Vascular Contributions to Dementia

CHERYL WELLINGTON

PROFESSOR, UNIVERSITY OF BRITISH COLUMBIA

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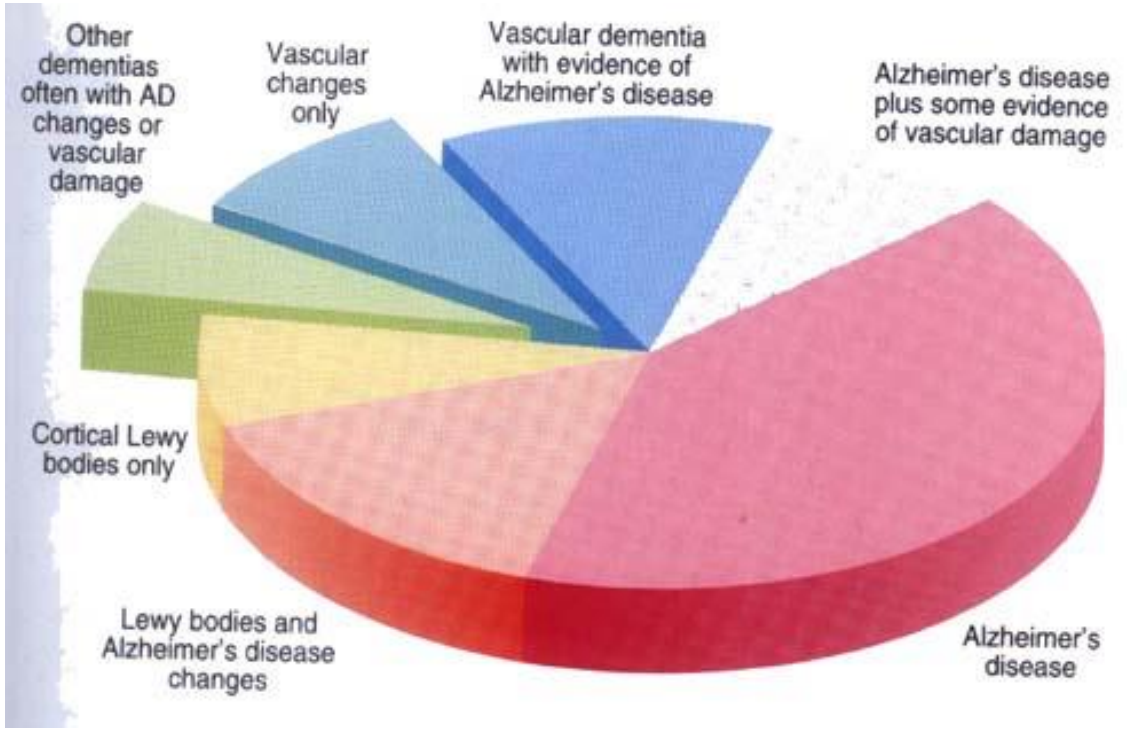
Dementia

- Alzheimer's Disease is the most common form of dementia, accounting for about 62% of cases.
- Other forms of dementia include:
  - Vascular dementia: 17%
  - Mixed dementia: 10%
  - Lewy body dementia: 4%
  - Fronto-temporal dementia: 2%
  - Parkinson's dementia: 2%
  - Other: 3%

Pathology is often mixed

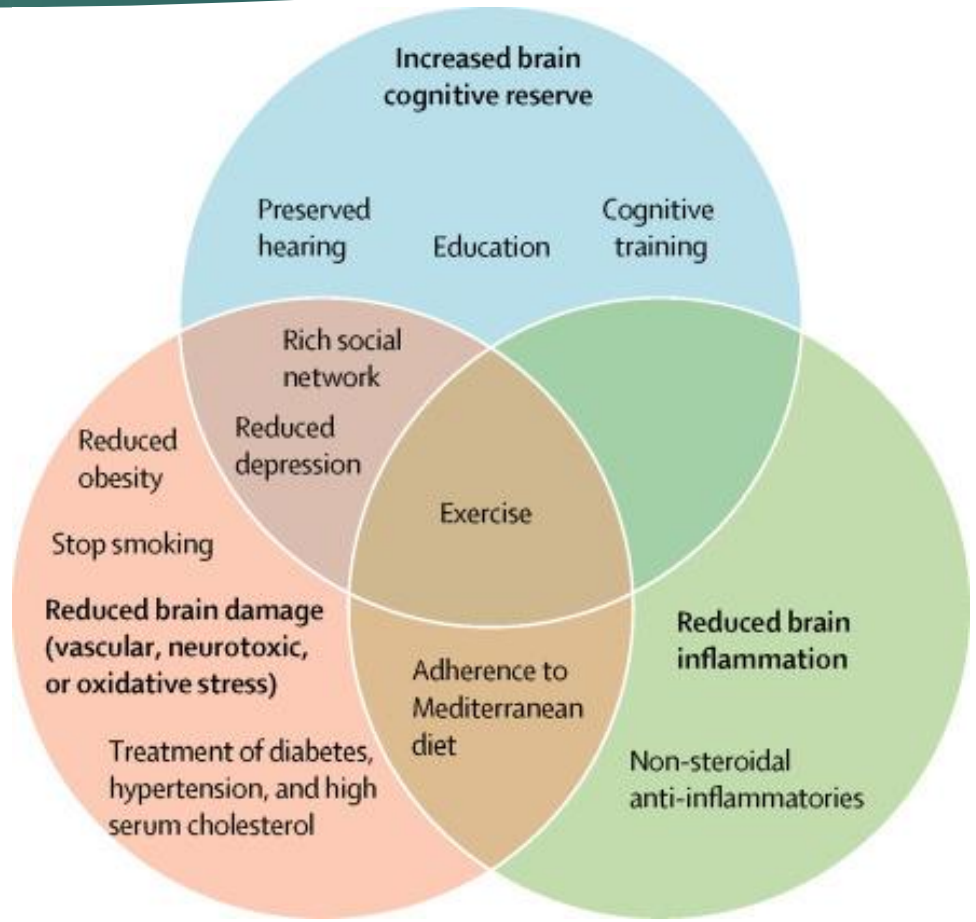
The majority of dementia cases have more than one type of pathological change.

Vascular damage is very frequently seen in the Alzheimer's Disease brain



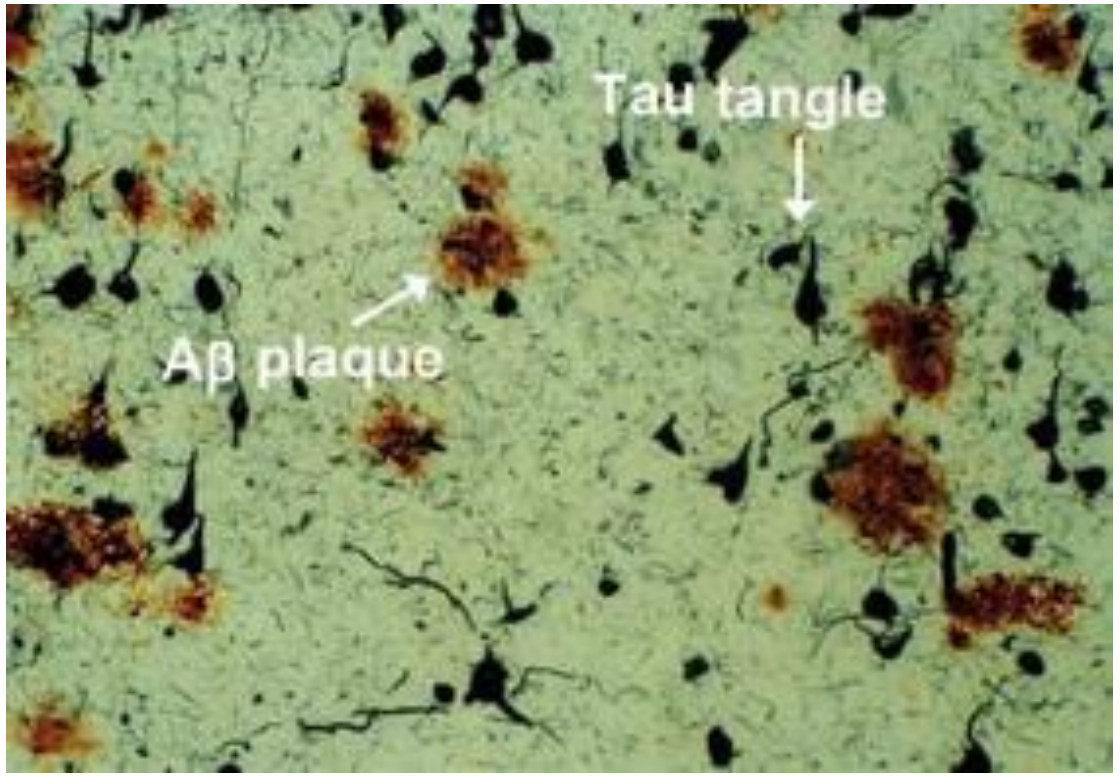
Lifestyle factors that affect dementia risk

