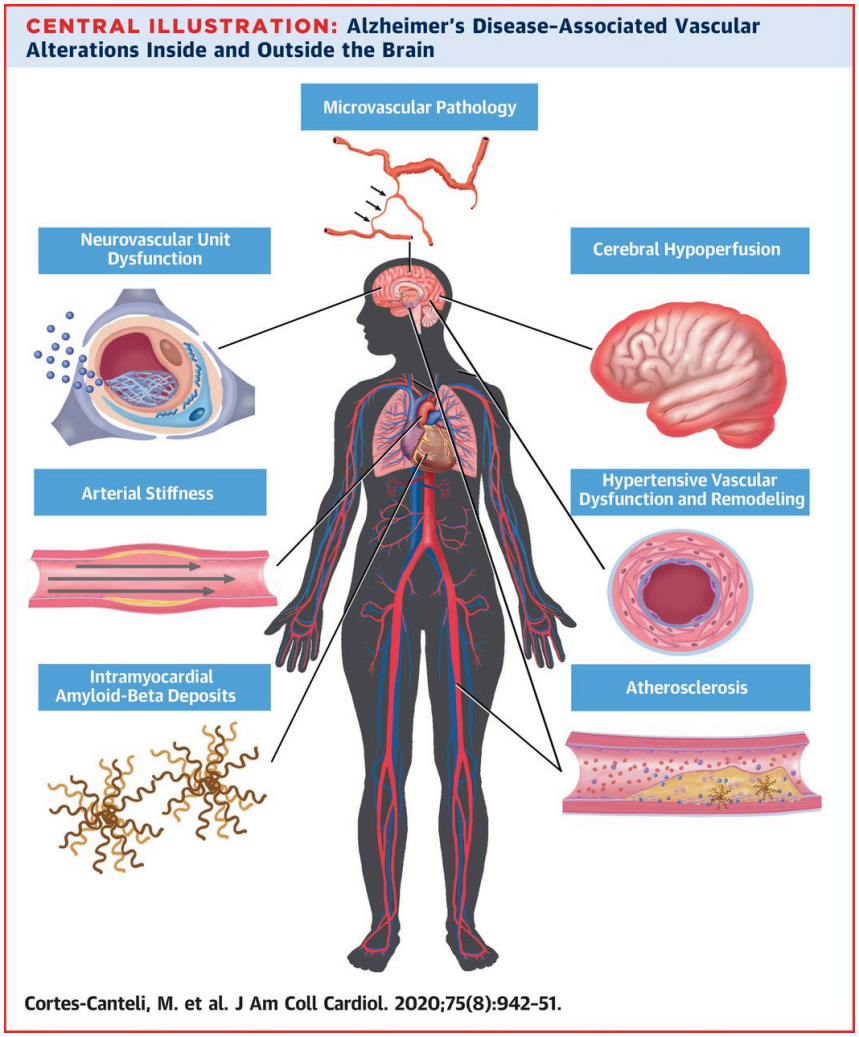
- About 40% of patients with AD do not carry the *APOE* e4 allele

Acquired risk factors for AD

- Hypertension
  - The primary risk factor for brain vascular disease
  - Arterial stiffness and blood pressure variability also play an independent role in causing AD
- Dyslipidemia
  - Peripheral blood LDL-C does not cross the blood brain barrier unless the barrier is damaged by vascular disease.
  - Most cholesterol in the brain is synthesized by astrocytes and provided as HDL-C

Acquired risk factors for AD

- Cerebrovascular disease
  - Cerebral small vessel disease is common in aging, does not occur in isolation, and is common in AD
  - Decreased blood flow occurs before amyloid deposition and probably causes decreased amyloid clearance
  - Cerebrovascular dz may also contribute to breakdown in blood brain barrier



Marta Cortes-Canteli, and Costantino Iadecola J Am Coll Cardiol 2020;75:942-951

Other risk considerations for AD

- Peripheral atherosclerosis
- Type 2 DM
- Hearing loss
- Obesity
- Physical inactivity
- Diet
- Lifelong learning (cognitive training)

A word about diabetes

- Hyperglycemia
  - increases amyloid beta accumulation on brain lesions,
  - exacerbates oxidative stress, neuroinflammation, and mitochondrial dysfunction,
  - impairs neuronal integrity,
  - and causes neurodegeneration

Double jeopardy of T2D

- Breakdown of blood brain barrier with increase in amyloid protein
- Decreased clearance of amyloid

A note on obesity

- Obesity is a pro-inflammatory state
- Elevated triglyceride levels impair brain function in the animal model
- Obesity induced systemic change in vasculature could cause cerebral white matter lesions
- Non-linear relationship with BMI suggests cumulative effects of these mechanisms

How could exercise help?

- Exercise increases the removal of misfolded amyloid protein, a process called *autophagy.*
- This process is part of the brain's *glymphatic* system.

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- Sleep also enhances the removal of amyloid protein, giving rise to the slang expression of "brainwashing" during sleep

Environmental Risk Factors

- Second hand smoke
- Air pollution
- Pesticides

Pathology of AD

- Most patients who have an antemortem diagnosis of AD have autopsy findings of AD
- 1/3 of patients over age 85 with no dementia have pathology findings of dementia
- Cerebrovascular disease is very common with dementia
- In older subjects, the risk of dementia with less AD pathology is associated with concomitant vascular disease or Lewy bodies.

Risk of AD and age

- Risk of AD doubles with each decade beyond age 60
- In CHS-CS study, only 19 of 160 participants age >93 were free of cognitive impairment
- In a medicare survey of 22,896 adults age 65 or older, dementia was second to HF as a leading cause of mortality
- Mortality statistics may underestimate deaths due to dementia, because deaths do not happen from AD per se.

A note on vascular dementia

- Cognitive impairment on a vascular basis is caused by a variety of ischemic lesions
  - Multiple infarcts affecting several brain regions (multi-infarct dementia)
  - A single infarct in areas involved in cognition (strategic infarct dementia) together are rare
- Vascular dementia results from discrete or confluent white matter lesions caused by alterations in the small arterioles of basal ganglia and subcortical white matter.

Importance of vascular system in Alzheimer disease

One specific study: ARIC

JAMA Neurol 2017 Oct; 71(10): 1246-1254

- Atherosclerosis Risk in Communities
- 15 792 participants aged 44-66 in 1987-1989
- Black 27.1%, White 72.9%
- Follow up
  - Baseline 1987-1989
  - Visit 2* 1990-1992
  - Visit 3 1993-1995
  - Visit 4* 1996-1998
  - Neurocognitive study (ARIC-NCS)* 2011-2013

