Heart-brain connection in aging and dementia

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KI-UW Madison International Postdoc Fellowship

Research Experience

Nov.2011-Sep. 2015

ARC KI

- Doctoral thesis: Cardiovascular risk factors, structural brain changes, and cognitive decline

Chengxuan Qiu 

 Laura Fratiglioni

2016-2017

ARC KI

- EIT-Health project: Late-life dementia risk score
- EU Horizontal 2020 project: Common mechanisms between AD and Stroke

Miia Kivipelto 

 Weili Xu

2019-

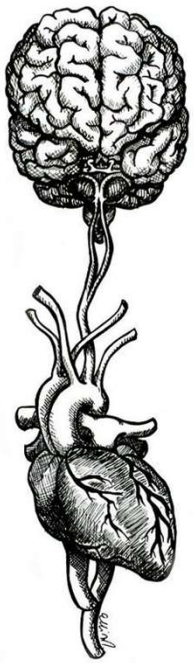
 Ozioma Okonkwo

ADRC UW-Madison

- Physical activity, cardiovascular burden, brain changes, and cognitive function

Background

The link between heart and brain

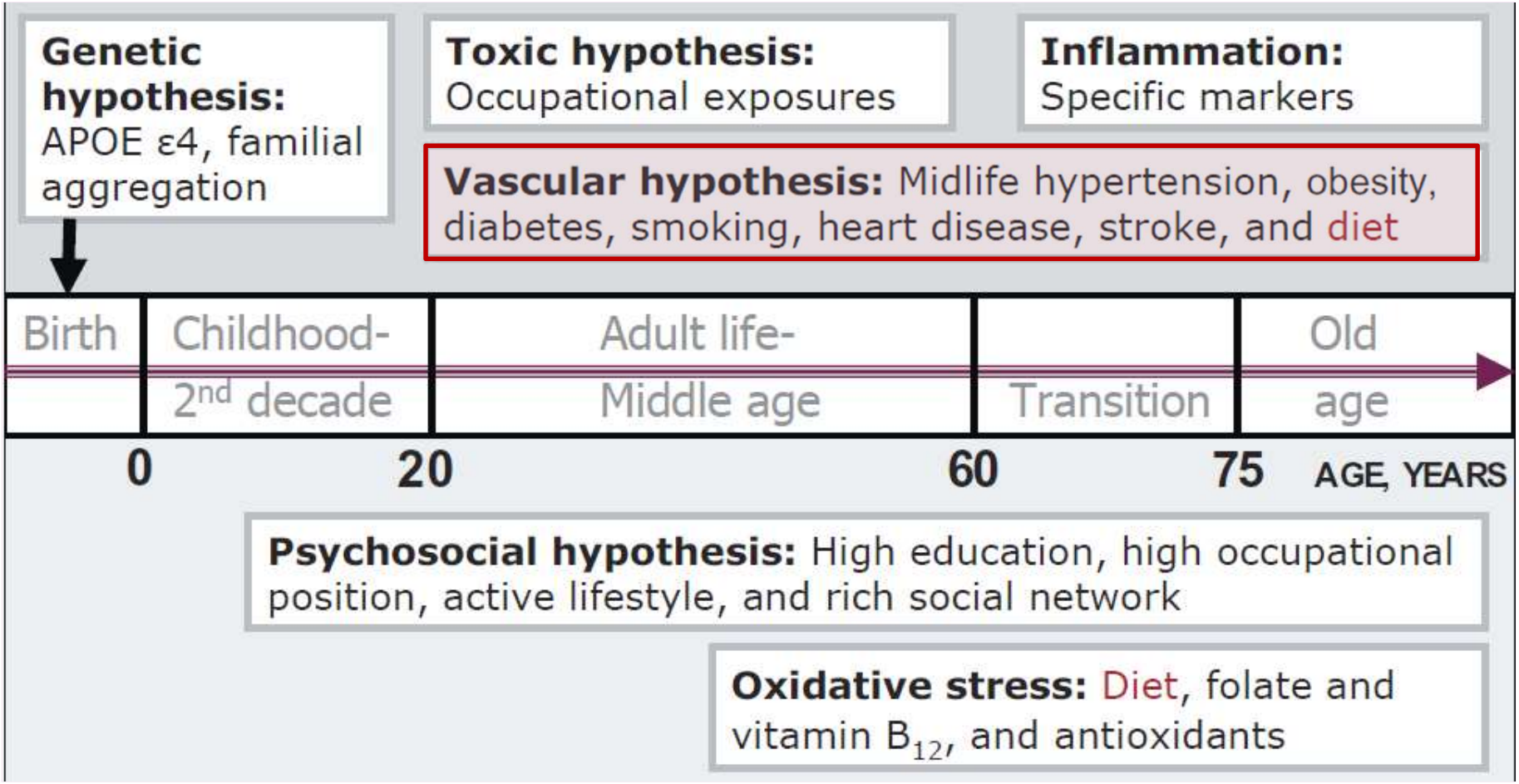


- Brain may age faster in people whose hearts pump less blood (Jefferson AL et al, *Circulation*. 2010)
  Framingham Offspring Study

- Cognitive decline may accelerate after heart attack, angina (Xie W et al, *J Am Coll Cardiol*. 2019)
  The English Longitudinal Study of Aging

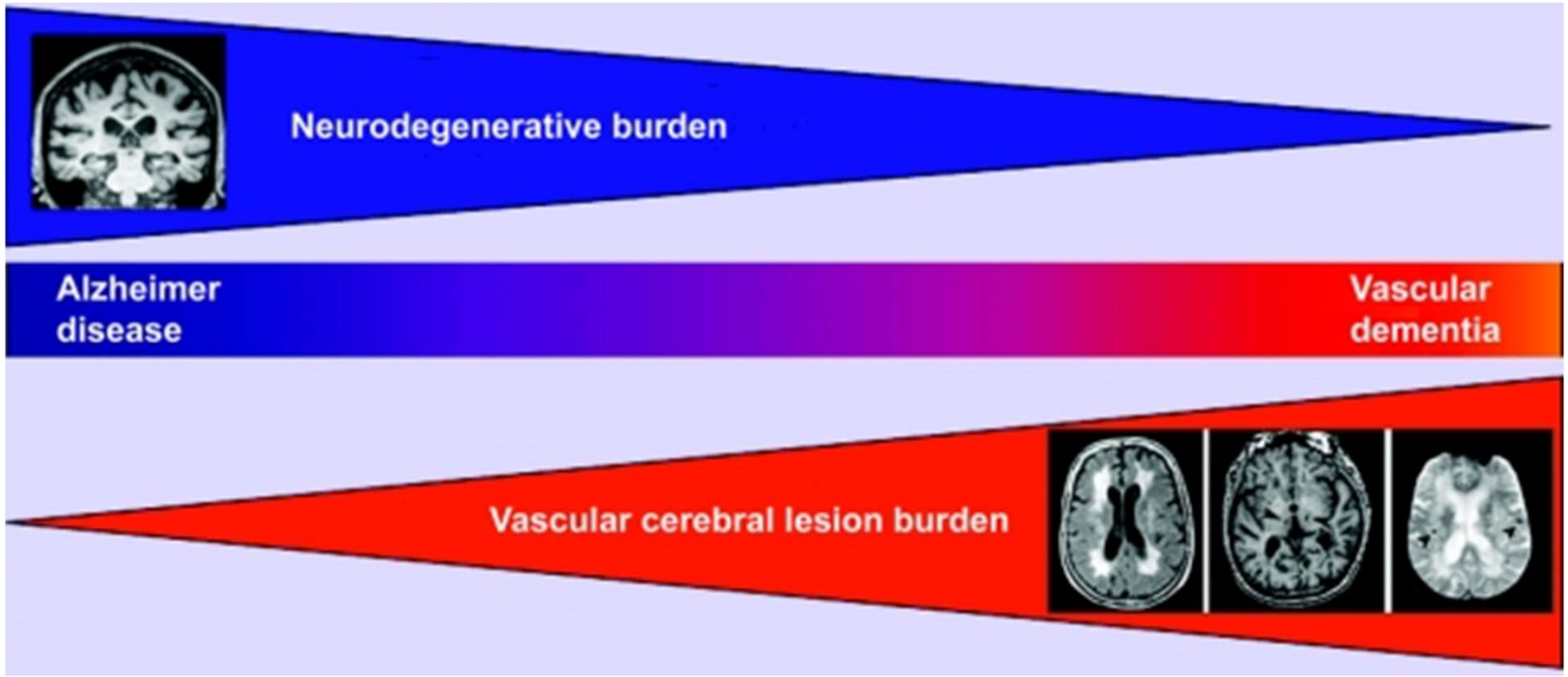
- Heart diseases and dementia in older adults: shared risk factors? (Viswanathan et al., Neurology 2009)