- Dementia risk is influenced by genes and lifestyle factors
- Major vascular risk factors include:
  - Smoking
  - high blood pressure
  - high LDL cholesterol
  - diabetes



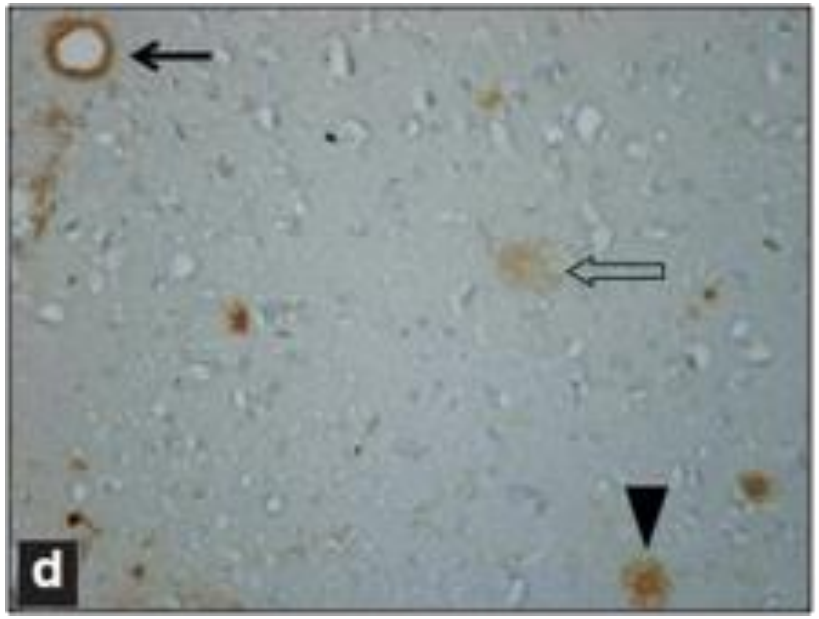
Alzheimer's Disease and amyloid

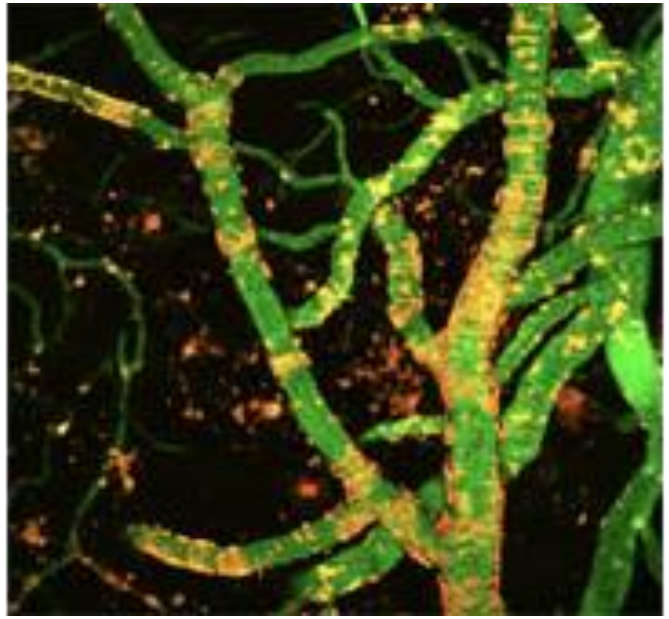
- Alzheimer's Disease is defined by amyloid plaques and neurofibrillary tangles in the brain

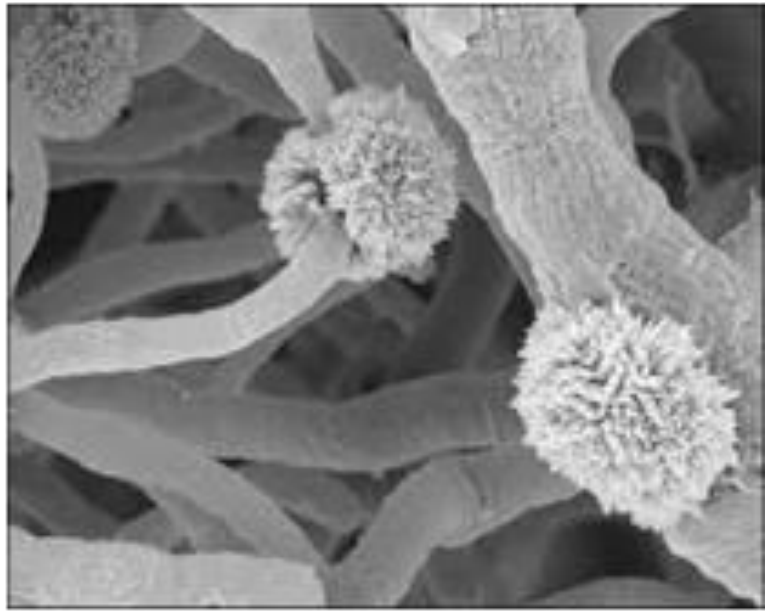


Amyloid can also be found in the brain's blood vessels

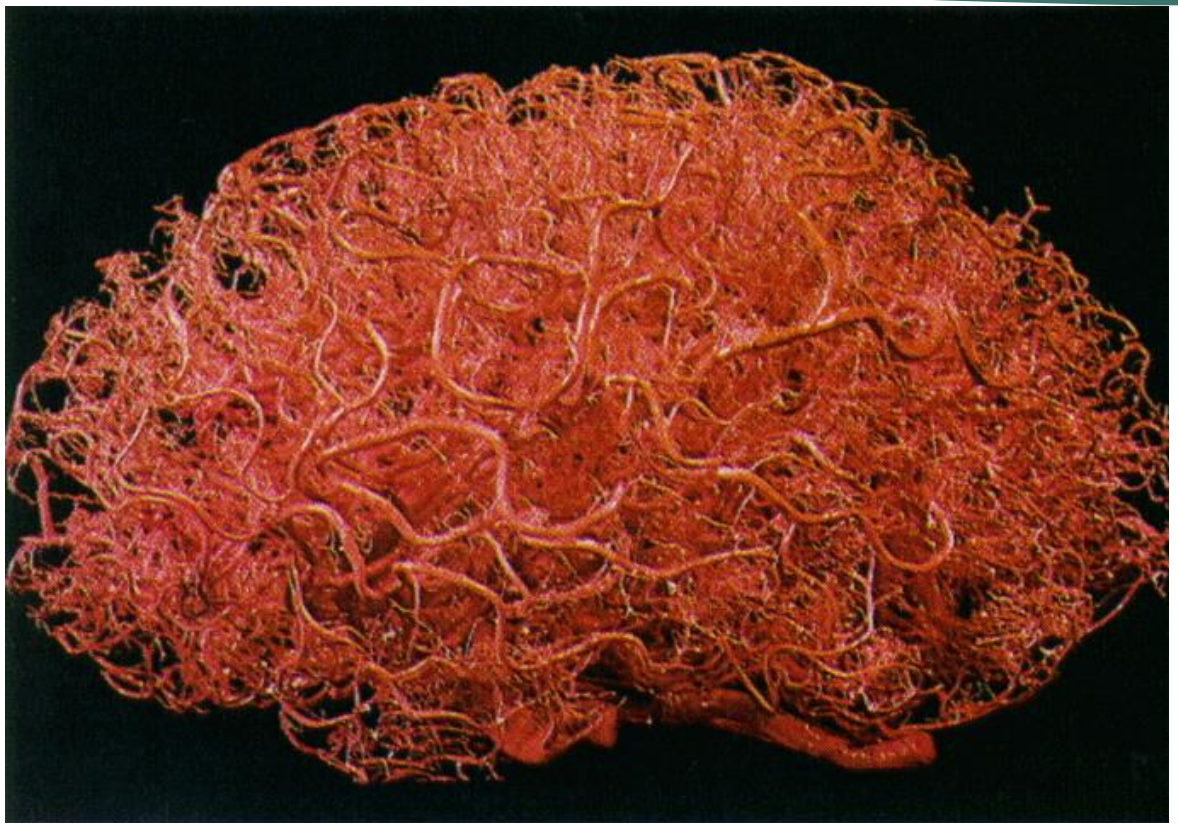
- Amyloid deposits in brain's mid-large size arteries is called cerebral amyloid angiopathy (CAA)
- CAA is found in most AD patients and is believed to weaken and stiffen the cerebral arterial walls