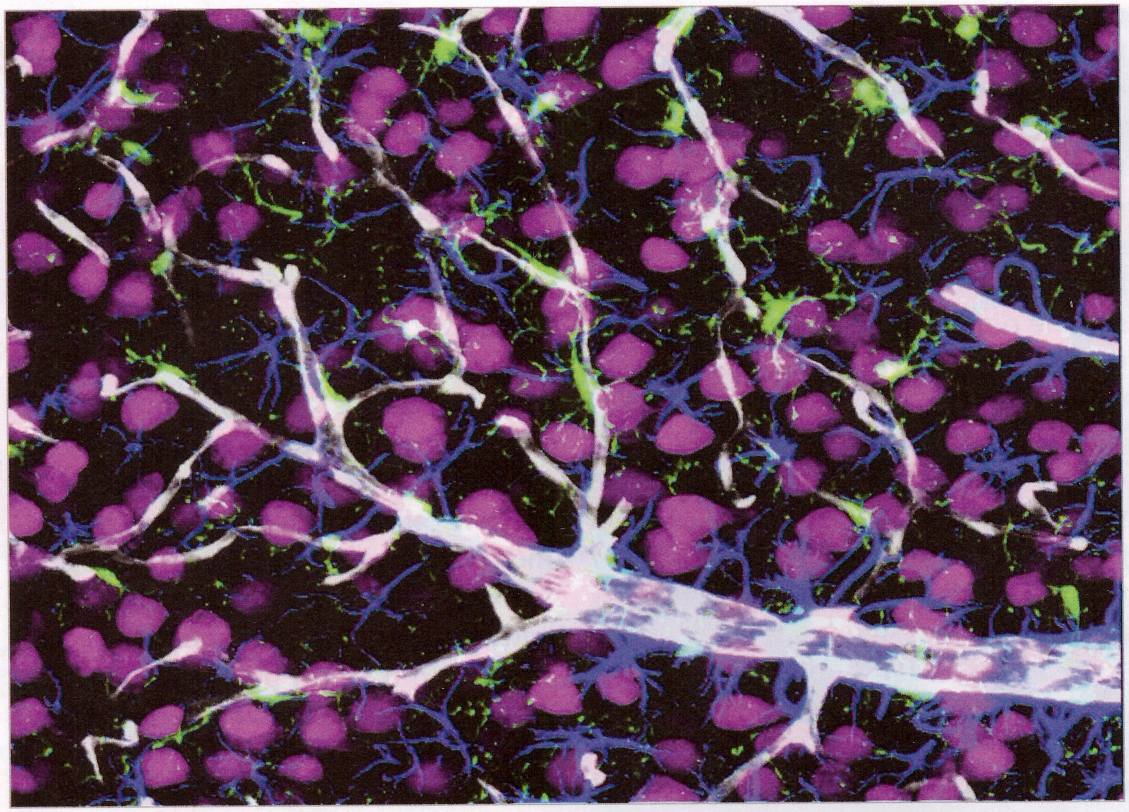
Risk Factors, ARIC-NCS

- Increased risk of dementia (N = 1516) was associated with
  - Black race
  - Baseline older age
  - Lower educational attainment
  - Current smoking
  - Diabetes
  - Prehypertension & hypertension
  - *APOE* e4 carriers
  - (Not total cholesterol)

Do statins cause dementia?

- Longest ever observational study in Australia reported Nov 26, 2019, *J Am Coll Cardiol.*
- Rigorous neurophysiologic testing including radiographic measurements of brain areas associated with memory and cognition
- No evidence that statins are associated with adverse memory effects or cognitive skills
- Actual improvement in subgroups of normal BP and in *APOE* e4 carriers

The blood-brain barrier



The neurovascular unit comprises neurons (pink), astrocytes (blue), microglia (green), and arterioles and capillaries (white). The blood brain barrier, formed by the endothelial cell membranes of blood vessels within the neurovascular unit, regulates amyloid-β clearance.

Sepsis

- Sepsis is a systemic inflammatory disease resulting from infection
- Symptoms: Spectrum from typical flu-like (eg fever, headache) to multifactorial syndrome known as sepsis-associated encephalopathy (previously called delirium)

Sepsis-associated encephalopathy

- Acute altered mental status
- Higher morbidity and mortality
- Long-term cognitive impairment
- Mechanism
  - Blood brain barrier as a nexus which integrates signals from brain and periphery in sepsis

Role of Blood Brain Barrier in Sepsis

- Neuroinflammation
- Increased barrier permeability
- Immune cell infiltration & mitochondrial dysfunction
- Potential barrier for tissue non-specific alkaline phosphatase (TNAP)

Pathophysiology of SAE

- Although pathophysiology is unclear, 3 main processes seem to be involved
  - Diffuse neuroinflammation
  - Circulatory dysfunction
  - Excitotoxicity
- Whereas neuroinflammation and microcirculatory changes are diffuse,

Pathophysiology of SAE

- Whereas neuroinflammation and microcirculatory changes are diffuse, fatal cases of sepsis consistently exhibit apoptosis in specific structures:
  - The amygdala
  - Nucleus tractus solitarii
  - Locus ceruleus
- These structures activate in stress and are especially sensitive to hypoxia

So, what can we do to strengthen the blood-brain barrier?

So, what can we do to strengthen the blood-brain barrier?

- We can make our blood vessels more healthy

- Everything that supports a healthy heart supports brain health
  - Avoid tobacco in all forms
  - Regular exercise
  - Take your statin to lower cholesterol!
  - Ideal blood pressure
  - Ideal body weight

So, what about the Mediterranean diet?

OLDWAYS
HEALTH THROUGH HERITAGE

Mediterranean Diet Pyramid

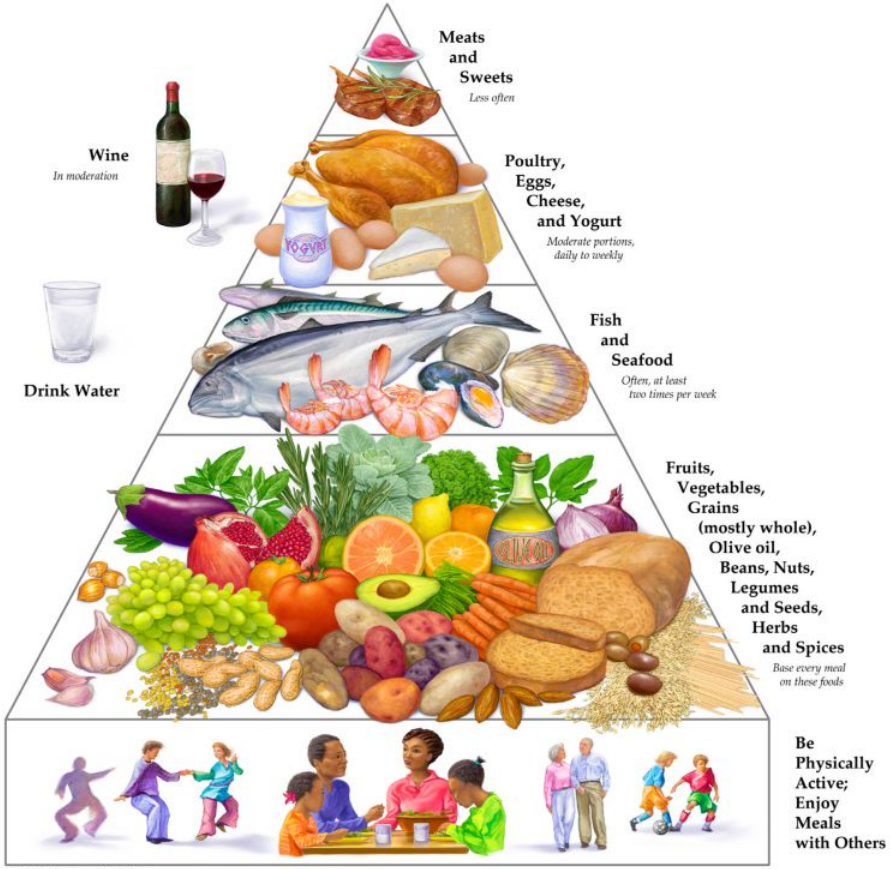


Illustration by George Middleton

www.oldwayspt.org

MEDITERRANEAN FOODS ALLIANCE
AN OLDWAYS PROGRAM

And, what about the Mediterranean diet and lifestyle?

- Diet
- Lifestyle
  - Leisure activities
  - Social activities
  - Sleep quality

Meat consumption and diabetes

- Poor control of diabetes is associated with worse outcomes for dementia.