A life-course perspective



(Fratiglioni L et al, *Nutr Rev.* 2010, Kivipelto M et al, *Nat Rev Neurol*. 2018)

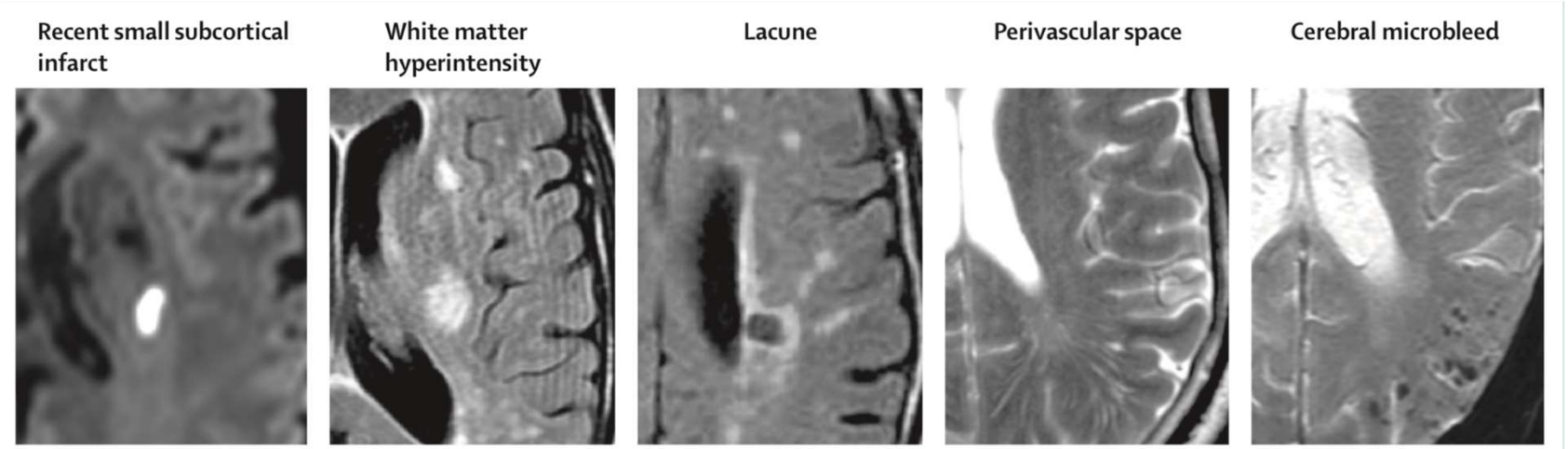
The Continuum from pure AD to vascular dementia



(Viswanathan et al., *Neurology* 2009)

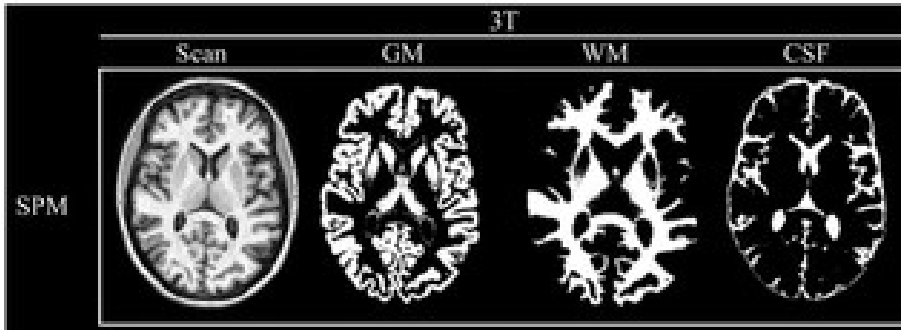
Markers of brain pathological changes

Markers of vascular pathologies/small vessel diseases



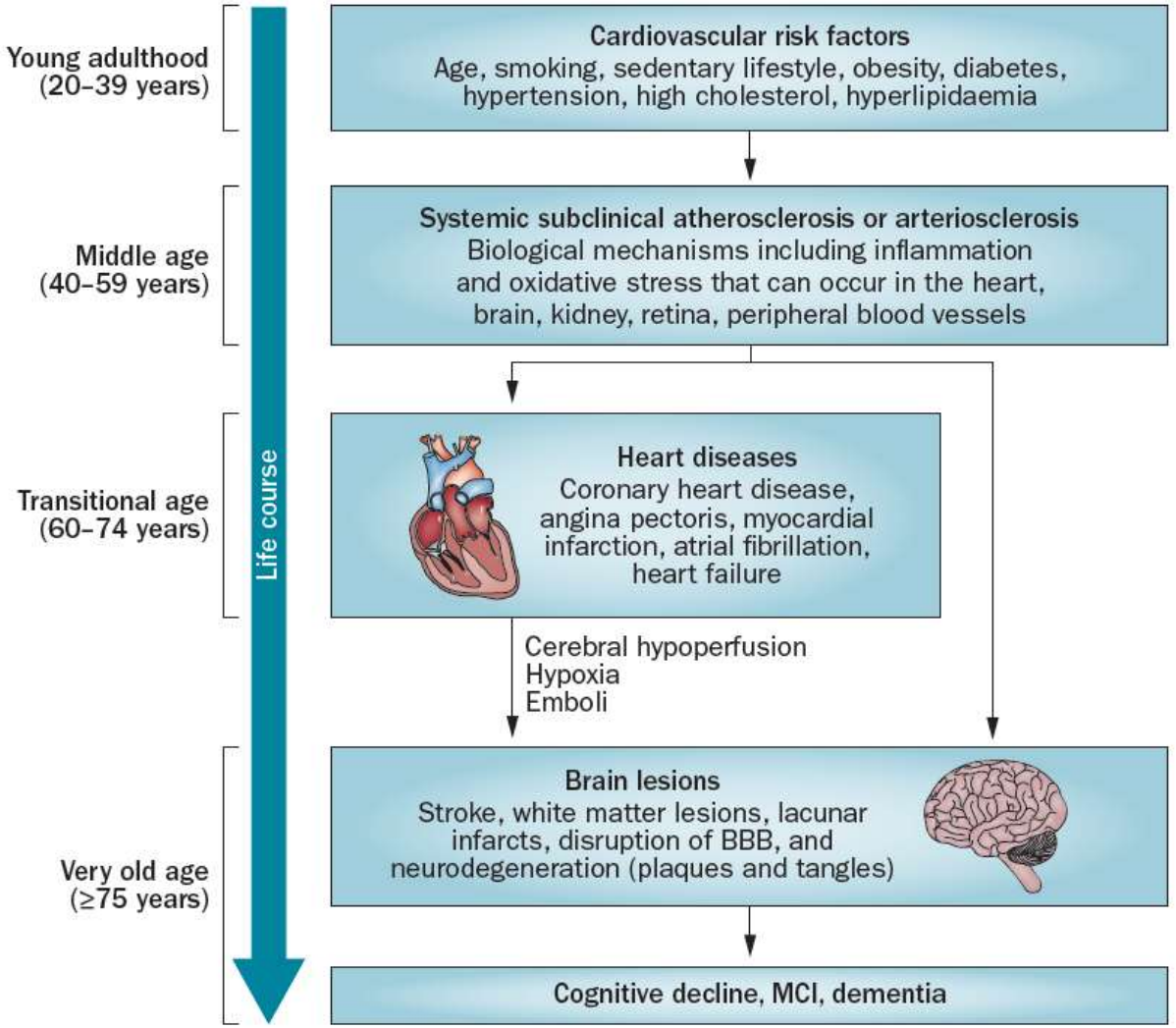
DWI	FLAIR	FLAIR	T2/T1,FLAIR	T2*/SWI
≤20 mm	*Variable*	*3-15 mm*	*≤3 mm*	*≤ 10 mm*

Markers of neurodegeneration



(Wardlaw JM et al, *Lancet Neurol.* 2013; Schott JM et al, *BMJ*. 2011; Heinen R, et al, *PLoS One*. 2016; Simon S. *J Anthropol Sci*. 2009)

Possible hypothesis



(Qiu & Fratiglioni. *Nat Rev Cardiol*. 2015)

Questions Remain…

- Q1. Do different types of brain measures mediate the association between cardiovascular risk burden and cognitive decline?