The importance of healthy vessels for brain function

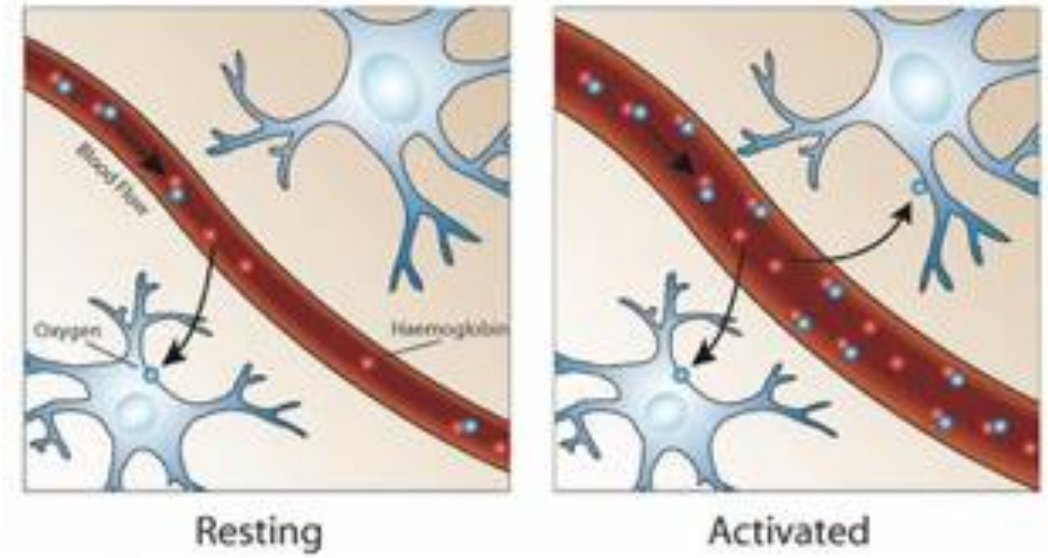


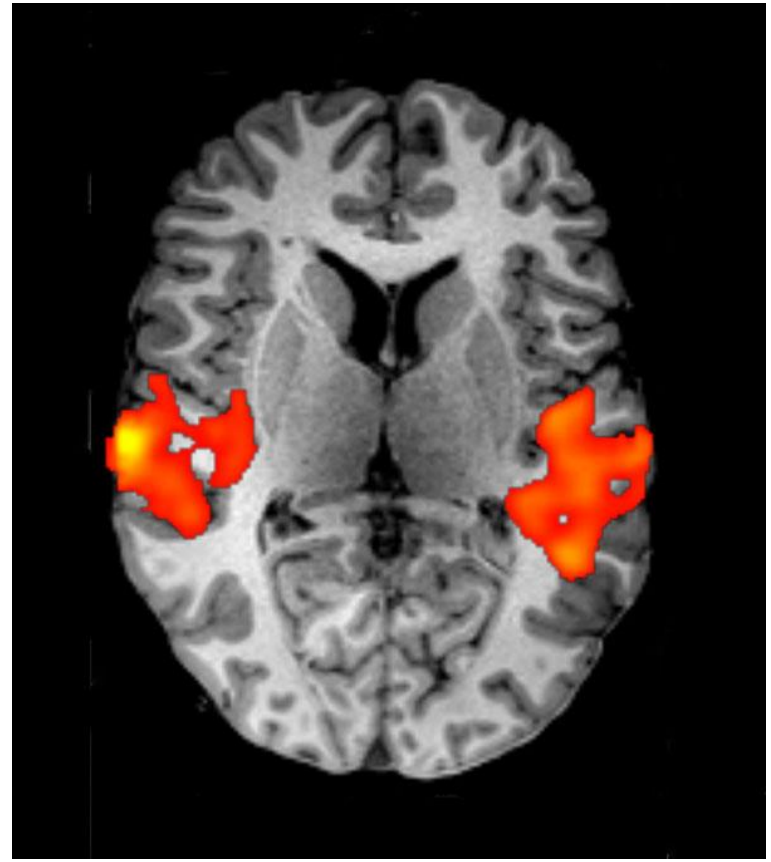
- The brain has over 400 miles of blood vessels!
- The brain also uses 25% of the total blood supply, even though it is only 2% of total body weight

Zlokovic & Apuuzo (1998) *Neurosurgery.*

Neuronal health is tightly coupled to vascular health

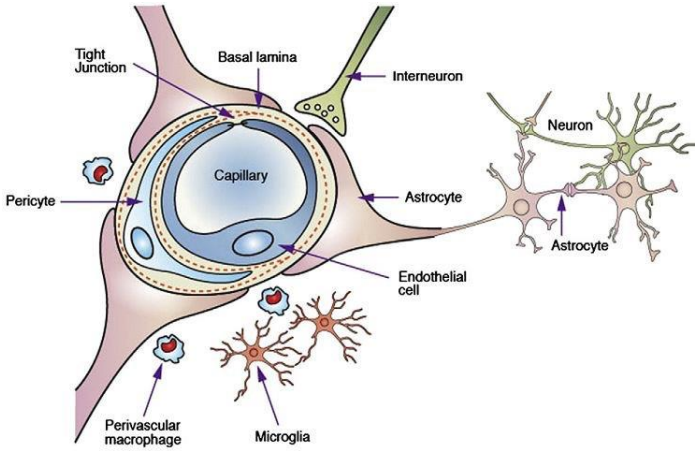
- Capillaries dilate to allow more blood flow in areas of neuronal activity
- This increased in oxygenation is what is measured in a functional MRI, or fMRI and is called the BOLD signal
- BOLD: Blood oxygenation level dependent