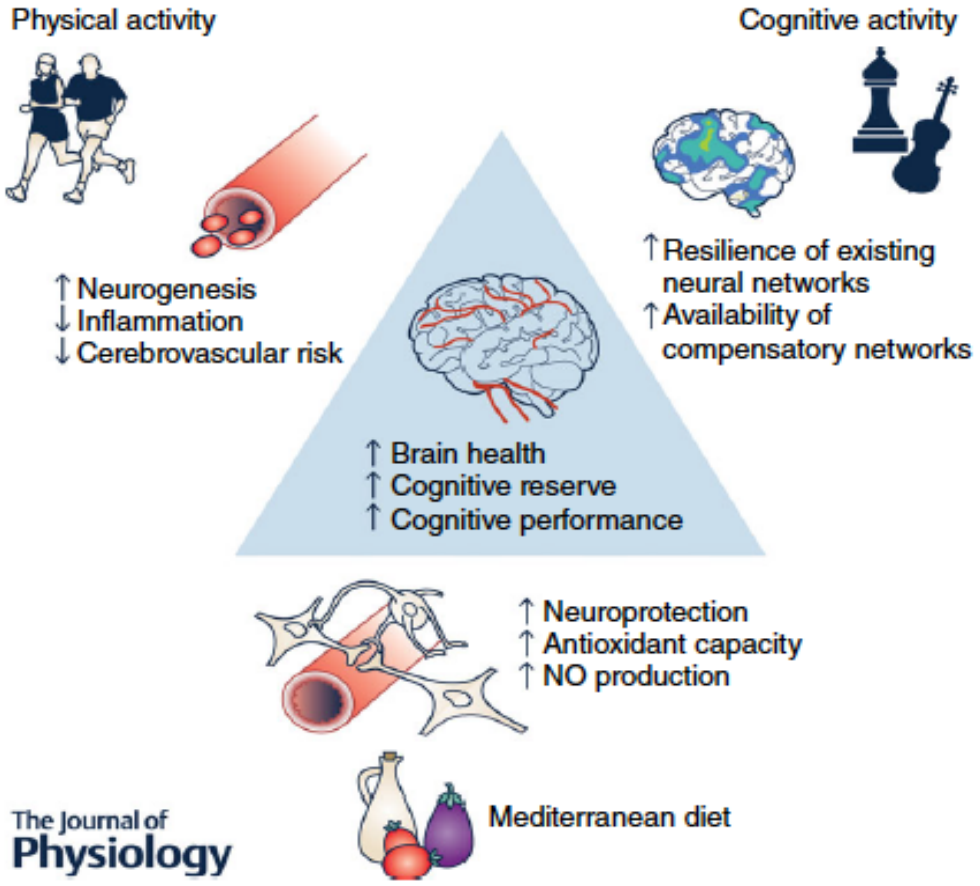
- Eating meat causes even greater declines in brain function

- Perrone L and Grant WB. *Jour Alzheimer's Disease* 45; 2015: 965-979

MIND: Vegetables and berries

- The MIND Diet (Mediterranean-DASH Diet Intervention for Neurodegenerative Delay)
- Uses the standard Mediterranean diet, but adds more vegetables and berries
- Research study participants who followed the diet most closely, when compared to those who followed it the least, had brains that were equivalent to 7.5 years younger!
- Morris MC, et al. *Alzheimers Dementia*, 2015; Sept 11(9): 1015-22

The Grand Summary



Let’s back up for a minute

Let’s back up for a minute

- In fact, let’s back up 2,000,000 years ago.
- To Olduvai Gorge in Tanzania, and the excavations of Mary and Louis Leakey in 1959…

- Introducing, Nutcracker man


NSF

Exponential increase in brain size

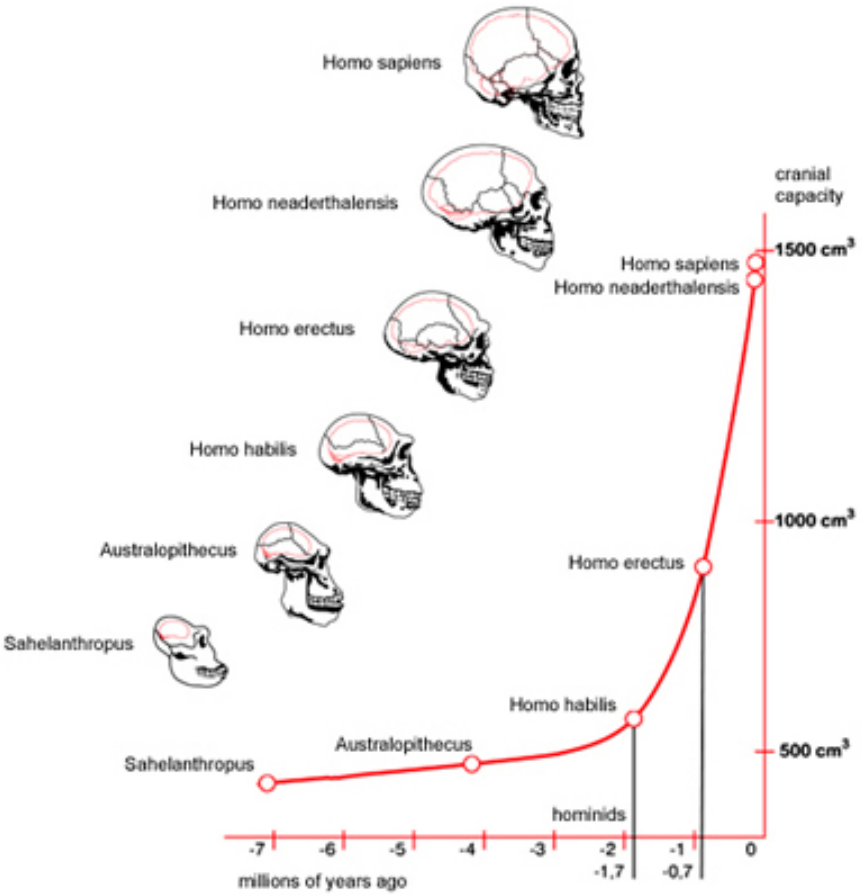


Figure 2. The growth rate of hominid cranial capacity began to rapidly increase starting around two million years ago. Figure adapted from Le Journal du Net (2010).

Current topic in paleo-anthroplogy

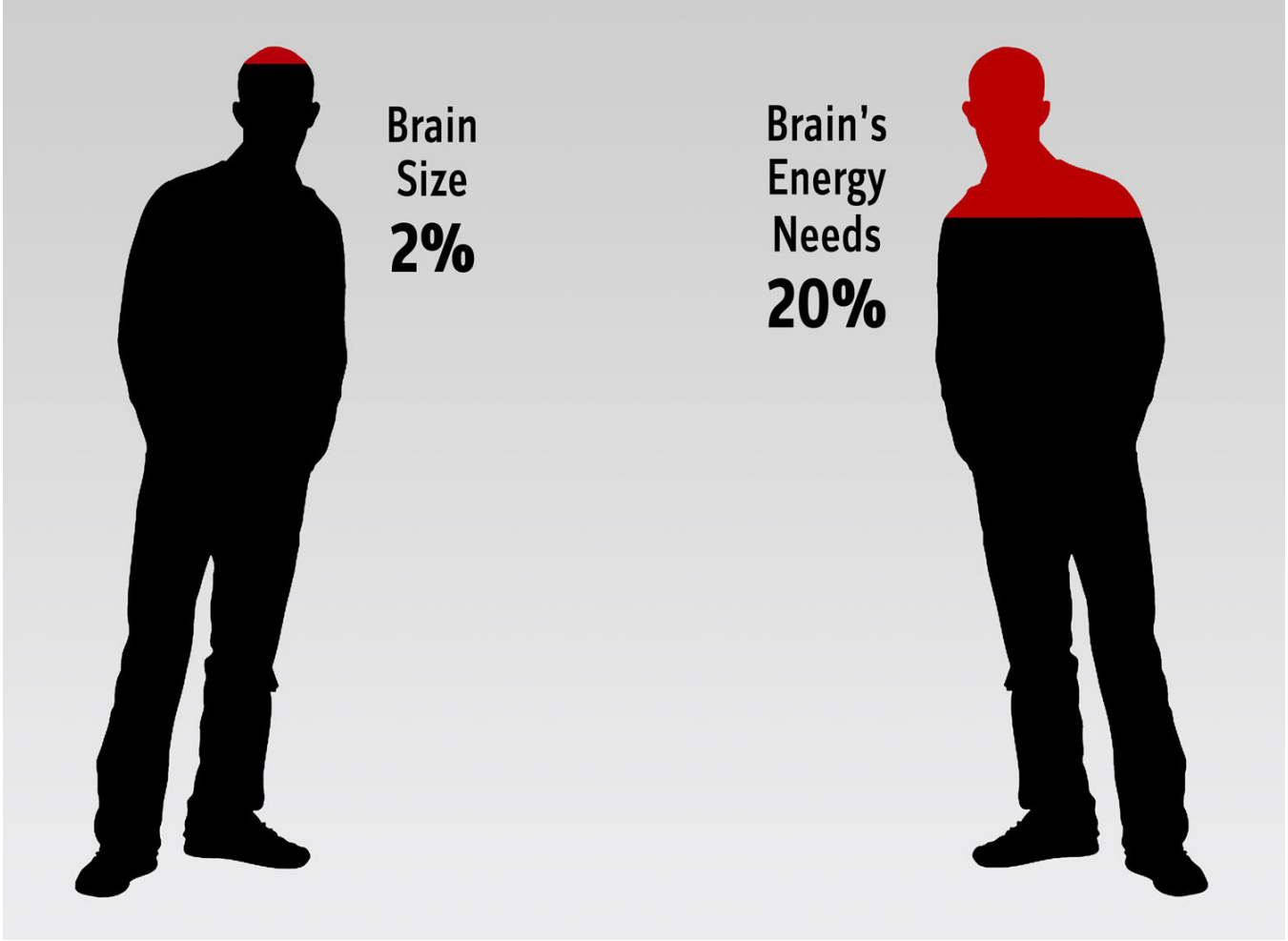
Did the Neanderthal fail to compete with our human ancestors because the Neanderthal had cognitive limitations compared to humans?