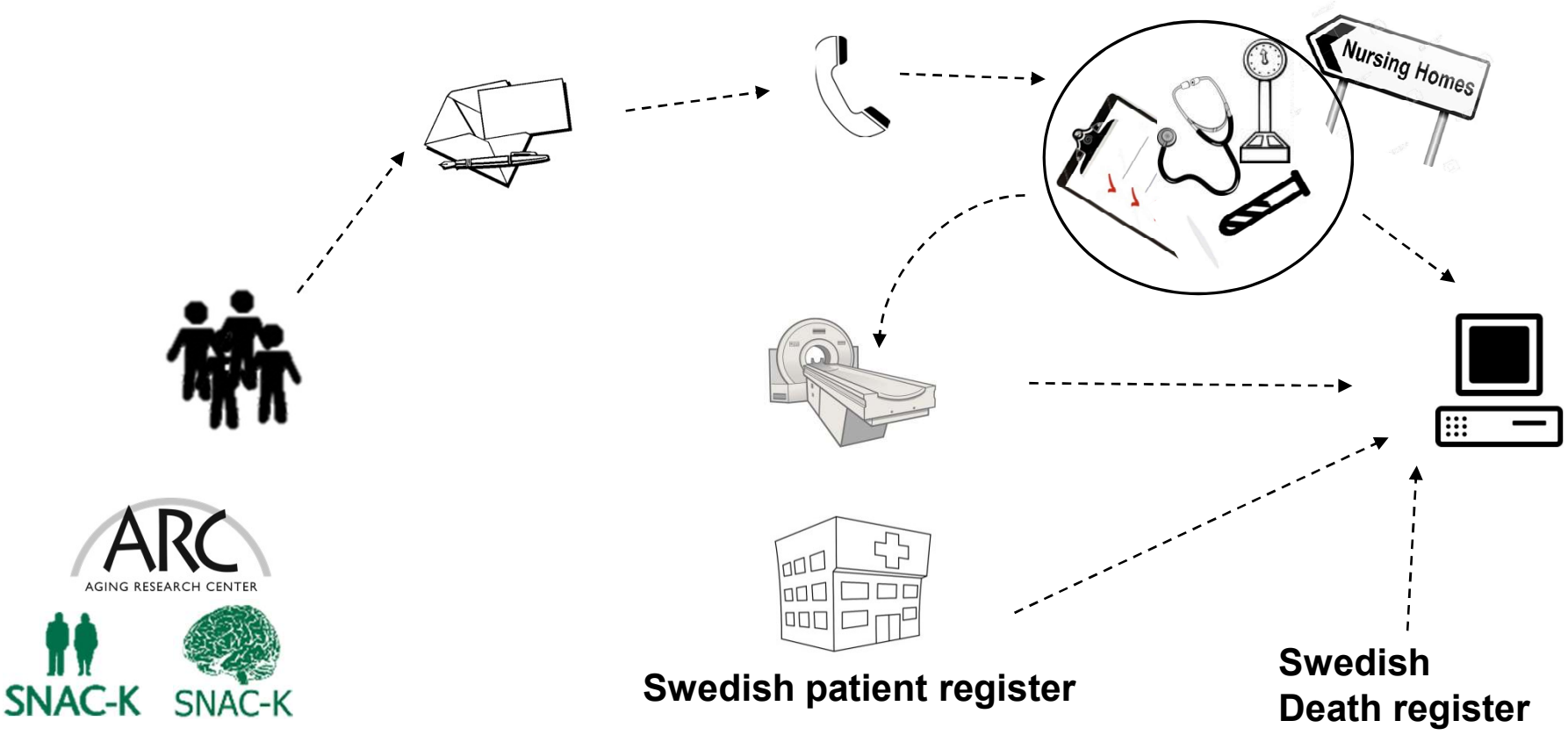
- Q2. Are cardiovascular risk factors associated with microstructural brain changes?

- Q3. Can dementia and cognitive decline be predicted by MRI load of cerebral microvascular lesion and neurodegeneration?

Methods

Swedish National study on Aging and Care in Kungsholmen (SNAC-K)

Karolinska Institutet



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SNAC-K SNAC-K

Methods

- **Study population (60-103 years)**
  - Baseline 3363 participants (MRI scan: 555 participants)
  - 15-year follow-up period

- **Dementia diagnosis and cognitive assessments**

  Every 3-year for old-old adults and every 6-year for young-old adults

- **Neuroimaging markers**
  - Hippocampal volume, Ventricular volume, and total gray matter volume
  - White matter hyperintensities, lacune, infarcts, perivascular space

- **Structured interview/clinical examination/questionnaires**

- **Patient register/Death register**

Cardiovascular risk burden

- **Vascular risk factors**
  - Hypertension, Diabetes, High cholesterol, Obesity
  - Smoking, Heavy drinking, Physical inactivity

- **Cardiovascular diseases**
  - Heart diseases (e.g., arterial fibrillation, coronary heart disease, heart failure)
  - Cerebrovascular diseases (e.g., TIA, ischemic stroke)

- **Cluster of vascular risk burden**
  - Framingham general cardiovascular risk score (FGCRS)

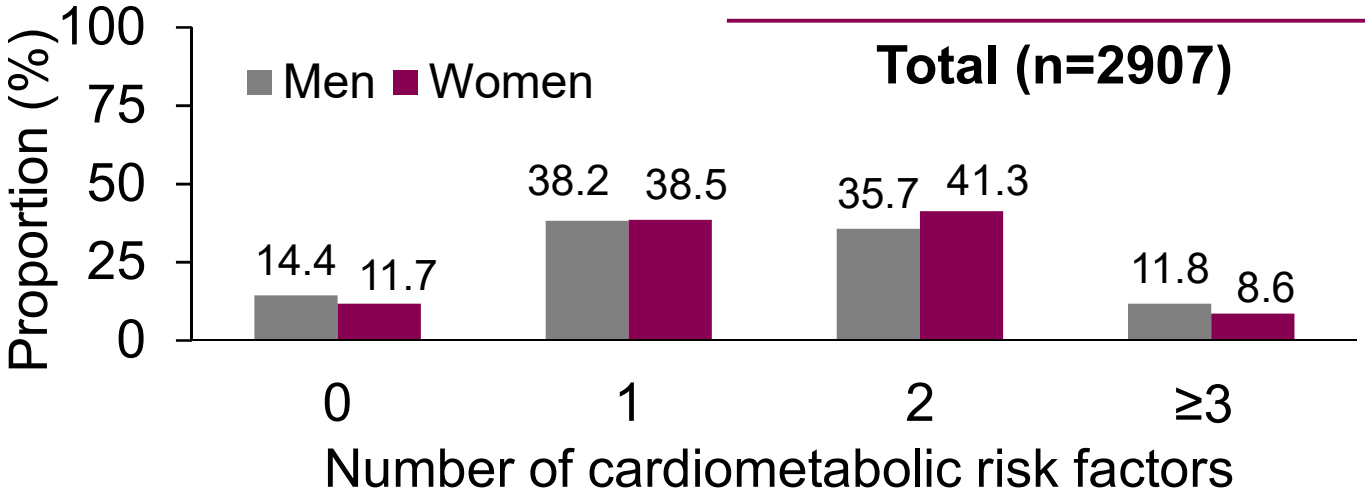
Findings

Distribution of vascular risk factors in our population

Wang R, et al. **Prevalence, pharmacological treatment, and control of cardiometabolic risk factors among older people in central Stockholm: a population-based study**. *PLoS One*. 2015 Mar 23;10(3):e0119582.

Prevalence and aggregation of cardiometabolic risk factors

Cardiometabolic risk factors	No. of subjects	Prevalence (%)	
		Crude	Age- and Sex-standardized
Hypertension	2496	74.9	76.4
High cholesterol	1523	49.7	48.6
Obesity	388	12.8	11.7
Diabetes	318	9.5	9.6



(Wang R et al., *PLoS One*. 2015)

Q1. Do different types of brain measures mediate the association between cardiovascular risk burden and cognitive decline?

Findings

Mediating effect of brain measures between cardiovascular risk burden and cognitive decline

Wang R, et al. **Mixed brain lesions mediate the association between cardiovascular risk burden and cognitive decline in old age: A population-based study**. *Alzheimers Dement*. 2017 Mar;13(3):247-256.