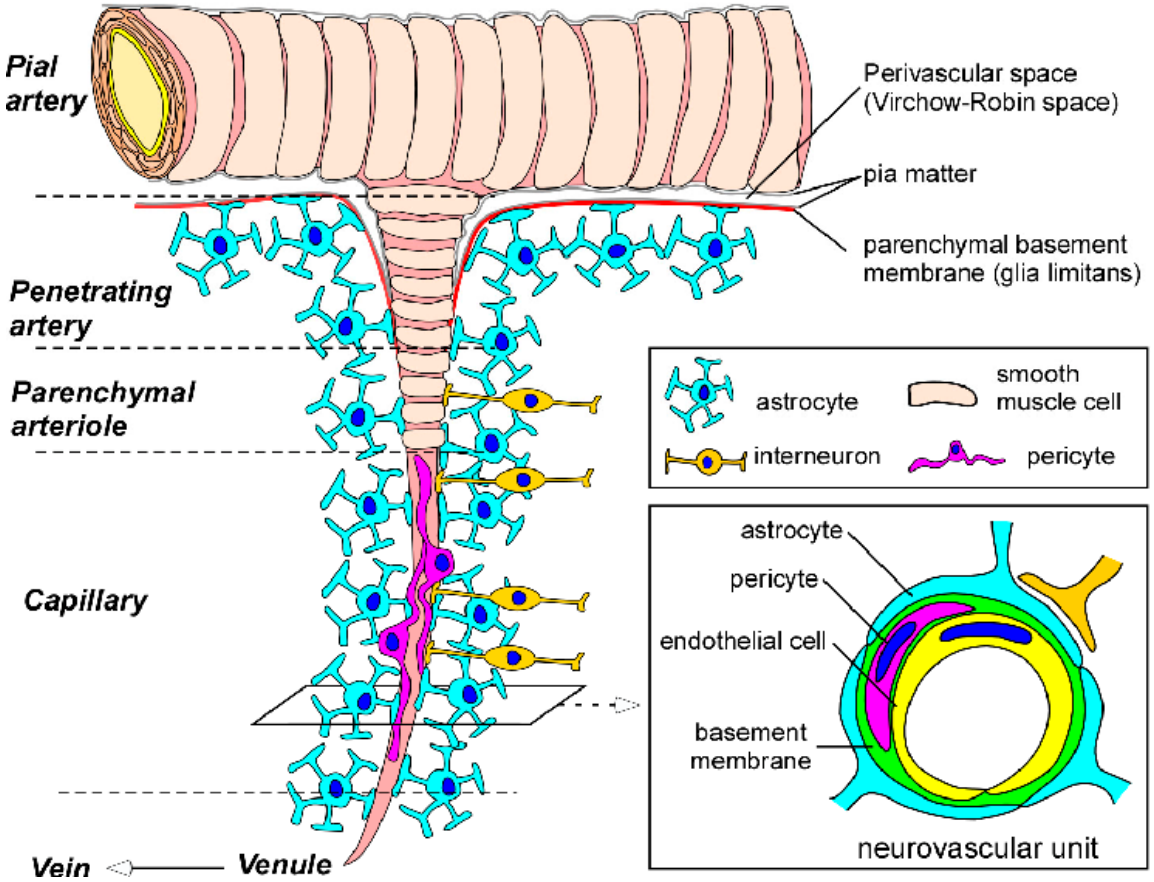




The Blood Brain Barrier is very important for brain health

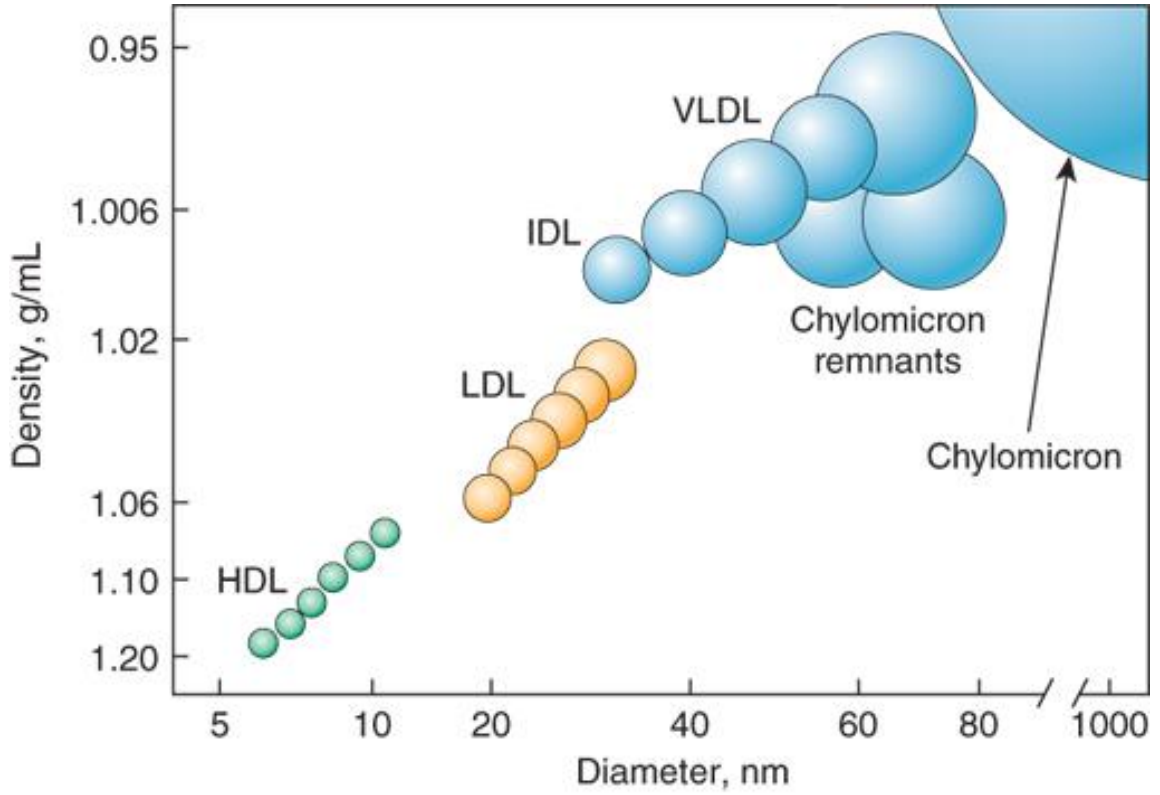
- The BBB protects neurons by only allowing certain things through
- The BBB is often damaged in Alzheimer's Disease





Let's talk about cholesterol

- Cholesterol is a type of fat that is not soluble in water
- Thus, cholesterol is carried in the blood by "lipoproteins"
- There are several types of lipoproteins in the blood
- Two well known lipoproteins are LDL (bad cholesterol) and HDL (good cholesterol)

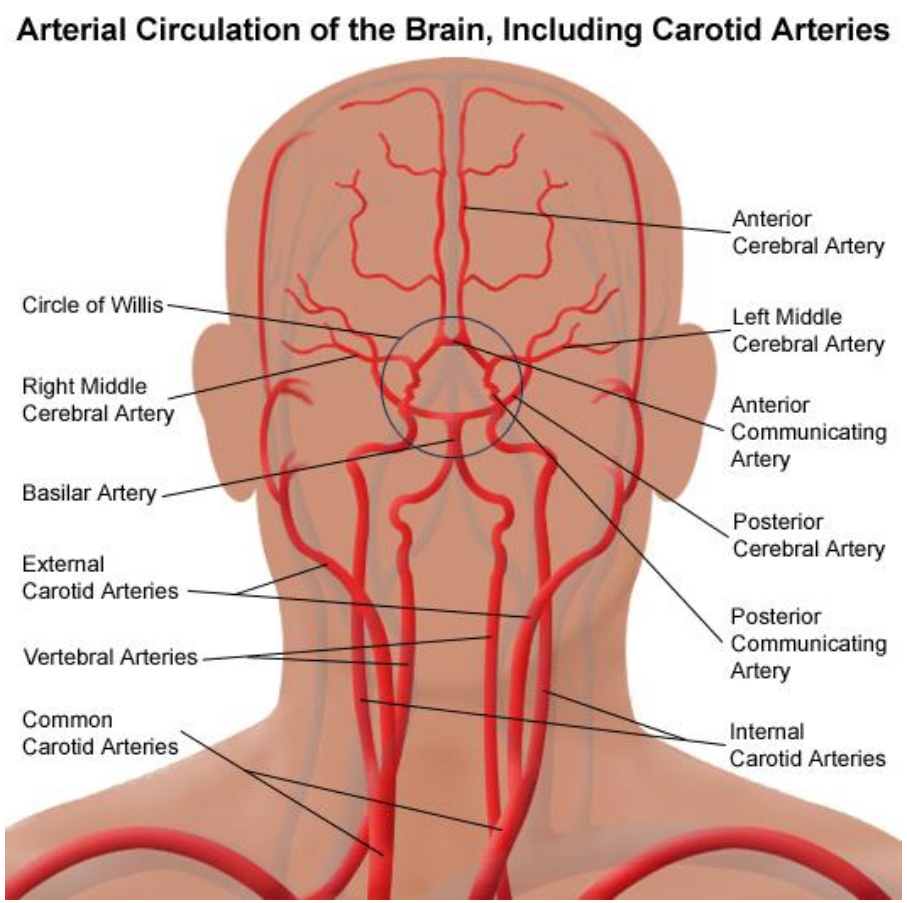


Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Atherosclerosis is a build up of cholesterol in blood vessels