Current topic in paleo-anthroplogy

Did the Neanderthal fail to compete with our human ancestors because the Neanderthal had cognitive limitations compared to humans?

The benchmark is to prove fish consumption in ancient camp sites.

Rapid growth in brain size accompanied by significant demand for energy.



Final summary

In the absence of mechanistic treatments for dementia, maintenance of vascular and cognitive health is the best available option to contain the catastrophic societal and economic impact of the upcoming dementia epidemic

Iadecola C. *Cell Mol Neurobiol*. 2016 Mar; 36(2): 151-4

WHO 2019 Prevention of Dementia

1. Get regular physical activity.

   Any activity for at least 150 minutes per week

   (AHA/ACC: strenuous activity for 75 minutes/week)

WHO 2019 Prevention of Dementia

2. Eating a plant-based diet is essential.

   A diet high in fruits, vegetables, whole grains, healthy fats and seafood is associated with significantly lower risk

WHO 2019 Prevention of Dementia

3. Avoid inflammatory foods

   like processed grains (white flour, white rice), added sugar, sodium and saturated fats like butter and fatty meat.

   Do not take any vitamins or supplements for brain health

WHO 2019 Prevention of Dementia

4. Avoid or quit smoking.

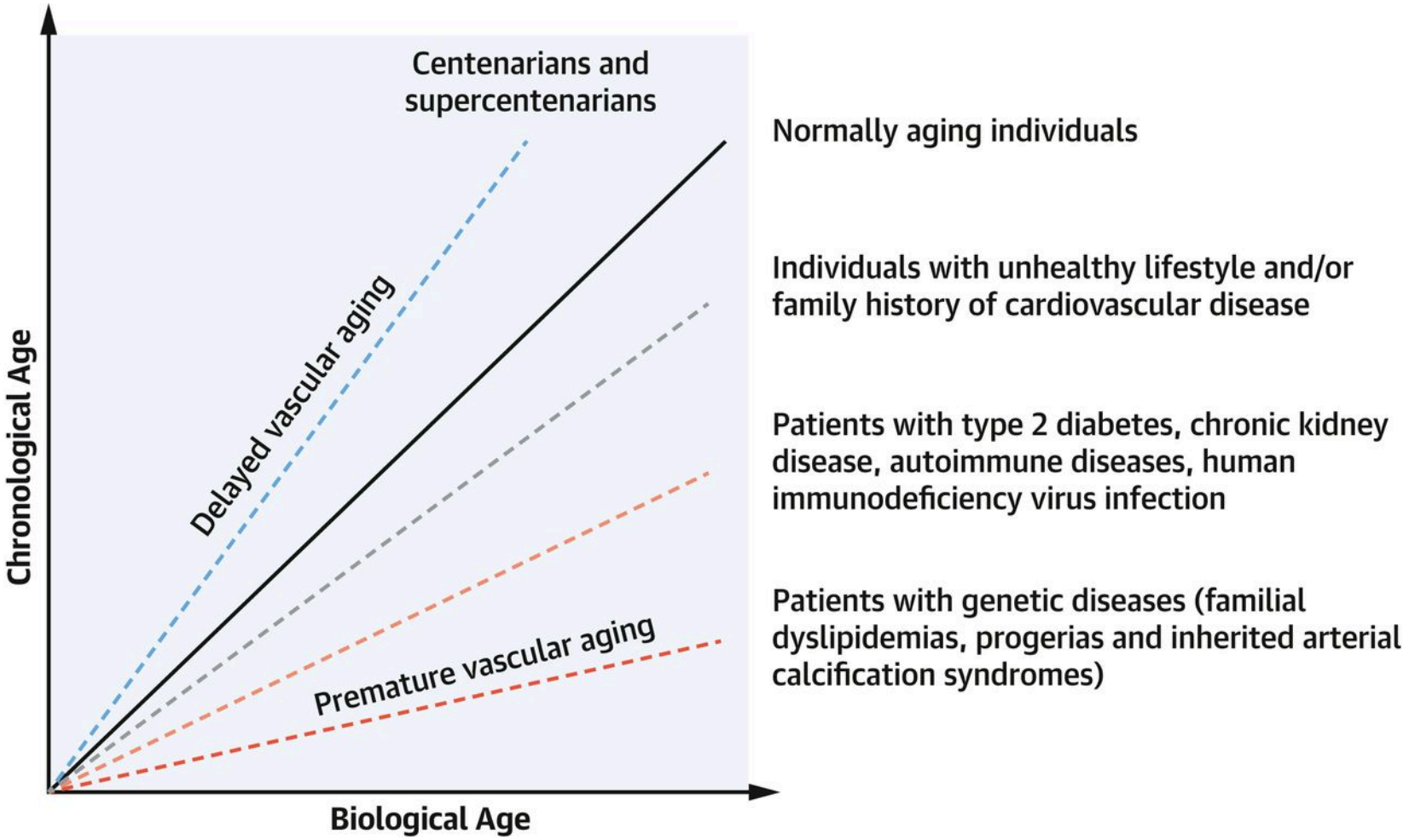
   Minimize alcohol use, especially in those who already have cognitive issues