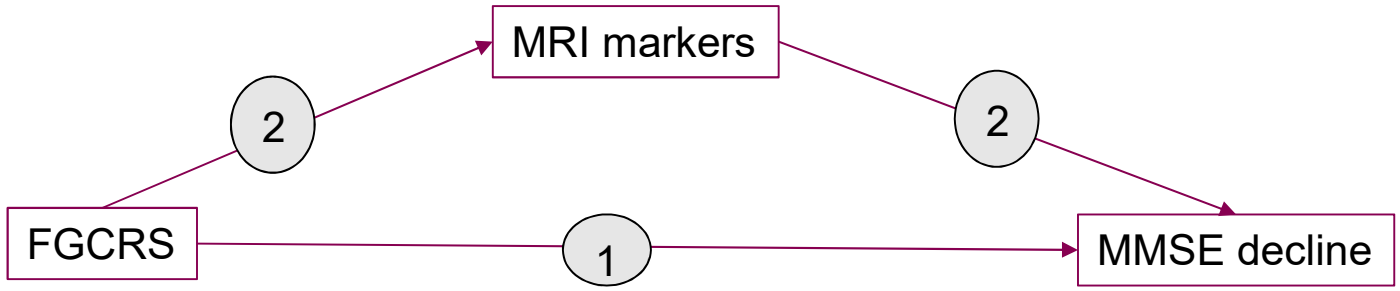
Pathways between Cardiovascular risk burden and cognitive decline

Step 1 In total SNAC-K population (n=3363)

- The association between vascular burden and MMSE decline
- Mixed effect linear regression model

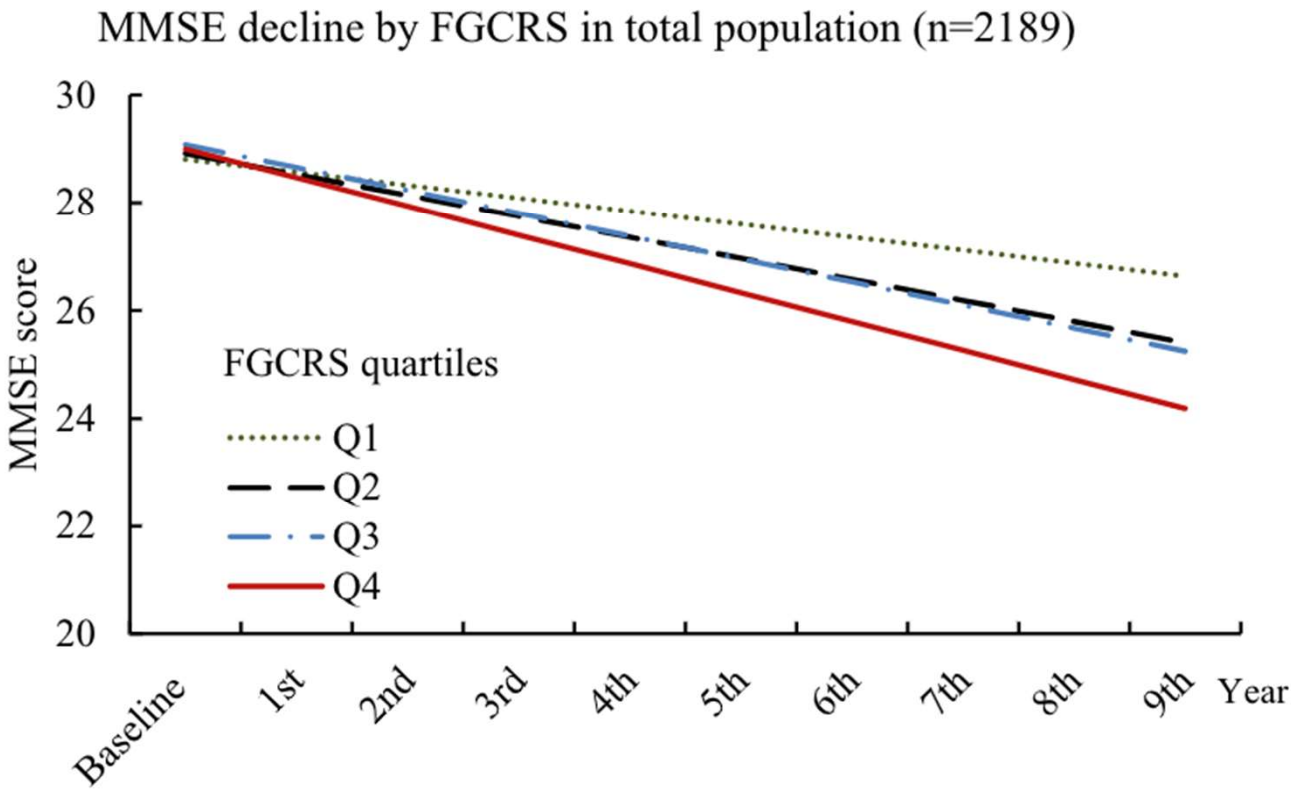
Step 2 In sub-group of MRI participants

- The association between vascular burden, brain pathologies, and MMSE decline
- Latent class growth model and SEM with mediation function



FGCRS: **F**ramingham **G**eneral **C**ardiovascular **R**isk **S**core

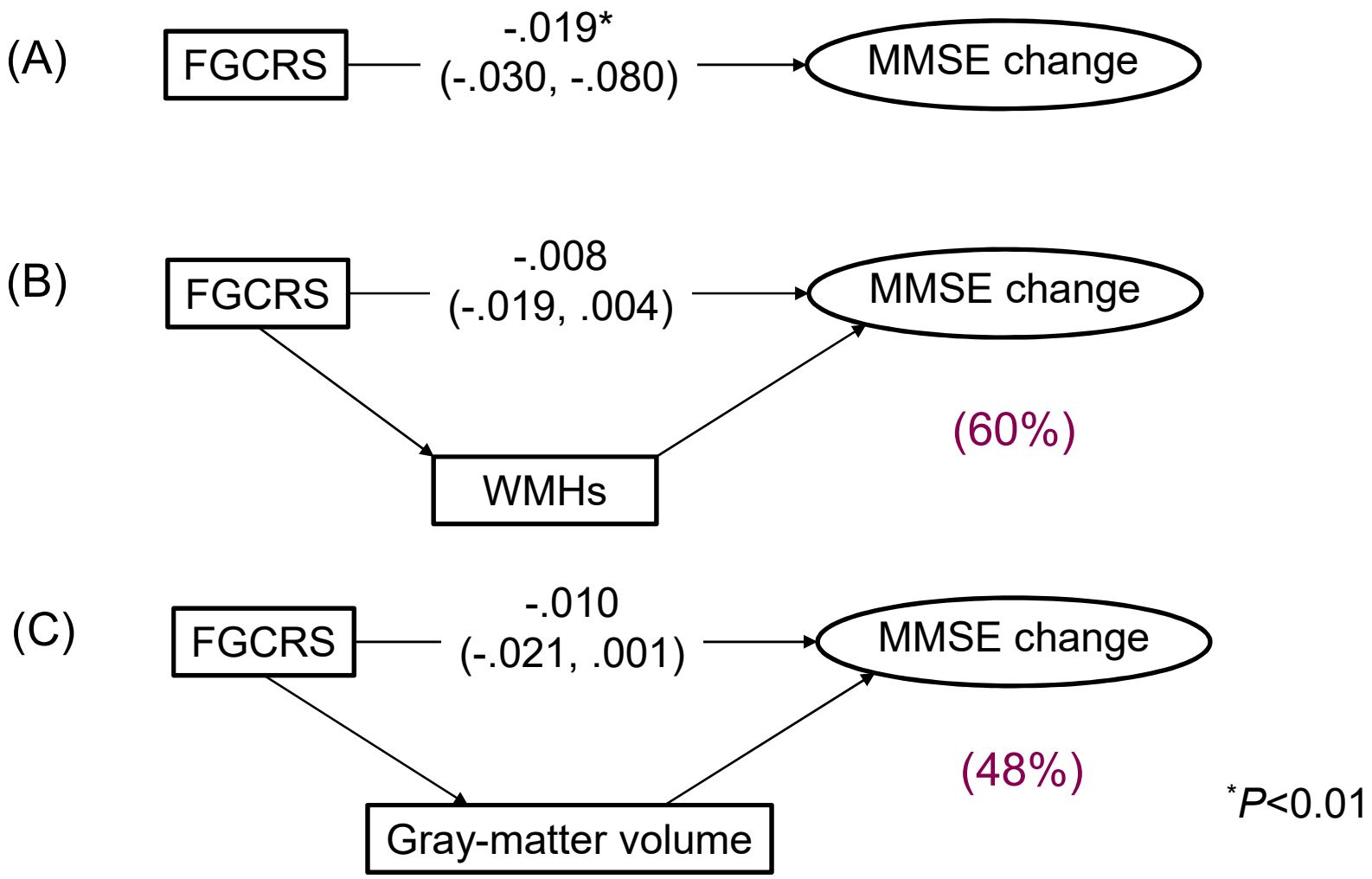
FGCRS and Cognitive Decline



FGCRS: **F**ramingham **G**eneral **C**ardiovascular **R**isk **S**core

(Wang R et al, *Alzheimers Dement*. 2017)