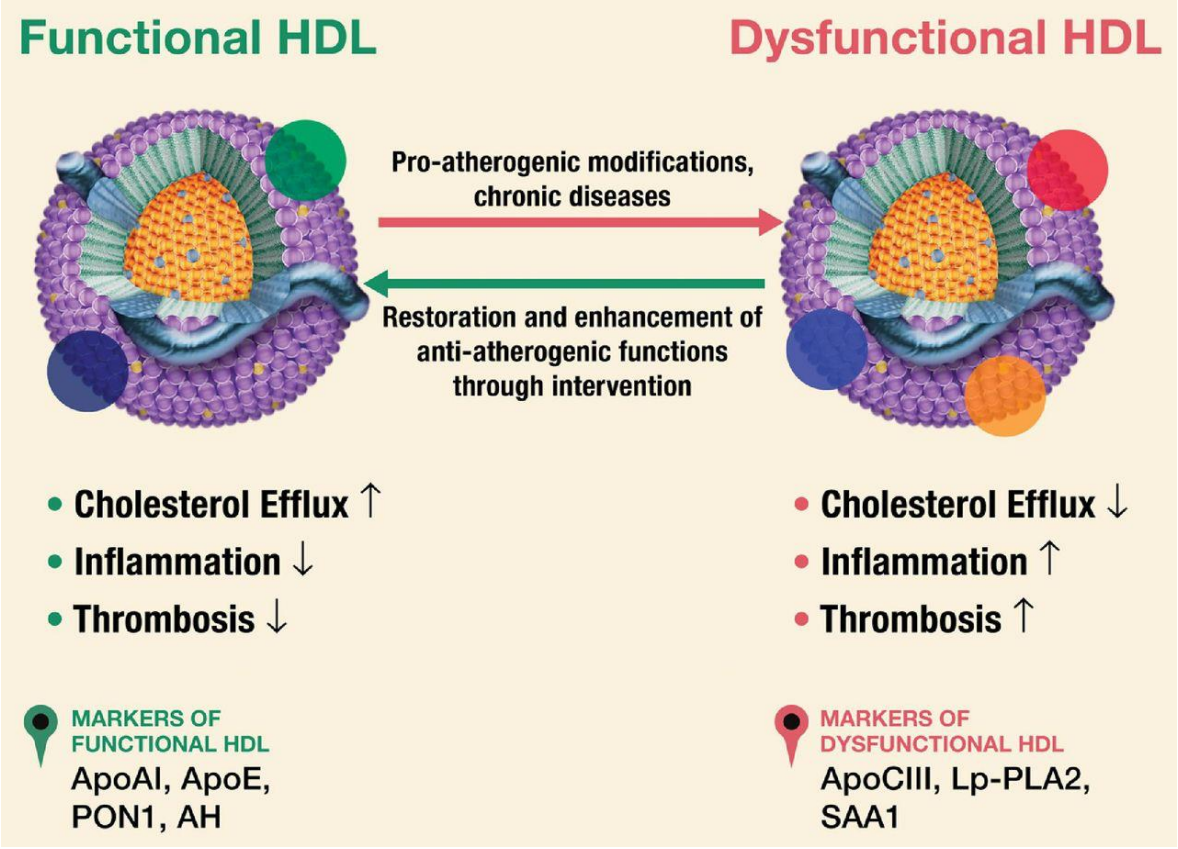
- Atherosclerosis occurs when cholesterol builds up in blood vessels and can increase risk of stroke

- Many Alzheimer's Disease patients have atherosclerosis in some brain vessels



HDL protects blood vessels throughout the body

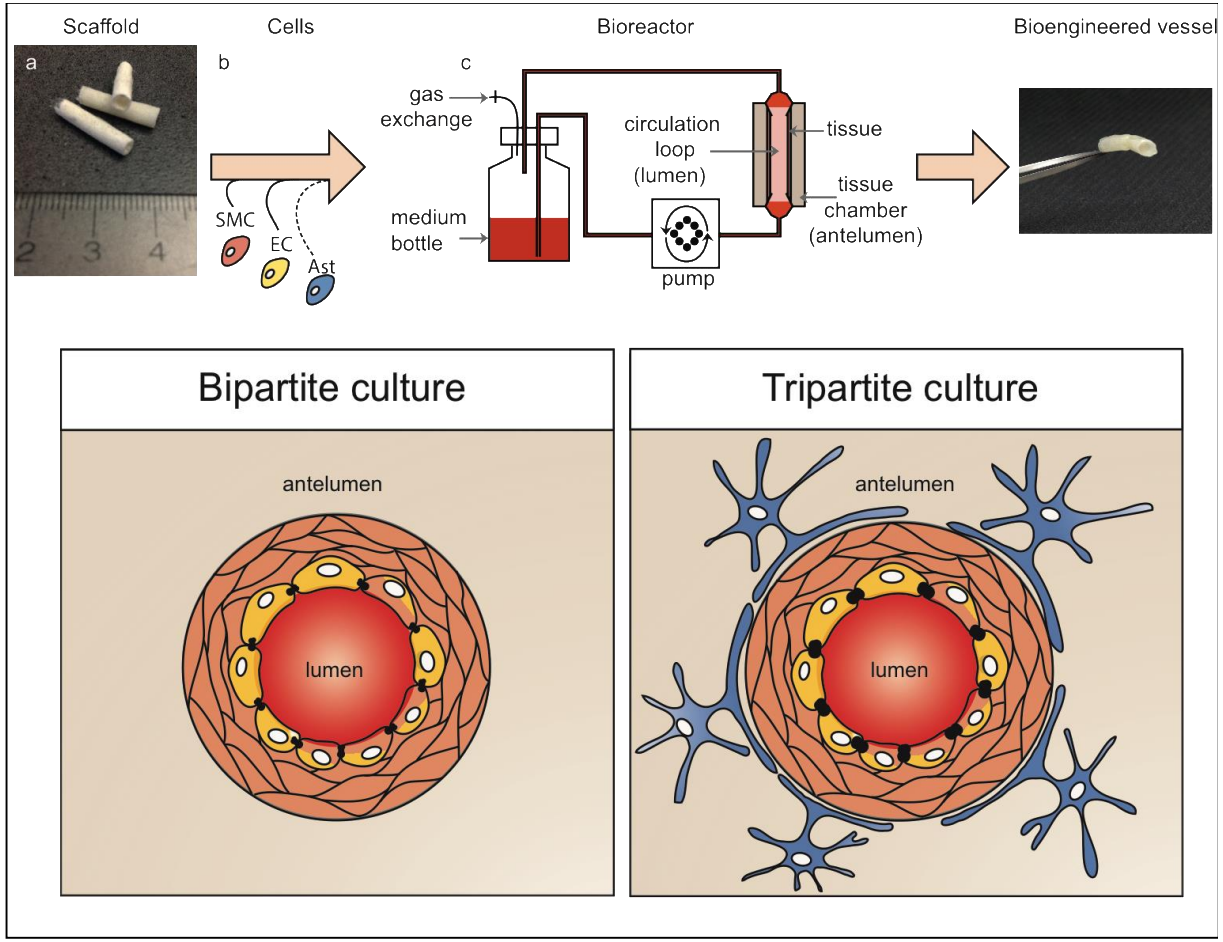
- HDL has many beneficial actions on blood vessels
- It prevents atherosclerosis, reduces blood clotting, lowers inflammation and maintains vessel flexibility
- These functions can be compromised in people with metabolic and cardiovascular disease, where HDL can become dysfunctional and exacerbate disease



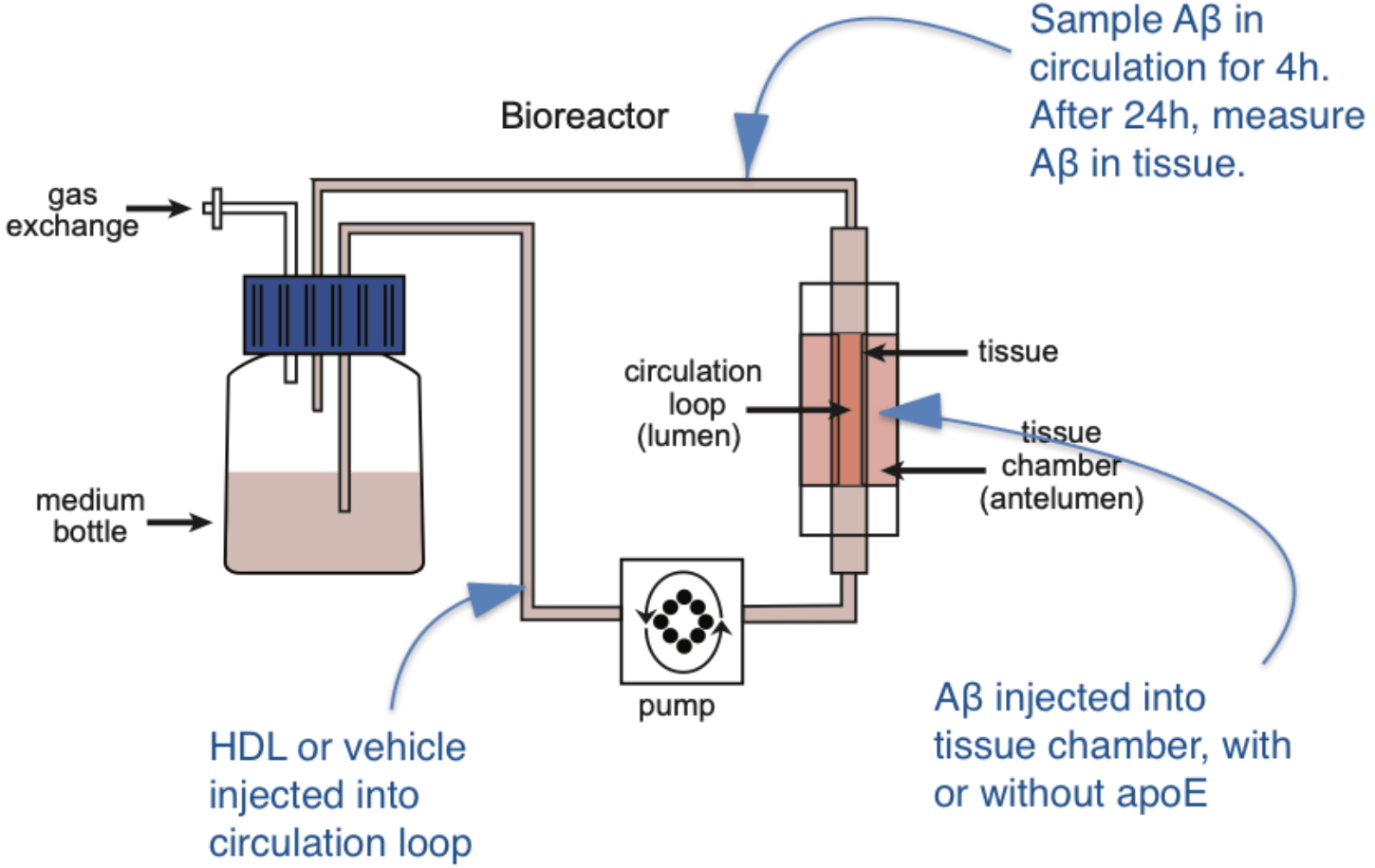
It is now possible to make synthetic human blood vessels in the test tube