WHO 2019 Prevention of Dementia

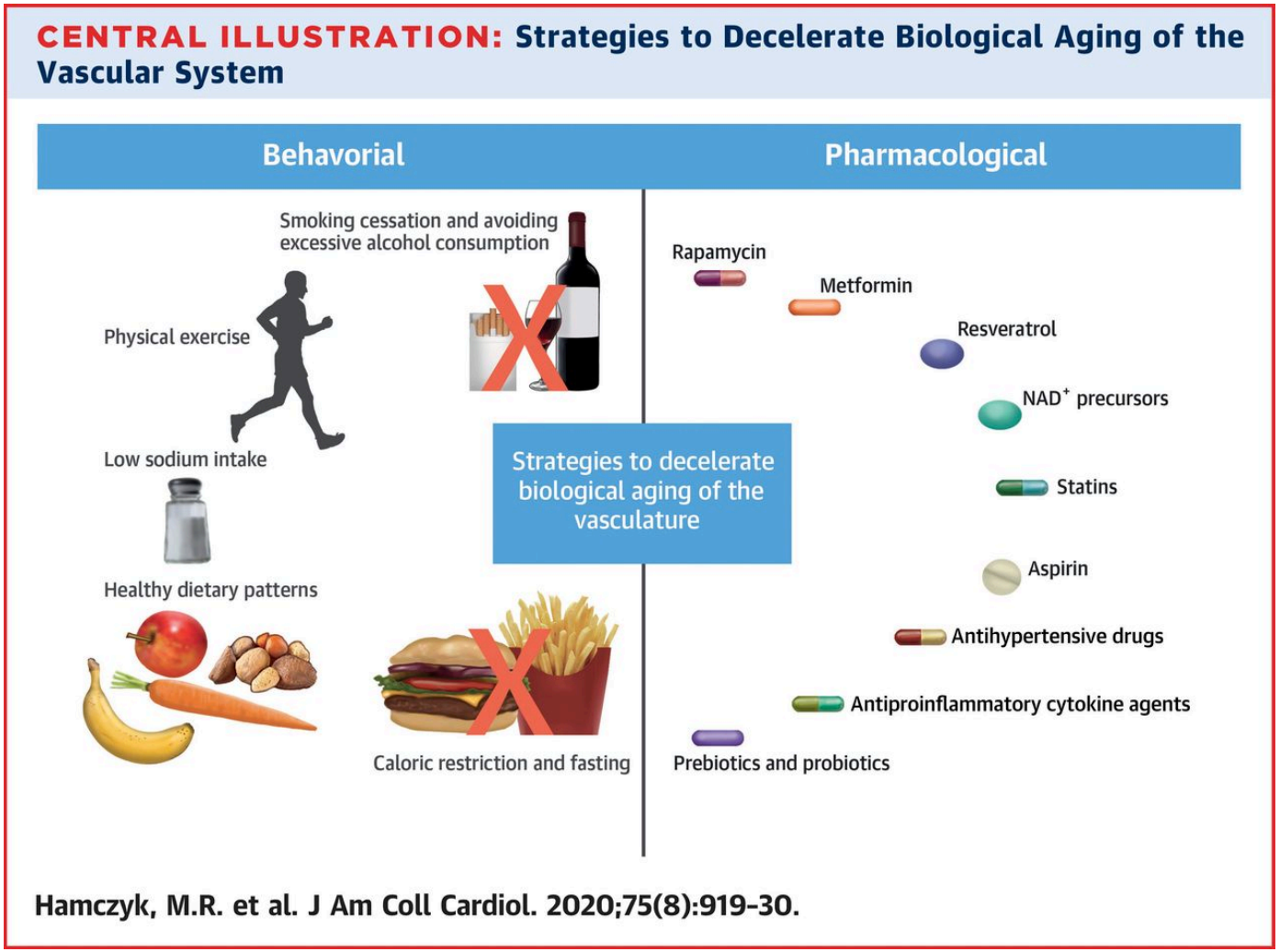
5. The evidence is less strong for these additional lifestyle issues: get enough good sleep, positive relationships and social engagement.

WHO 2019 Prevention of Dementia

6. Any condition that clogs the arteries of the heart will clog other arteries of the body, including the brain. These traditional risk factors include obesity, high blood pressure, high cholesterol and diabetes.



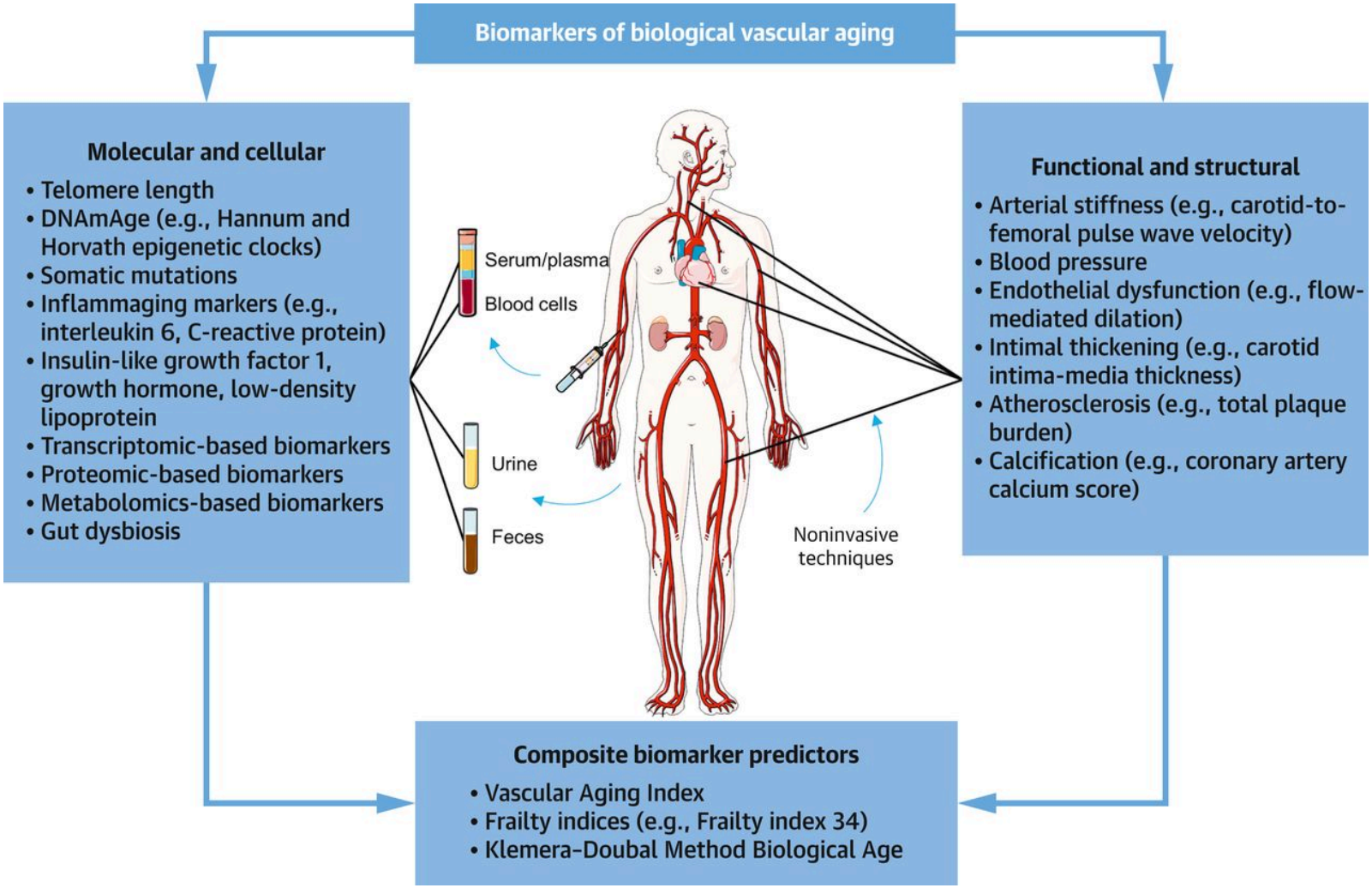
Magda R. Hamczyk et al. J Am Coll Cardiol 2020;75:919-930