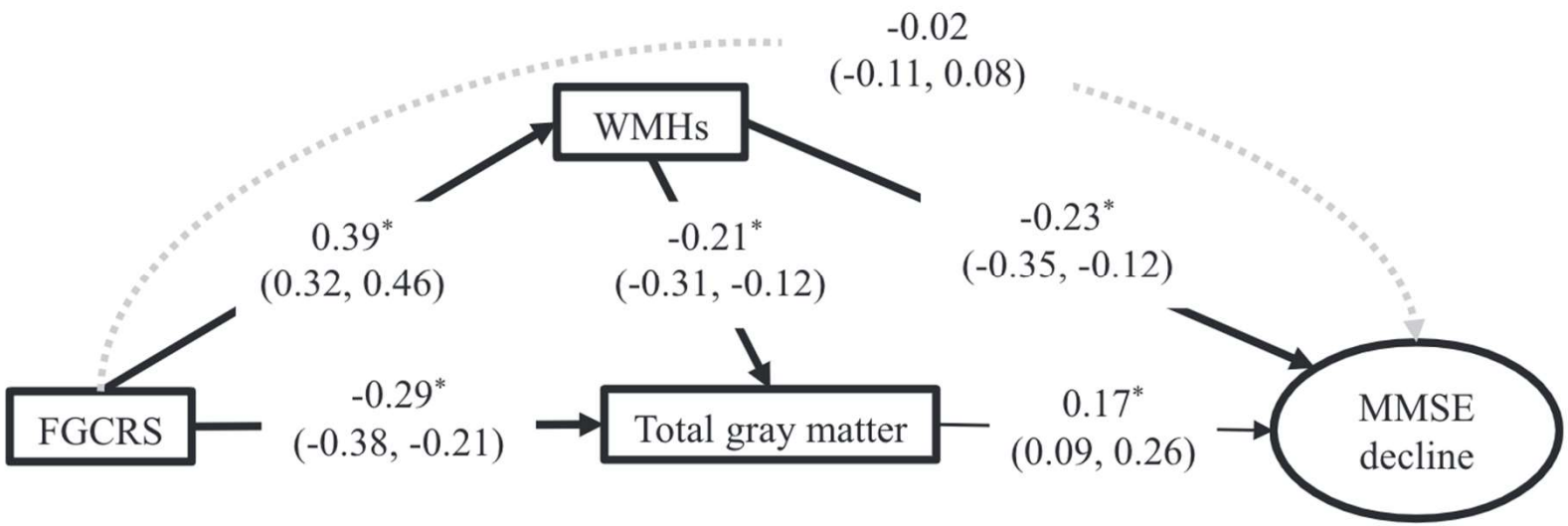
Mediating Role of Brain Measures



(Wang R et al, *Alzheimers Dement*. 2017)

FGCRS: **F**ramingham **G**eneral **C**ardiovascular **R**isk **S**core
WMHs: **W**hite **M**atter **H**yperintensitie**s**

Mediating effect of WMHs and total gray matter



FGCRS: **F**ramingham **G**eneral **C**ardiovascular **R**isk **S**core
WMHs: **W**hite **M**atter **H**yperintensitie**s**

*P<0.01

(Wang R et al, *Alzheimers Dement*. 2017)

Q2. Are cardiovascular risk factors associated with microstructural brain changes?

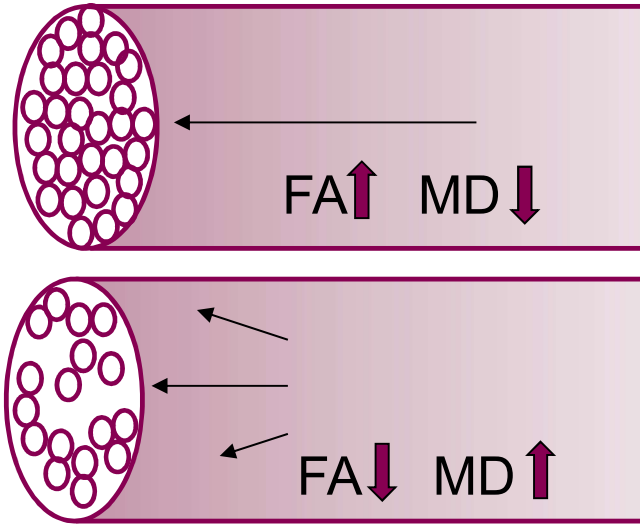
Findings

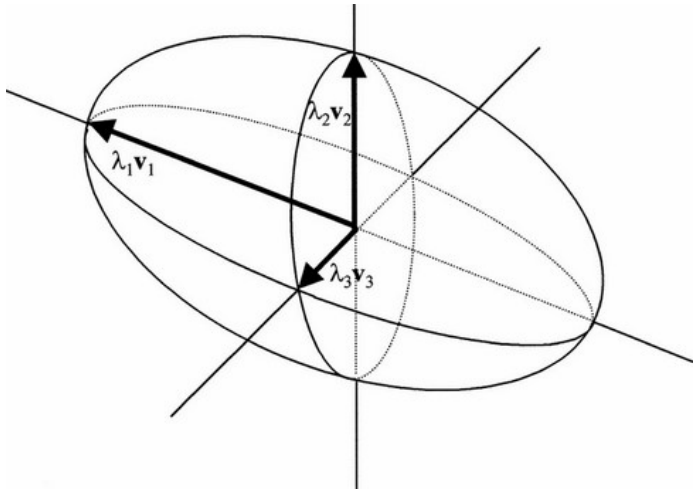
Diabetes, hypertension, smoking, and heavy drinking are associated with reduced microstructural white matter integrity

Wang R, et al. **Effects of vascular risk factors and APOE ε4 on white matter integrity and cognitive decline**. *Neurology*. 2015 Mar 17;84(11):1128-35.