Using tissue engineering methods, our group has successfully made synthetic human blood vessels in the test tube, which mimic those in the human brain

Vessels are cultivated in a bioreactor and allow us to study how components on the "blood side" affect the "brain side"



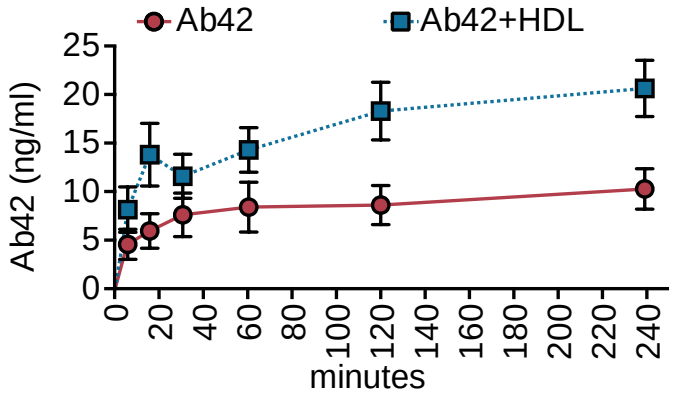
Experiments using engineered tissues

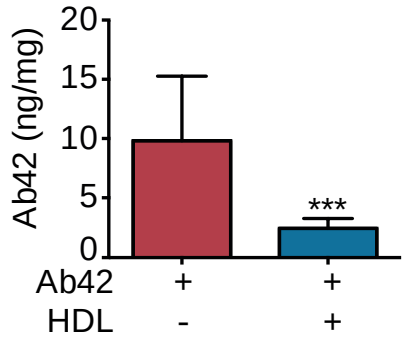


Adding HDL to the blood side of engineered tissues reduces cerebral amyloid angiopathy

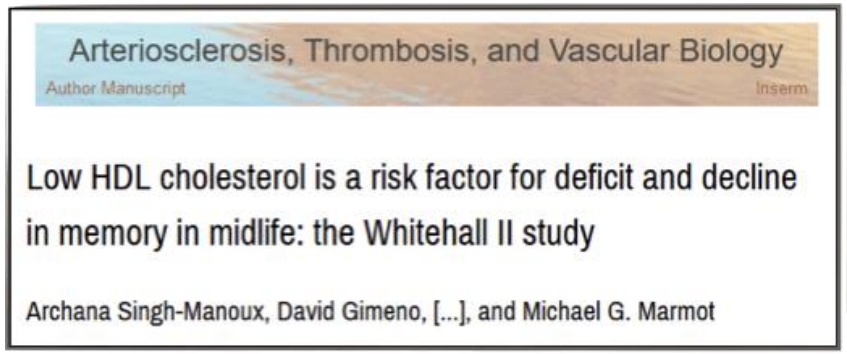
- The top graph shows the rate of appearance of Aβ42 in the "blood" side over 4h, indicating successful clearance

- The bottom graph shows how much Aβ is left stuck in the engineered vessel after 24h





In people, high HDL is good for memory



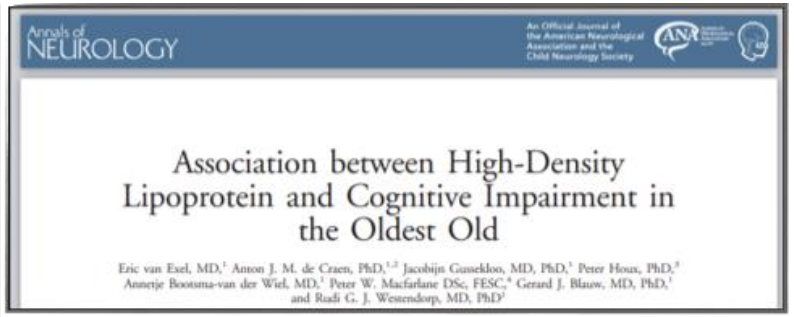
Arteriosclerosis, Thrombosis, and Vascular Biology

Author Manuscript

Inserm

Low HDL cholesterol is a risk factor for deficit and decline in memory in midlife: the Whitehall II study

Archana Singh-Manoux, David Gimeno, [...], and Michael G. Marmot

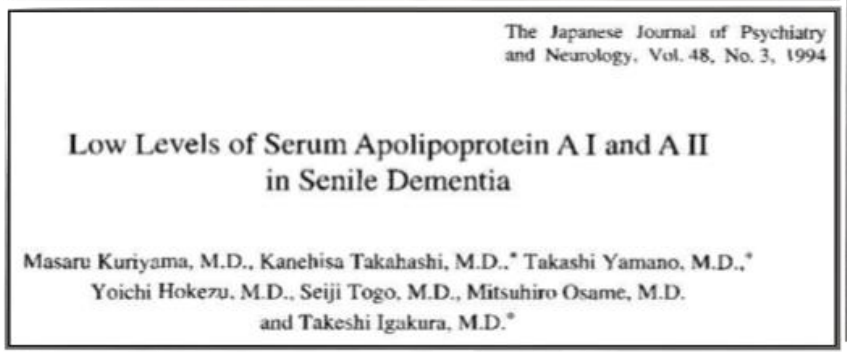


Annals of NEUROLOGY

An Official Journal of the American Neurological Association and the Child Neurology Society

Association between High-Density Lipoprotein and Cognitive Impairment in the Oldest Old

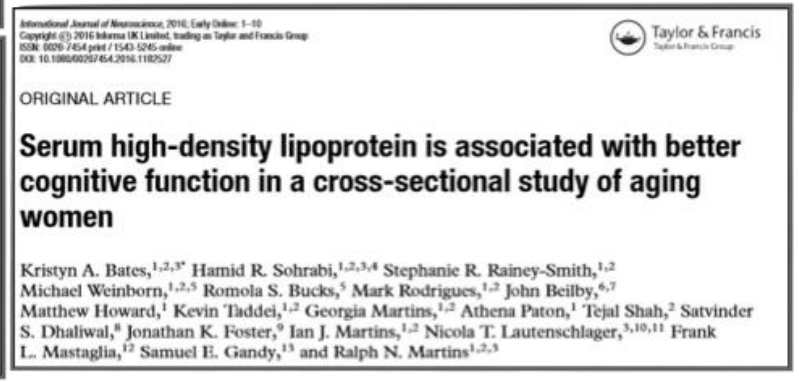
Eric van Exel, MD,[1] Anton J. M. de Craen, PhD,[1,2] Jacobijn Gussekloo, MD, PhD,[1] Peter Houx, PhD,[3] Annetje Bootsma-van der Wiel, MD,[1] Peter W. Macfarlane DSc, FESC,[4] Gerard J. Blauw, MD, PhD,[1] and Rudi G. J. Westendorp, MD, PhD[2]



The Japanese Journal of Psychiatry and Neurology, Vol. 48, No. 3, 1994

Low Levels of Serum Apolipoprotein A I and A II in Senile Dementia

Masaru Kuriyama, M.D., Kanehisa Takahashi, M.D.,* Takashi Yamano, M.D.,* Yoichi Hokezu, M.D., Seiji Togo, M.D., Mitsuhiro Osame, M.D. and Takeshi Igakura, M.D.*