Magda R. Hamczyk et al. J Am Coll Cardiol 2020;75:919-930

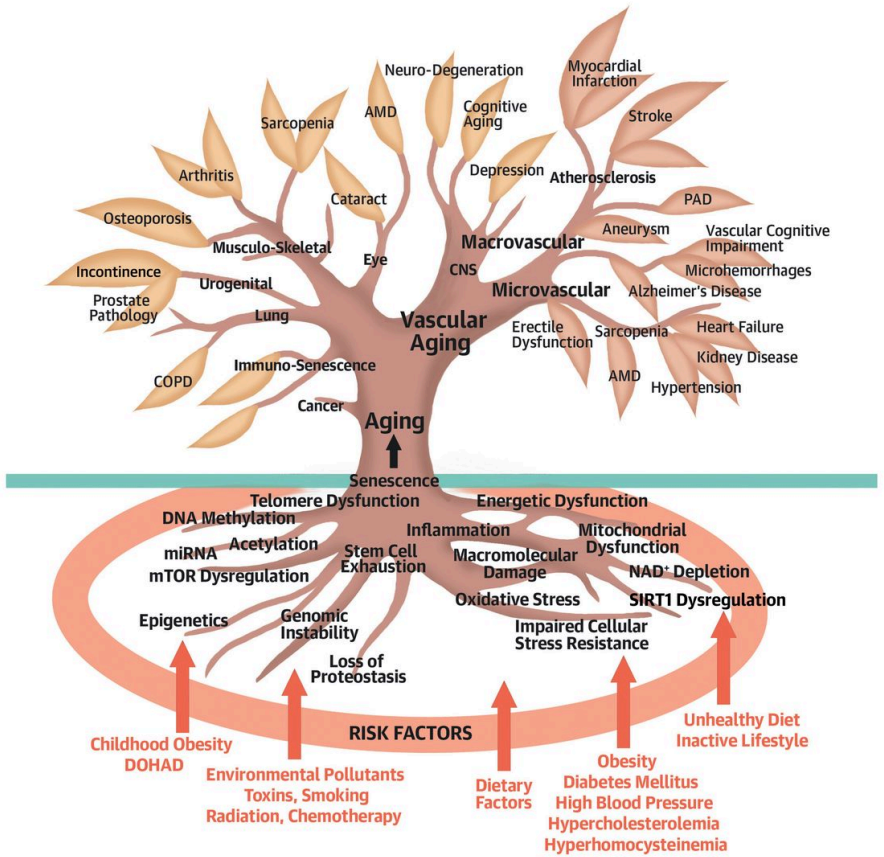
Thank you.

Are there any questions?



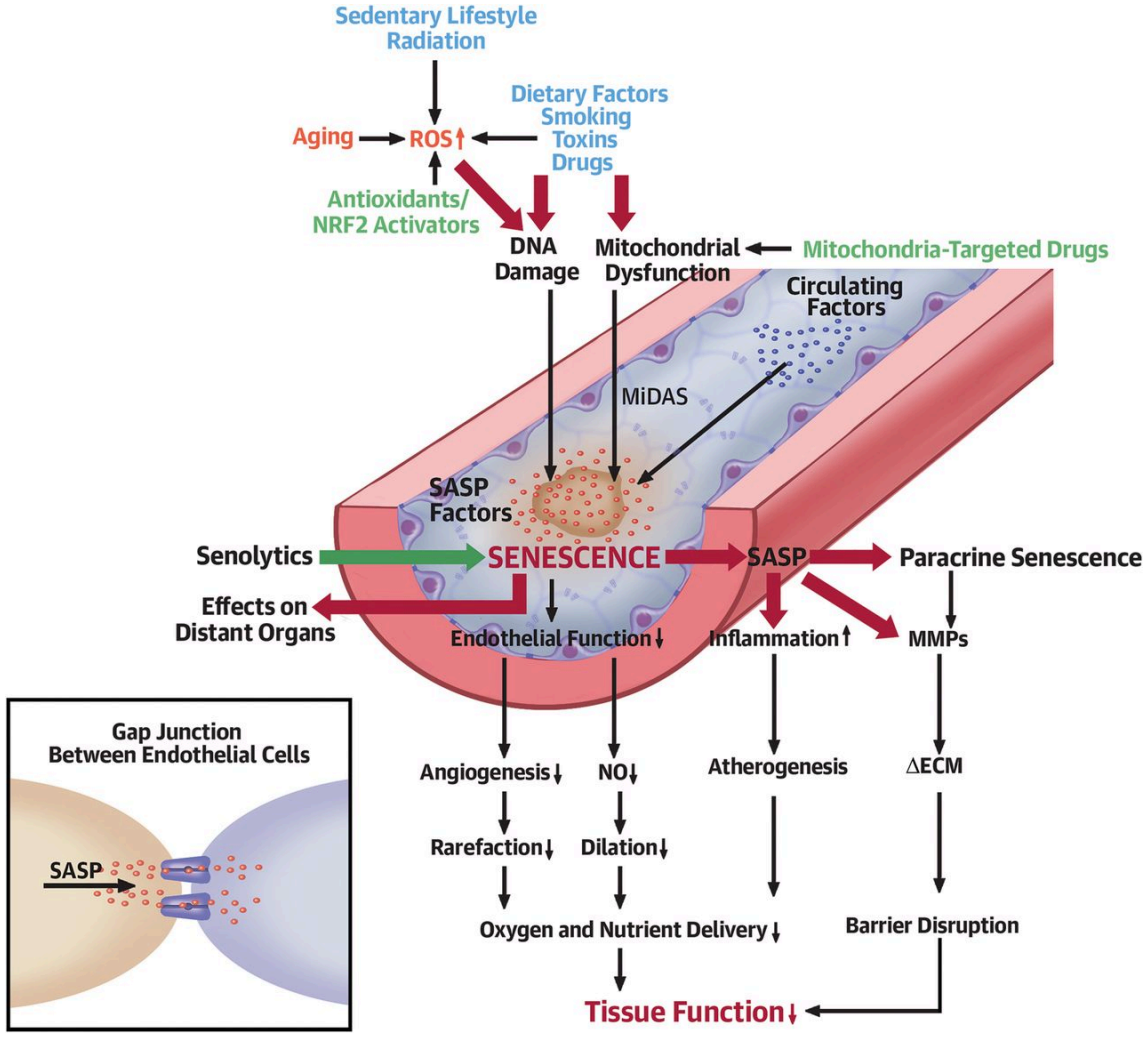
Magda R. Hamczyk et al. J Am Coll Cardiol 2020;75:919-930

CENTRAL ILLUSTRATION: Multiple Shared Mechanisms of Aging Contribute to the Pathogenesis of Diverse Age-Related Diseases in Each Organ System, Including the Vasculature, Simultaneously



Ungvari, Z. et al. J Am Coll Cardiol. 2020;75(8):931-41.