Measures of White-Matter Microstructure

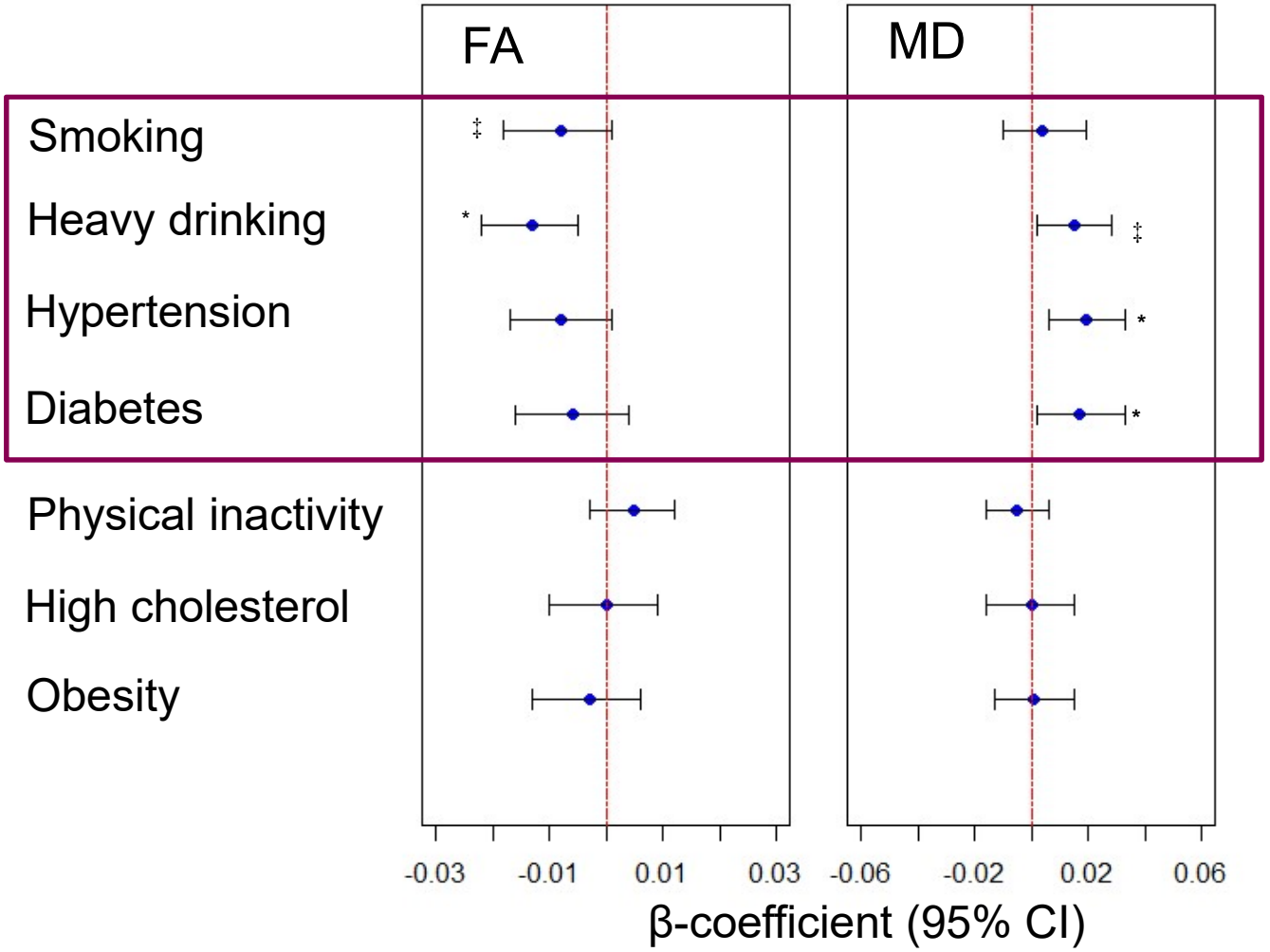
- Fractional Anisotropy (FA)
- Mean Diffusivity (MD)





(Lövdén M et al., Neuroimage 2014)

Vascular Risk Factors and Microstructural White Matter Integrity



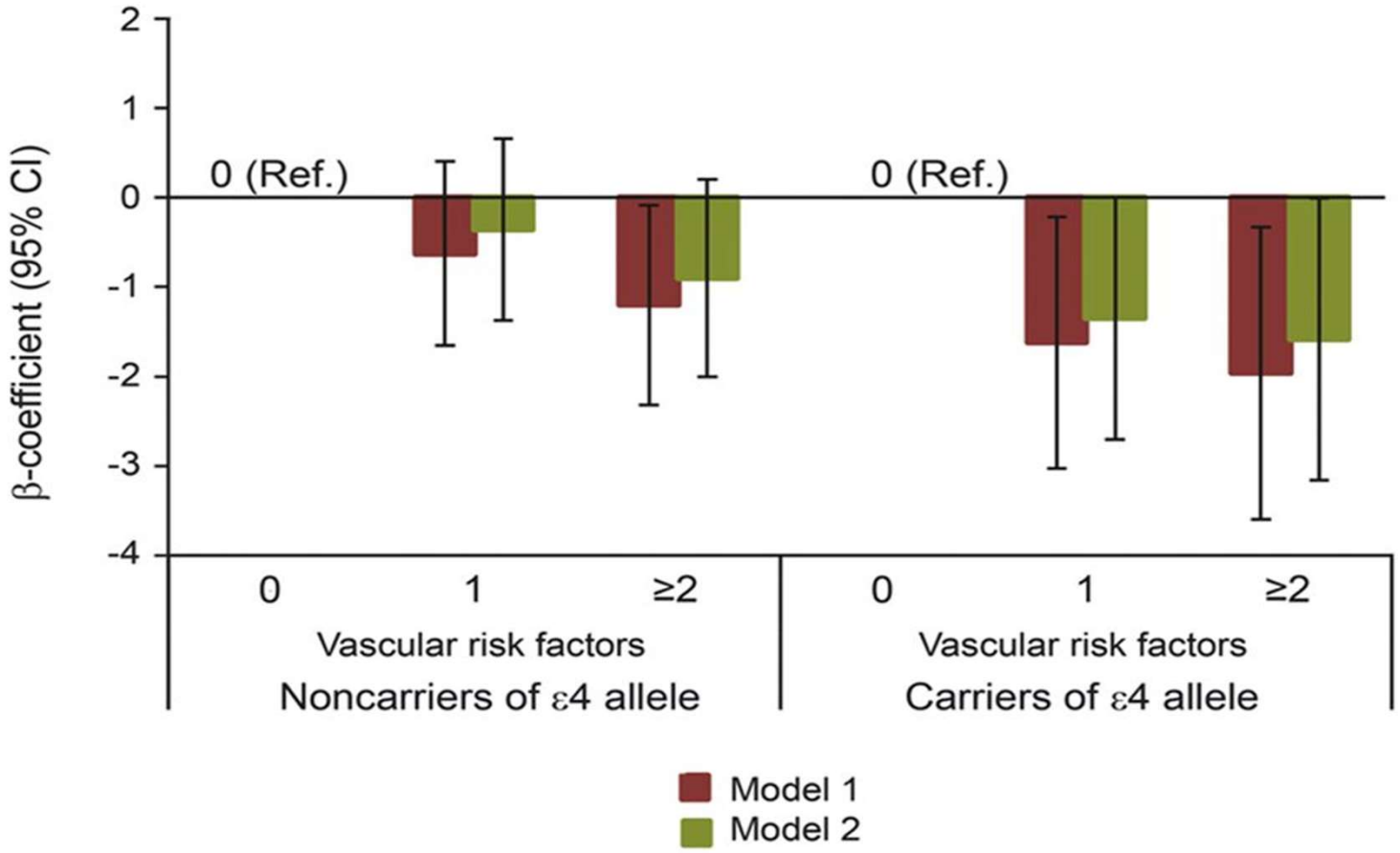
‡ 0.05<*P*<0.1
* *P*<0.05

FA: **F**ractional **A**nisotropy
MD: **M**ean **D**iffusivity

(Wang et al., *Neurology* 2016)

APOE ε4, Vascular risk factors, and Microstructural WM integrity

FA



FA: **F**ractional **A**nisotropy

(Wang et al., *Neurology* 2016)

Q3. Can dementia and cognitive decline be predicted by MRI load of cerebral microvascular lesion and neurodegeneration?

Findings

Both cerebral microvascular lesion and neurodegeneration loads are strongly associated with cognitive decline and dementia

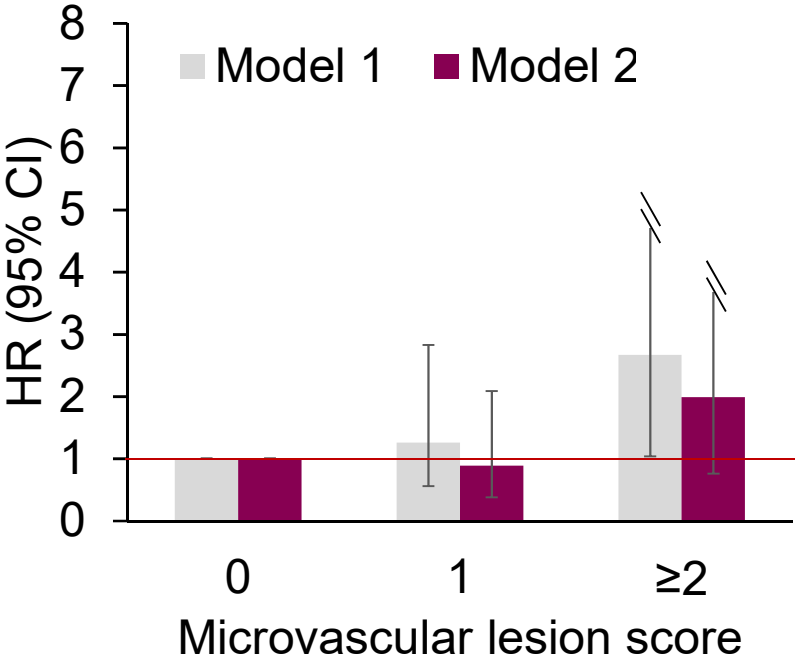
Wang R, et al. **MRI load of cerebral microvascular lesions and neurodegeneration, cognitive decline, and dementia**. *Neurology*. 2018 Oct 16;91(16):e1487-e1497.