International Journal of Neuroscience, 2010; Early Online: 1–10

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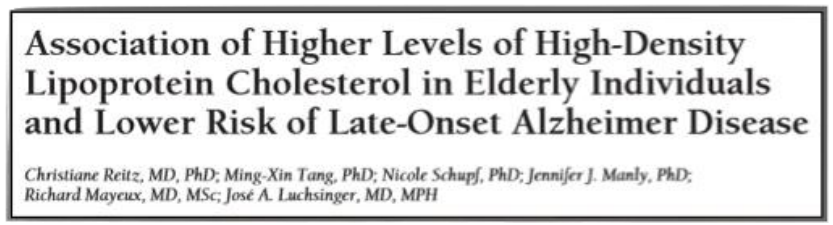
Taylor & Francis

ORIGINAL ARTICLE

Serum high-density lipoprotein is associated with better cognitive function in a cross-sectional study of aging women

Kristyn A. Bates,[1,2,3*] Hamid R. Sohrabi,[1,2,3,4] Stephanie R. Rainey-Smith,[1,2] Michael Weinborn,[1,2,5] Romola S. Bucks,[5] Mark Rodrigues,[1,2] John Beilby,[6,7] Matthew Howard,[1] Kevin Taddei,[1,2] Georgia Martins,[1,2] Athena Paton,[1] Tejal Shah,[2] Satvinder S. Dhaliwal,[8] Jonathan K. Foster,[9] Ian J. Martins,[1,2] Nicola T. Lautenschlager,[3,10,11] Frank L. Mastaglia,[12] Samuel E. Gandy,[13] and Ralph N. Martins[1,2,3]



Association of Higher Levels of High-Density Lipoprotein Cholesterol in Elderly Individuals and Lower Risk of Late-Onset Alzheimer Disease

Christiane Reitz, MD, PhD; Ming-Xin Tang, PhD; Nicole Schupf, PhD; Jennifer J. Manly, PhD; Richard Mayeux, MD, MSc; José A. Luchsinger, MD, MPH

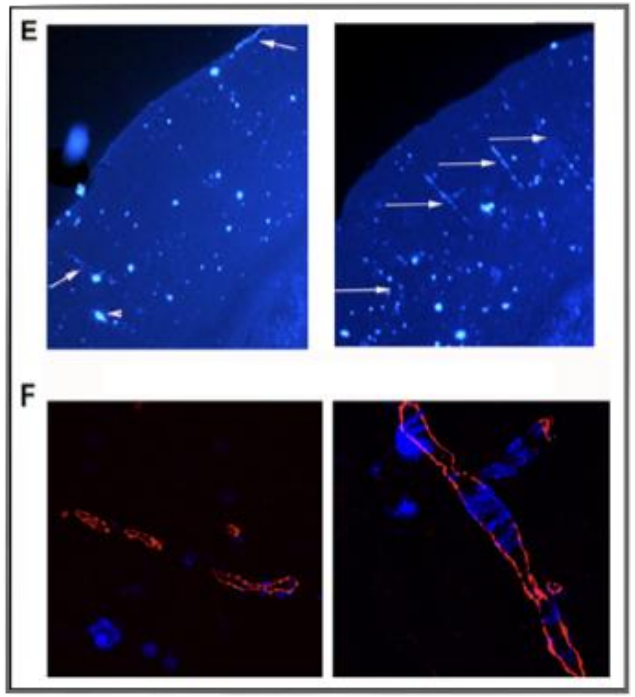
In mice, HDL levels correlate with cerebral amyloid angiopathy

Apolipoprotein A-I Deficiency Increases Cerebral Amyloid Angiopathy and Cognitive Deficits in APP/PS1ΔE9 Mice[*][S]

Received for publication, March 26, 2010, and in revised form, August 20, 2010 Published, JBC Papers in Press, August 25, 2010, DOI 10.1074/jbc.M110.127738

Iliya Lefterov[‡1], Nicholas F. Fitz[‡1], Andrea A. Cronican[‡], Allison Fogg[‡], Preslav Lefterov[‡], Ravindra Kodali[§¶], Ronald Wetzel[§¶], and Radosveta Koldamova[‡2]

From the [‡]Department of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, Pennsylvania 15219 and the [§]Department of Structural Biology and [¶]Pittsburgh Institute for Neurodegenerative Disorders, University of Pittsburgh, Pittsburgh, Pennsylvania 15260



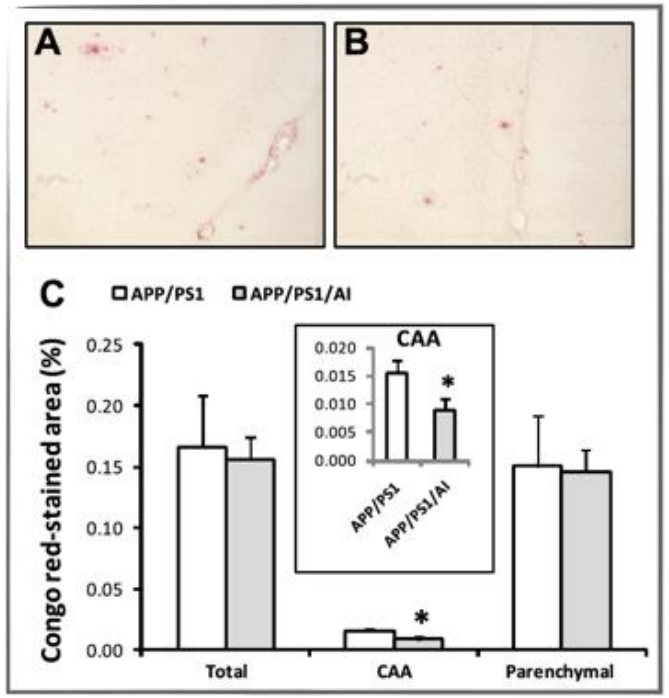
JBC 2010

Overexpression of Human Apolipoprotein A-I Preserves Cognitive Function and Attenuates Neuroinflammation and Cerebral Amyloid Angiopathy in a Mouse Model of Alzheimer Disease[*][S]

Received for publication, March 26, 2010, and in revised form, September 13, 2010 Published, JBC Papers in Press, September 16, 2010, DOI 10.1074/jbc.M110.127829

Terry L. Lewis[‡1], Dongfeng Cao[‡¶], Hailin Lu[‡], Robert A. Mans[‡‖], Yan Ru Su[**], Lisa Jungbauer[‡‡], MacRae F. Linton[**], Sergio Fazio[**], Mary Jo LaDu[‡‡], and Ling Li[‡¶‖2]

From the Departments of [‡]Medicine, [§]Pathology, and [‖]Neurobiology, University of Alabama at Birmingham, Birmingham, Alabama 35294, the [¶]Department of Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, Minnesota 55455, the [**]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee 37232, and the [‡‡]Department of Anatomy and Cell Biology, University of Illinois, Chicago, Illinois 60612



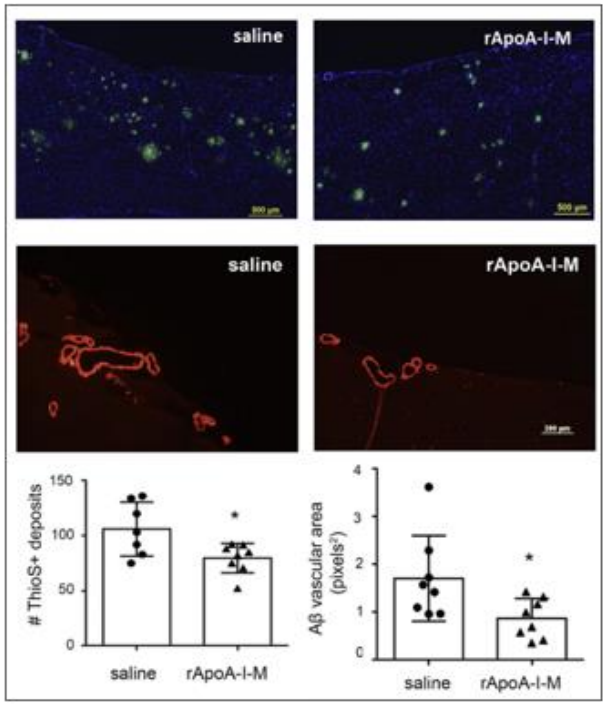
JBC 2010

Treating mice with HDL can help remove amyloid from the brain

Intravenous treatment with human recombinant ApoA-I Milano reduces beta amyloid cerebral deposition in the APP23-transgenic mouse model of Alzheimer's disease