Zoltan Ungvari et al. J Am Coll Cardiol 2020;75:931-941



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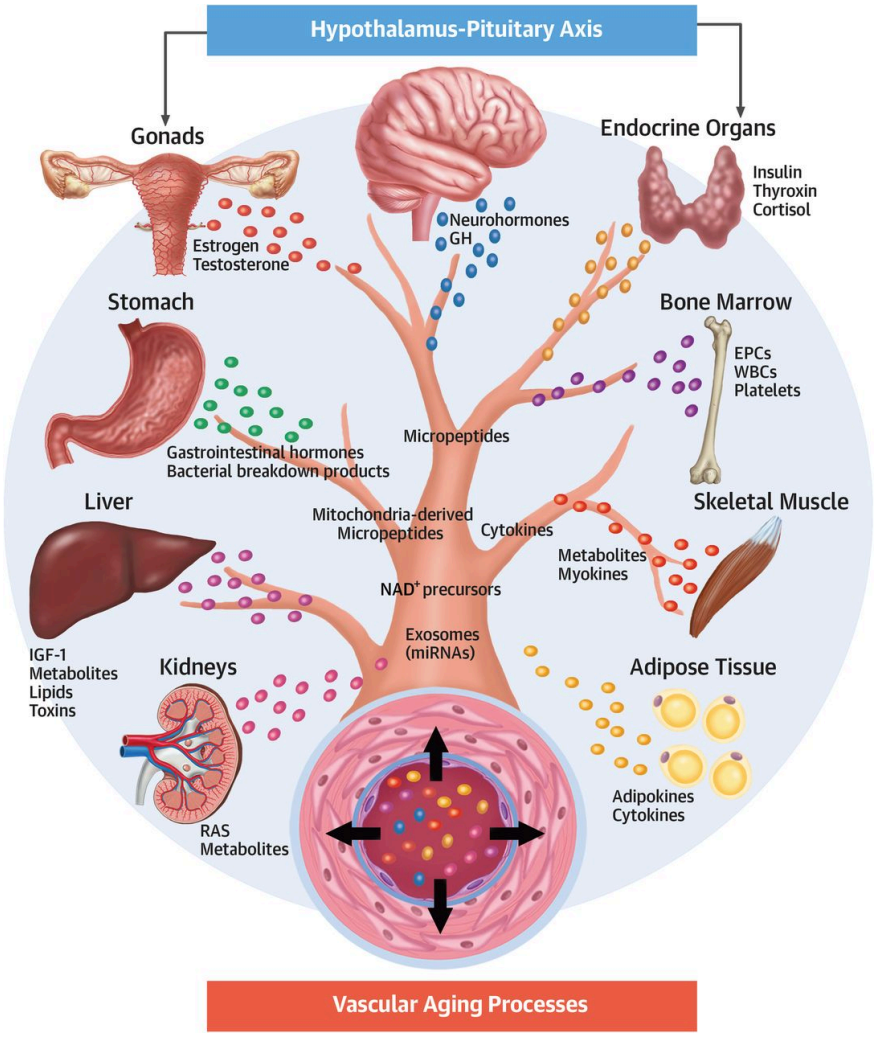

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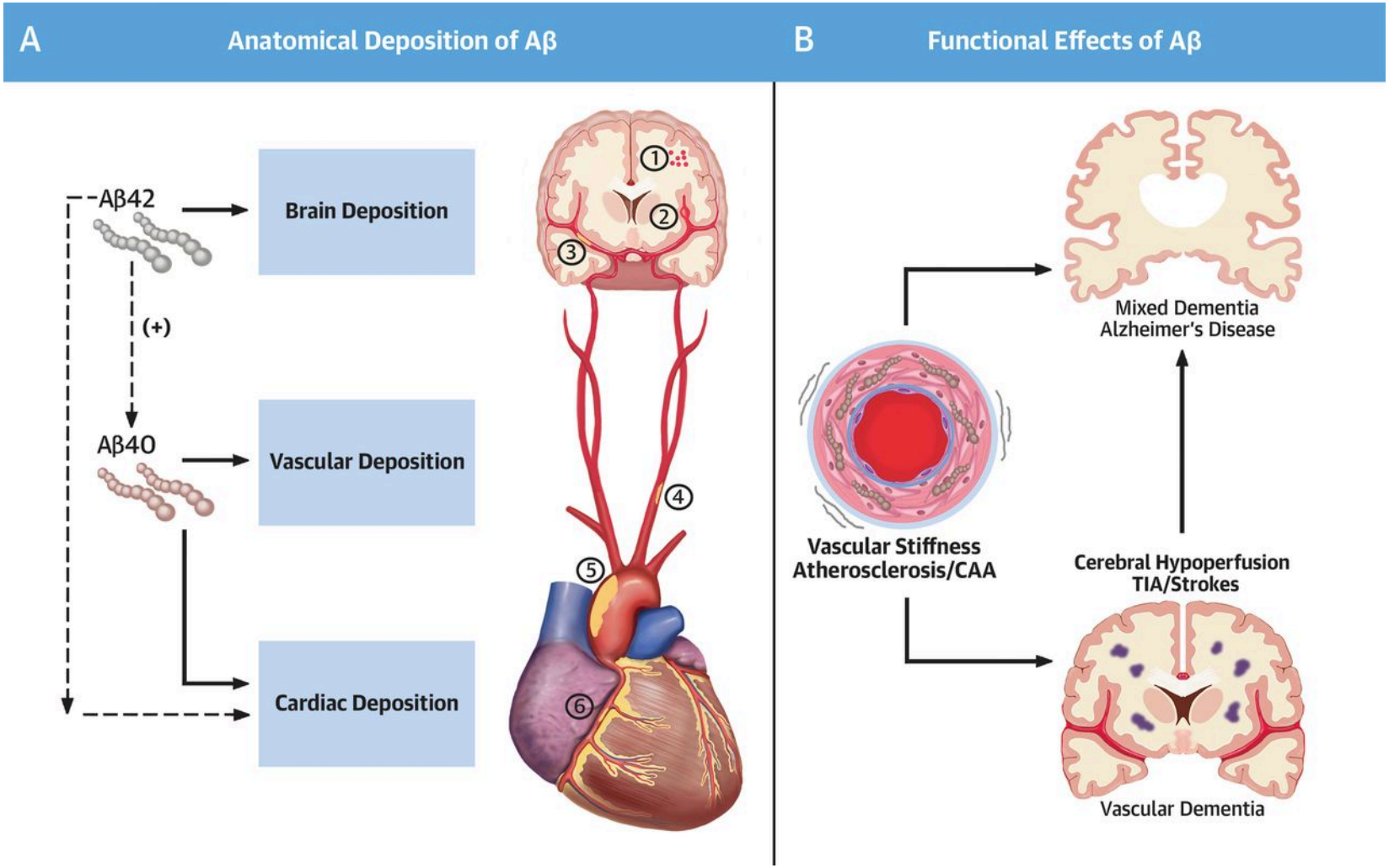
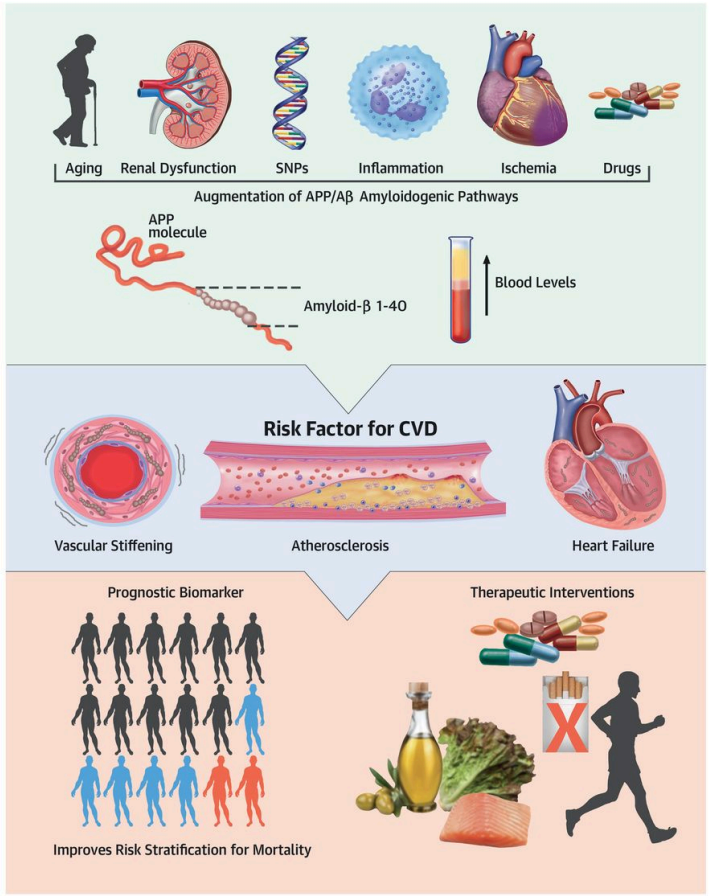