Calculating MRI scores

- Microvascular lesion score
  - White matter hyperintensities
  - Lacune
  - Infarcts
  - Enlarged perivascular space

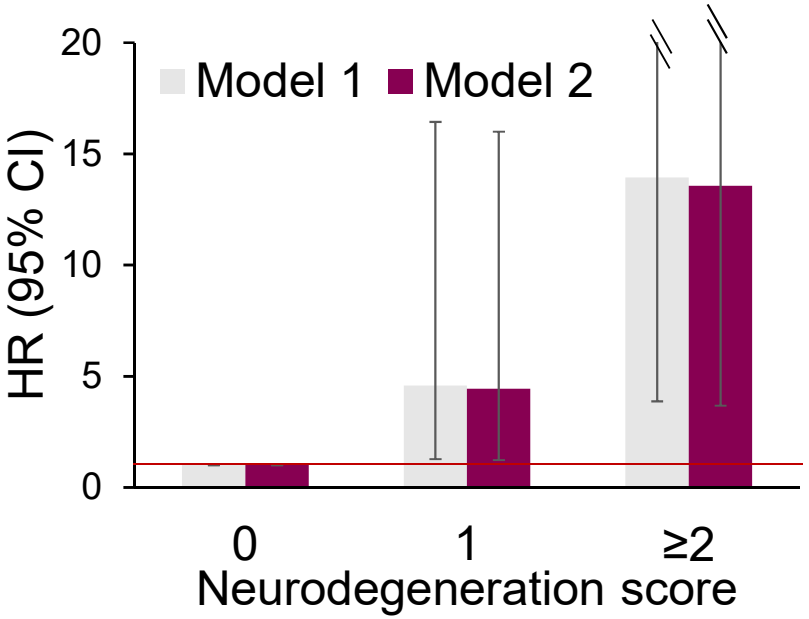
- Neurodegeneration score
  - Enlarged ventricles
  - Smaller hippocampus
  - Smaller gray matter volume

Different types of MRI scores and dementia



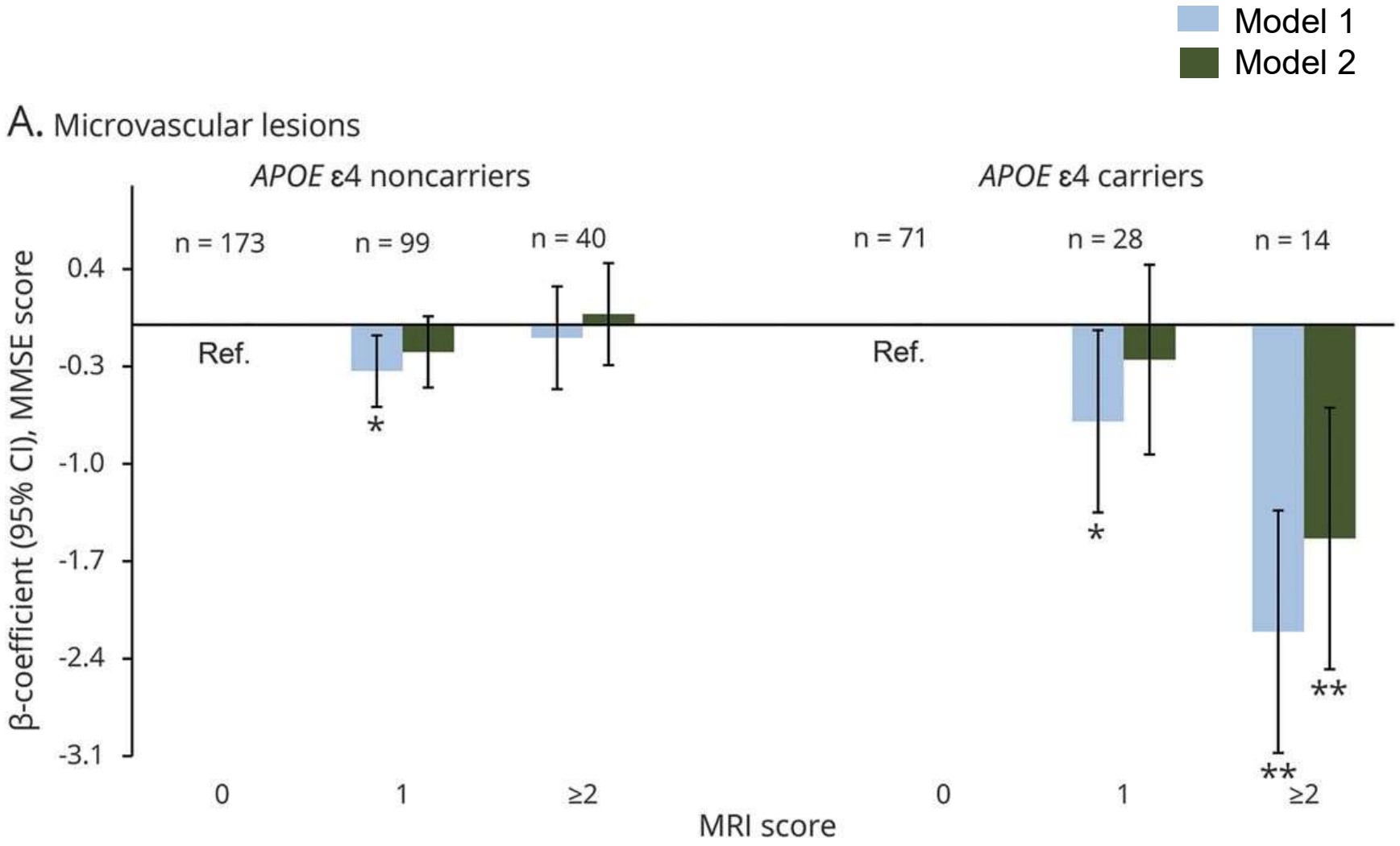
Model 1 adjusted for demographic factors, vascular risk factors, and APOE genotypes

Model 2 baseline MRI scores were added simultaneously to model 1



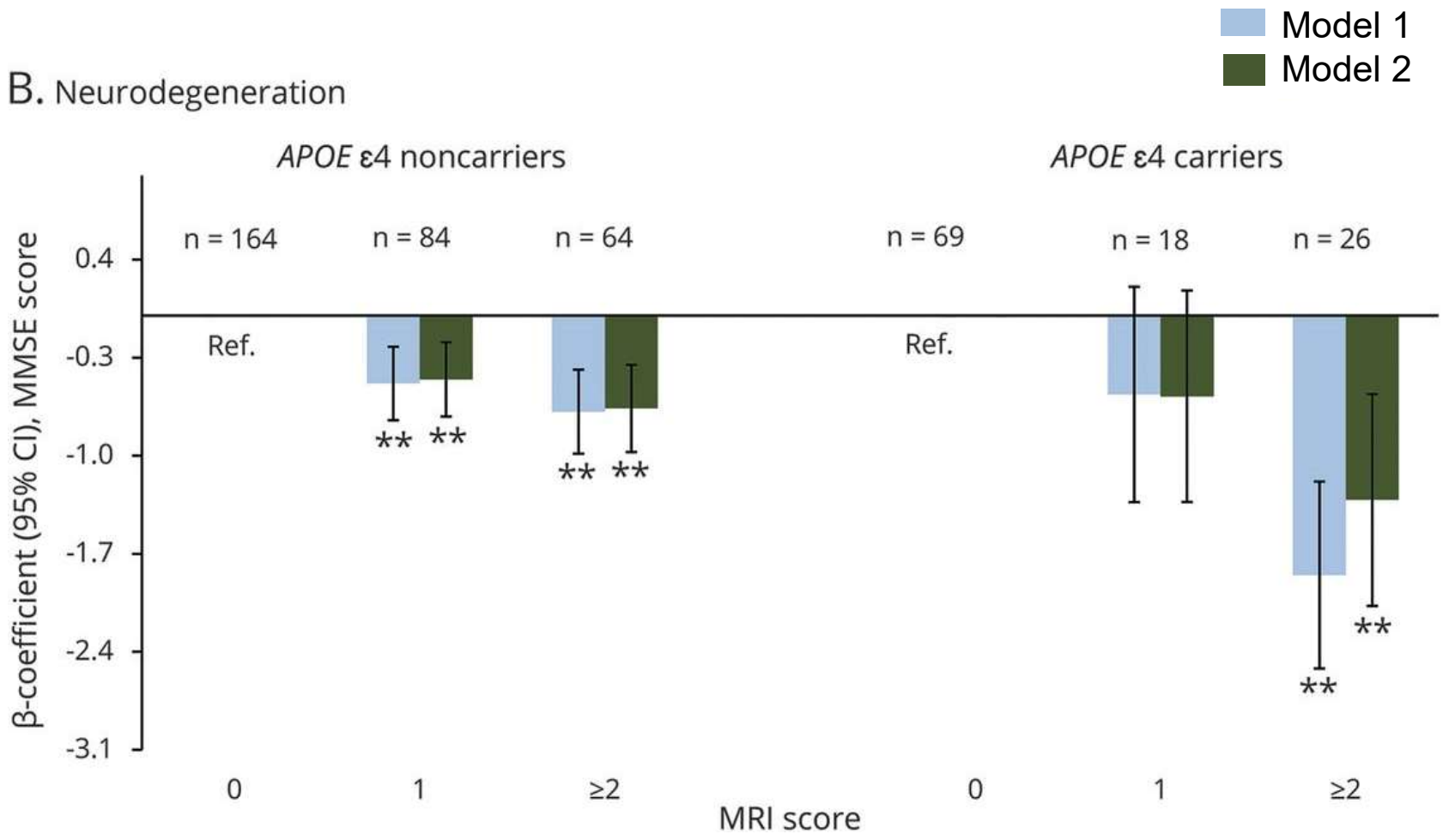
(Wang et al., *Neurology* 2018)