Sofía Fernández-de Retana [a], Alex Montañola [a], Paula Marazuela [a], Maialen De La Cuesta [a], Aina Batlle [a], Marc Fatar [b], Saskia Grudzenski [b], Joan Montaner [a], Mar Hernández-Guillamon [a,*]

[a] Neurovascular Research Laboratory, Vall d'Hebron Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain
[b] Department of Neurology, Universitätsmedizin Mannheim, Heidelberg University, Mannheim, Germany

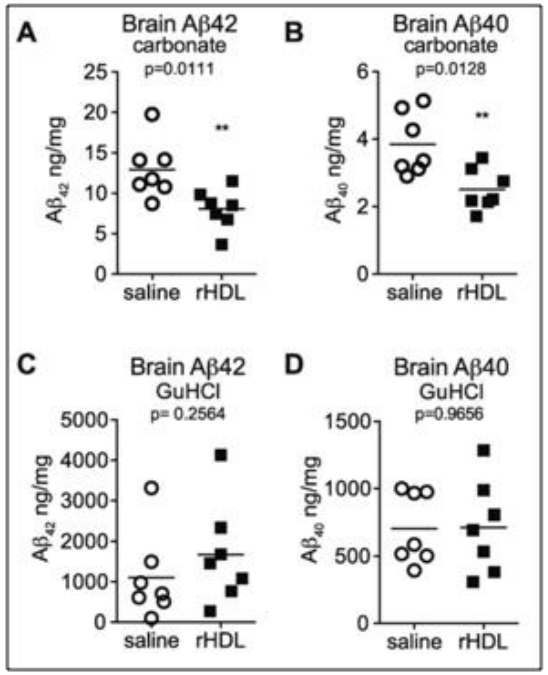


Neurobiology of Aging, 2017

Reconstituted high-density lipoproteins acutely reduce soluble brain Aβ levels in symptomatic APP/PS1 mice☆

Jérôme Robert [a,1], Sophie Stukas [a,1], Emily Button [a], Wai Hang Cheng [a], Michael Lee [a], Jianjia Fan [a], Anna Wilkinson [a], Iva Kulic [a], Samuel D. Wright [b], Cheryl L. Wellington [a,*]

[a] Department of Pathology and Laboratory Medicine, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, British Columbia, Canada
[b] Cardiovascular Therapeutics, CSL Limited, Parkville, Australia



BBA 2015

What you can do now

- Maintaining good cardiovascular health will help the brain to age well and possibly prevent or delay the onset of dementia and Alzheimer's Disease

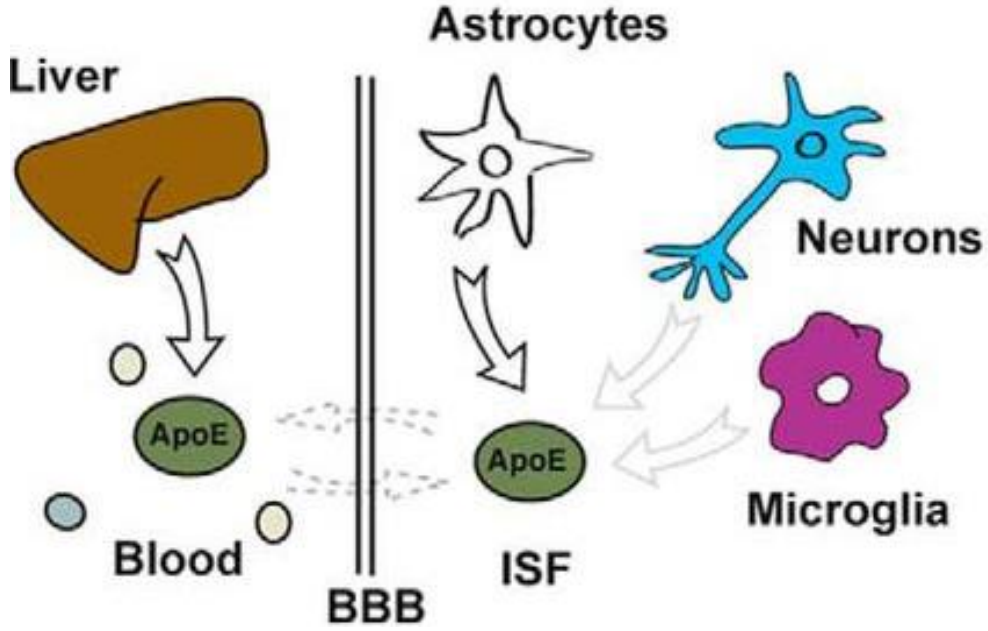
- Tips:
  - Stop smoking
  - Exercise
  - Treat high blood pressure, high cholesterol and diabetes

Where this research can go

- There are a number of late stage trials testing HDL drugs for heart disease.
- These drugs could be tested to prevent Alzheimer's Disease or to slow its progression.

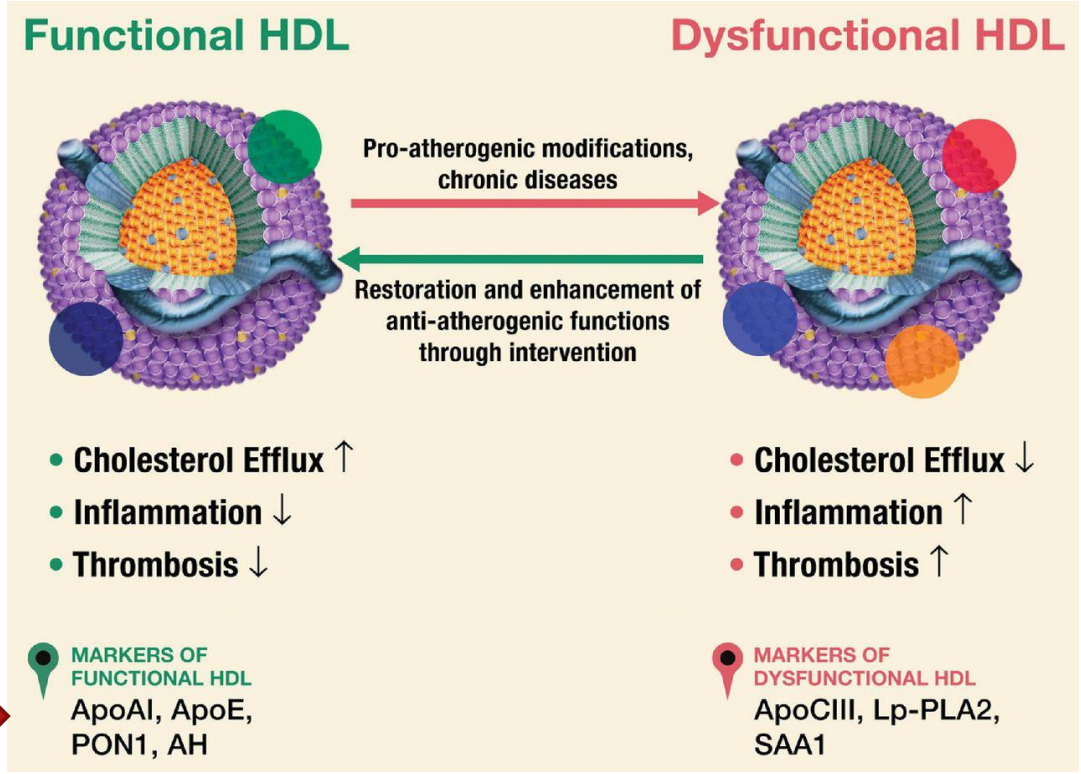
How this research gives us a new perspective on apoE in Alzheimer Disease

- ApoE is the most important genetic risk factor for Alzheimer's Disease; this has been known since 1993
- One in six people have the "risky" genetic variant, called apoE4
- ApoE is made in the brain, liver and certain types of immune cells, but does not cross the blood brain barrier
- Until recently, only "brain" apoE was considered important for Alzheimer's Disease



A new view of apoE

- Very new research shows that HDL with lots of apoE protects from heart disease, and there are now ways to measure this using a blood test
- It may be that brain apoE is only part of the picture and apoE made outside the brain can also affect Alzheimer's Disease
- It may be possible to design synthetic HDL with apoE as a new therapeutic strategy for Alzheimer's Disease



Summary

- Cardiovascular risk factors (smoking, high blood pressure, high cholesterol, diabetes, physical activity) also increase Alzheimer Disease risk
- New research suggests that HDL, the "good cholesterol", may also play a more important role in Alzheimer's Disease than previously imagined
- HDL with lots of apoE on it is particularly good for the heart; we do not yet know if this is also true for the brain
- Good cardiovascular health is associated with more HDL with apoE

Thank you!