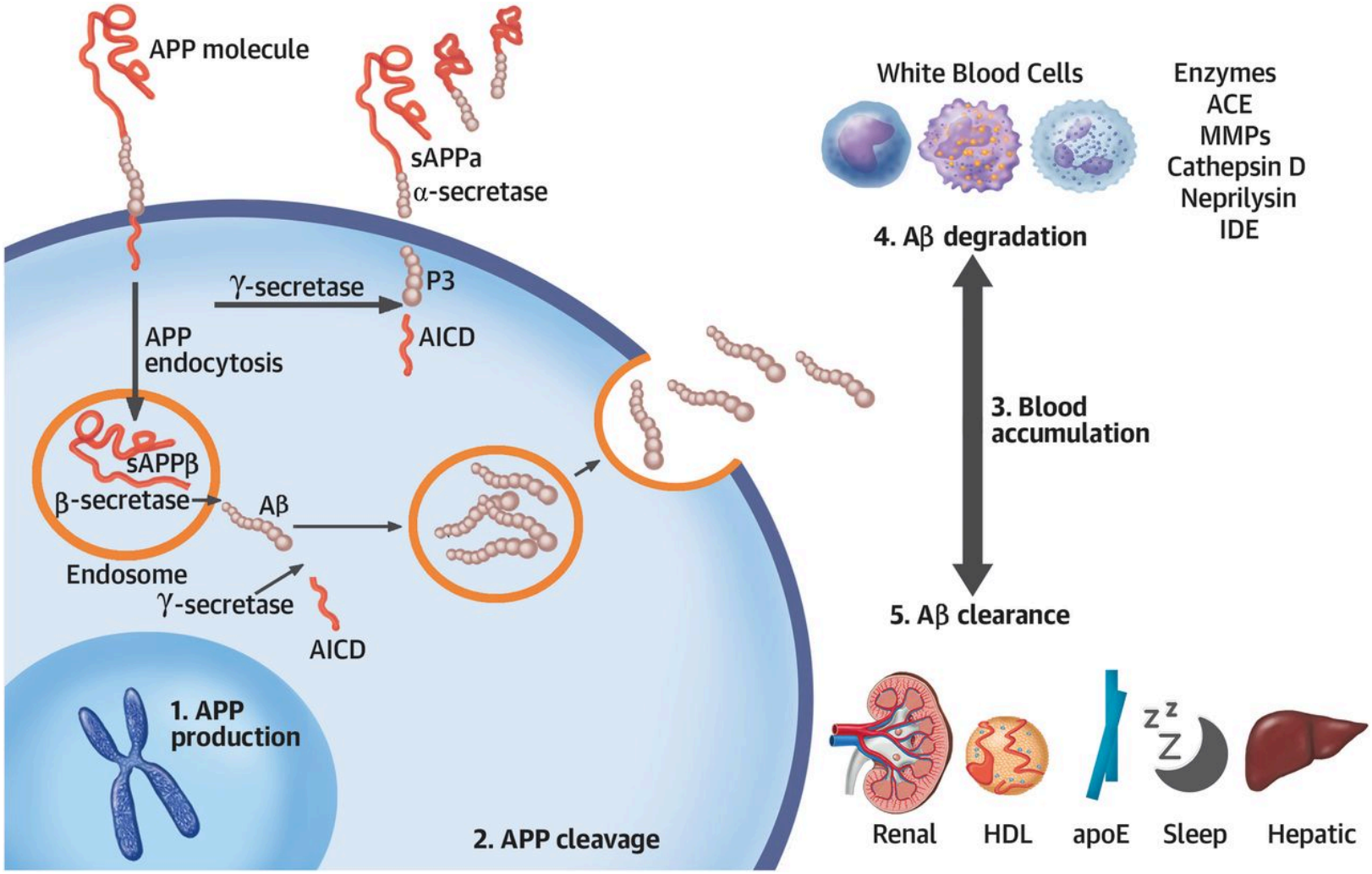
Dimitrios A. Stakos et al. J Am Coll Cardiol 2020;75:952-967

CENTRAL ILLUSTRATION: The Alzheimer's Disease Amyloid-Beta Hypothesis in Cardiovascular Aging and Disease



Stakos, D.A. et al. J Am Coll Cardiol. 2020;75(8):952-67.

Dimitrios A. Stakos et al. J Am Coll Cardiol 2020;75:952-967



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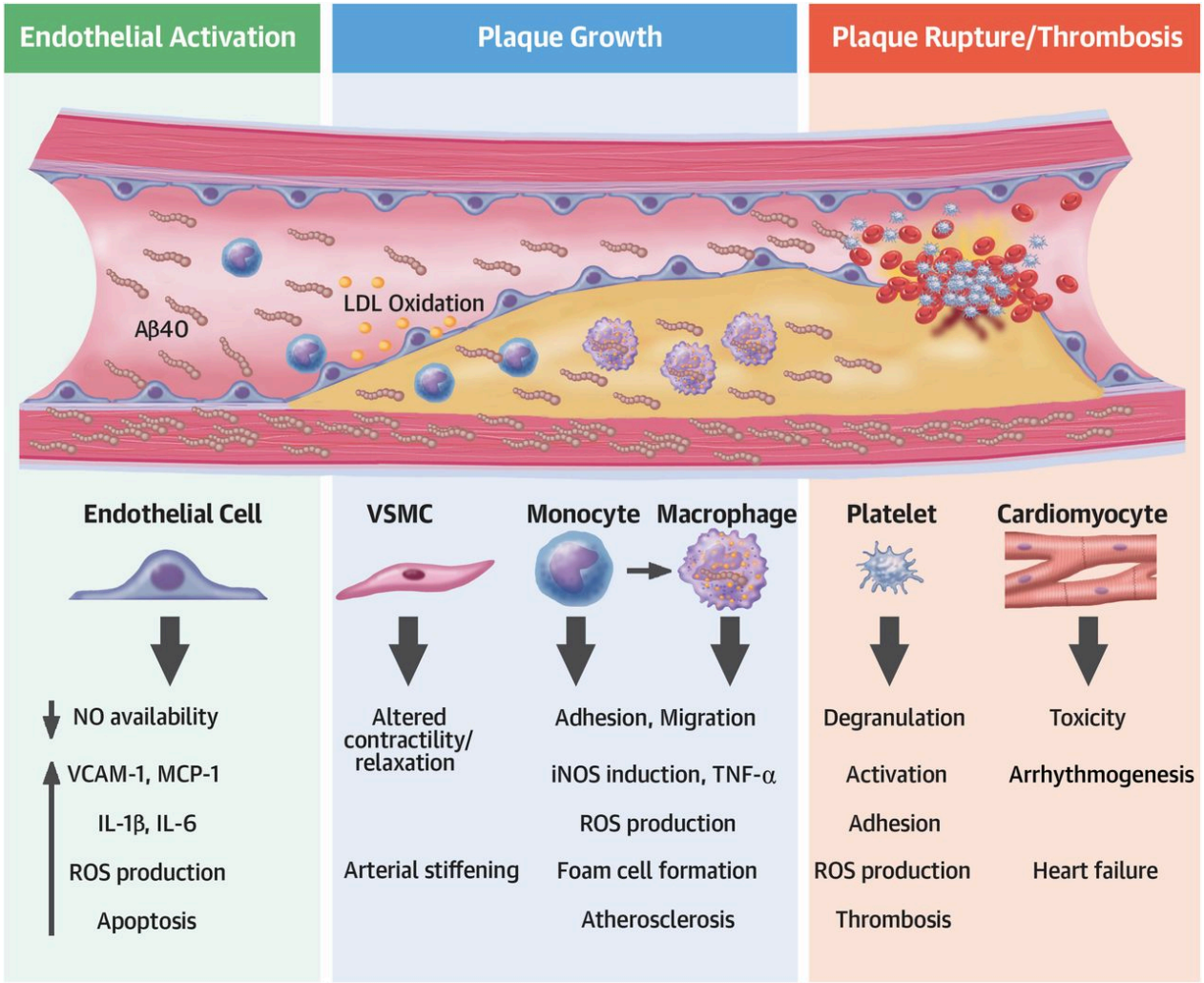

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