Effect of *APOE* ε4 allele



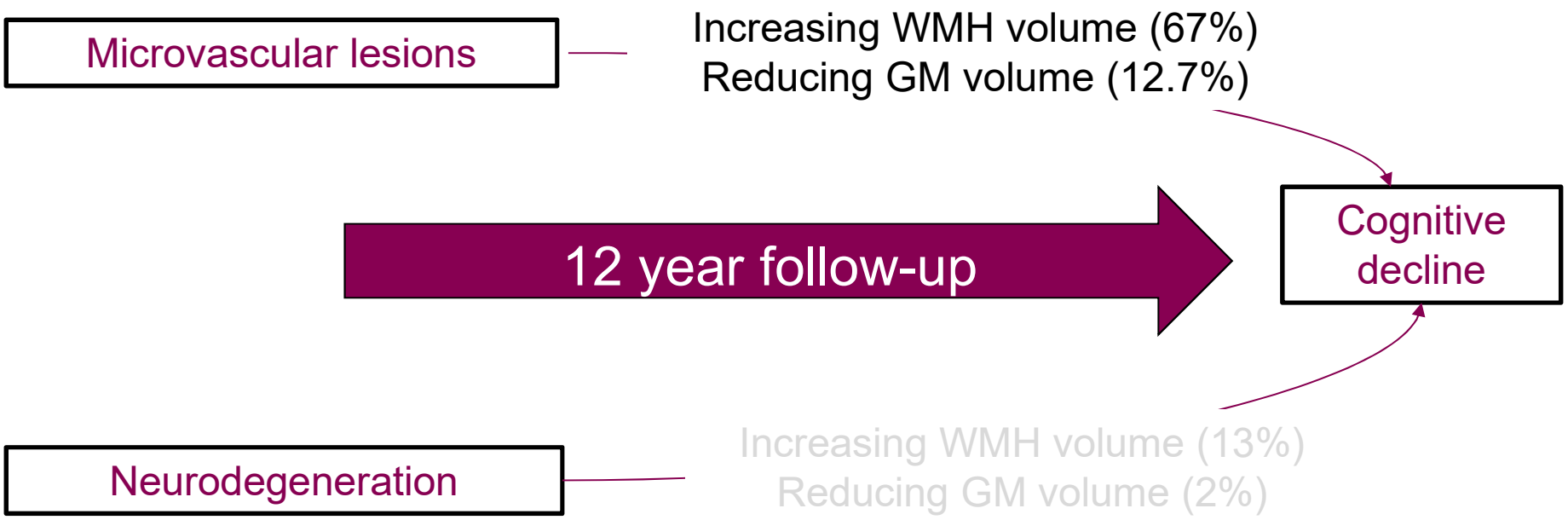
**P<0.01, *0.01<P<0.05

Effect of *APOE* ε4 allele



**P<0.01, *0.01<P<0.05

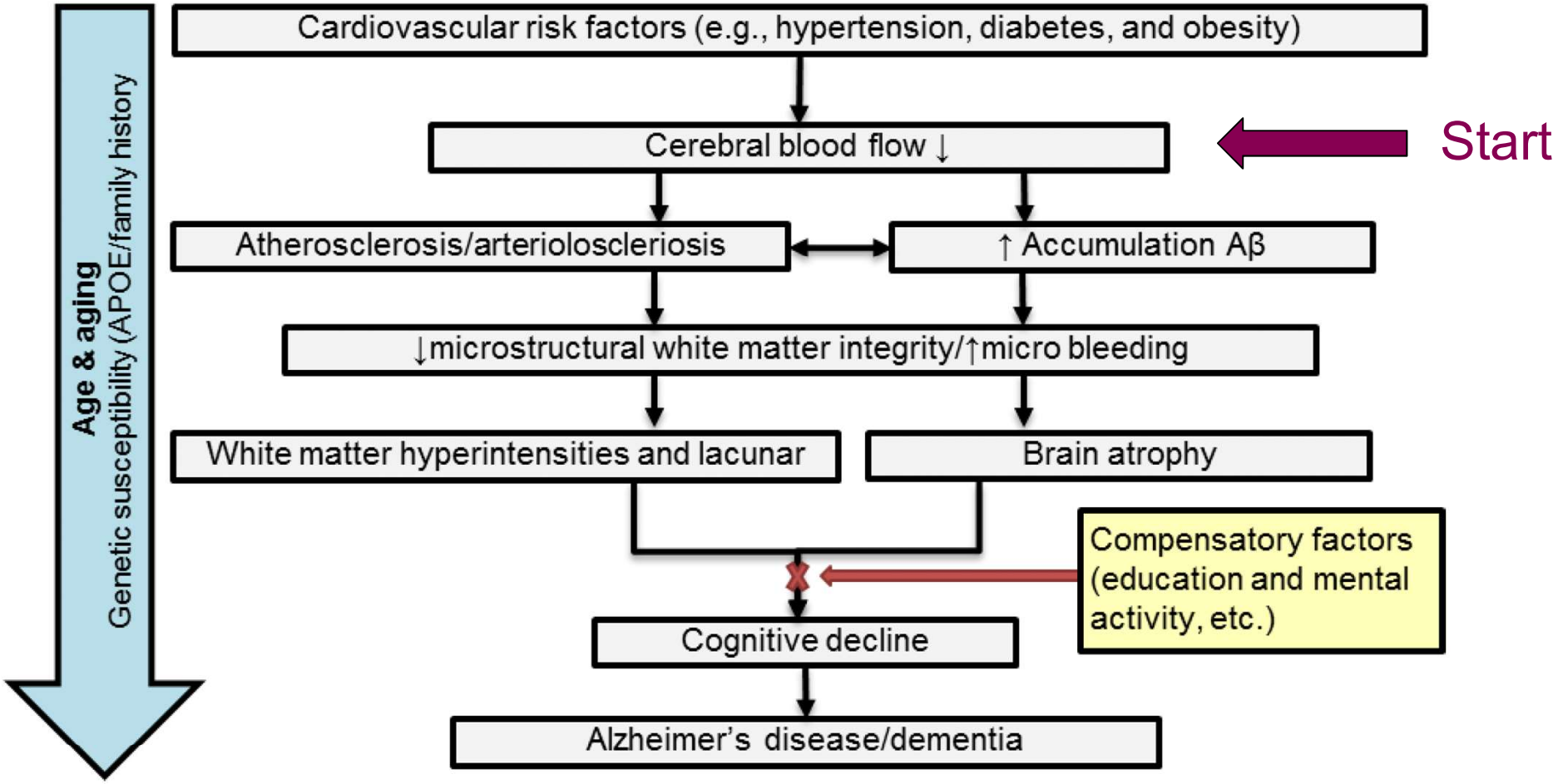
Pathways of different MRI measures to cognitive decline



(Wang et al., *Neurology* 2018)

Future Directions

Hypothetic model: pathophysiological pathways linking cardiovascular risk factors to dementia



(Wang et al., *VR application* 2017, granted)

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Thank you !

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