Dementia Risk Factors

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DISCLOSURES

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Learning Objectives

- To understand the epidemiology of mild cognitive impairment/dementia
- To understand risk factors for mild cognitive impairment/dementia, particularly modifiable ones
- To gain mechanistic insight into how risk and protective factors impact (and interact) to cause mild cognitive impairment/dementia

“Preventing cognitive impairment/dementia seems to be a more promising strategy, at least to date, than the pharmacological treatment of these conditions once they are established; importantly, there is substantive overlap in the preventive strategies (diet/lifestyle/drugs) for preserving brain health with those that effectively forestall CVD-renal disease”

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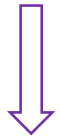
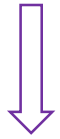
The Brain Dysfunction Continuum

Normal



Mild Cognitive Impairment (MCI)



Dementia

This transition can take decades

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Adapted from Nordestgaard LT et al. Int. J. Mol. Sci. 2022;23:9777.

REVIEW Open Access

Modifiable risk factors for dementia and dementia risk profiling. A user manual for Brain Health Services—part 2 of 6

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Abstract

We envisage the development of new Brain Health Services to achieve primary and secondary dementia prevention. These services will complement existing memory clinics by targeting cognitively unimpaired individuals, where the focus is on risk profiling and personalized risk reduction interventions rather than diagnosing and treating late-stage disease. In this article, we review key potentially modifiable risk factors and genetic risk factors and discuss assessment of risk factors as well as additional fluid and imaging biomarkers that may enhance risk profiling. We then outline multidomain measures and risk profiling and provide practical guidelines for Brain Health Services, with consideration of outstanding uncertainties and challenges. Users of Brain Health Services should undergo risk profiling tailored to their age, level of risk, and availability of local resources. Initial risk assessment should incorporate a multidomain risk profiling measure. For users aged 39–64, we recommend the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) Dementia Risk Score, whereas for users aged 65 and older, we recommend the Brief Dementia Screening Indicator (BDSI) and the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI). The initial assessment should also include potentially modifiable risk factors including sociodemographic, lifestyle, and health factors. If resources allow, *apolipoprotein E ε4* status testing and structural magnetic resonance imaging should be conducted. If this initial assessment indicates a low dementia risk, then low intensity interventions can be implemented. If the user has a high dementia risk, additional investigations should be considered if local resources allow. Common variant polygenic risk of late-onset AD can be tested in middle-aged or older adults. Rare variants should only be investigated in users with a family history of early-onset dementia in a first degree relative. Advanced imaging with 18-fluorodeoxyglucose positron emission tomography (FDG-PET) or amyloid PET may be informative in high risk users to clarify the nature and burden of their underlying pathologies. Cerebrospinal fluid biomarkers are not recommended for this setting, and blood-based biomarkers need further validation before clinical use. As new technologies become available, advances in artificial intelligence are likely to improve our ability to combine diverse data to further enhance risk profiling. Ultimately, Brain Health Services have the potential to reduce the future burden of dementia through risk profiling, risk communication,

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Ranson JM et al. Modifiable risk factors for dementia and dementia risk profiling. A user manual for Brain Health Services—part 2 of 6. Alzheimer's Research and Therapy 2021;13:169.

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Epidemiology of Mild Cognitive Impairment (MCI)

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Recommendations

General criteria for MCI

Not normal, not demented (Does not meet criteria (DSM IV, ICD 10) for a dementia syndrome)

Cognitive decline

-Self and/or informant report and impairment on objective cognitive tasks
and / or
-Evidence of decline over time on objective cognitive tasks

Preserved basic activities of daily living / minimal impairment in complex instrumental functions

Adapted from Winblad B et al. Journal of Internal Medicine 2004;256:240-246.

Worldwide Prevalence of Mild Cognitive Impairment (MCI) in Community Dwellers ≥50 Years of Age

Meta-analysis of 66 articles, 242,084 participants

- Mild Cognitive Impairment 15.56%[1]
  - amnestic MCI 10.03%
  - non-amnestic MCI 8.72%
- Correlates of MCI
  - age
  - lower education level

Bai W et al. Age and Aging 2022;51:1-14

[1]prevalence is 21.27% in those ≥80 years

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Age-specific Prevalence of Mild Cognitive Impairment (MCI)

Age	%
60-64	6.7
65-69	8.4
70-74	10.1
75-79	14.8
80-84	25.2

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Petersen RC et al. Neurology 2018;90:126-135.

Epidemiology of Dementia

Epidemiology of Dementia

Clinical diagnosis defined as cognitive symptoms that interfere with the ability to function at usual activities

- Dementia affects more than 50 million individuals worldwide
- Alzheimer's disease
  - Early onset (< 65)
  - Late onset (> 65)
- Cerebrovascular dementia
  - Evidence of prior stroke, intracranial hemorrhage and/or current cerebrovascular disease

Adapted from Nordestgaard LT et al. Int. J. Mol. Sci. 2022;23:9777.

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Epidemiology of Dementia

Cause	% of Cases
Alzheimer's disease	60-80
Cerebrovascular disease	5-10
Frontotemporal degeneration (FTD)[1]	3% (65 and older) 10% (65 and younger)
Hippocampal sclerosis (HP)	3-13%
Lewy body disease	~ 5%
Mixed pathologies	> 50% most common cause in ≥ 85
Parkinson's disease (PD)	~ 4% (~ 1/4 with PD develop dementia)

Adapted from Alzheimer's Association Report. 2023 Alzheimer's disease facts and figures. Alzheimer's Dement. 2023;19:1958-1695.

[1] McKhann GM et al. Alzheimer's Dementia 2011;7:263-269.

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Alzheimer's Disease (AD) Epidemiology

- 6.7 million American adults ≥ 65 years have AD
  - This number is projected to rise to almost 14 million by 2060
- AD is the 5th leading cause of death in Americans ≥ 65
  - AD deaths ↑'d by 145% between 2000-2019 while deaths from stroke, heart disease and HIV all ↓'d
- In this age group, average per person payment for Medicare services for AD patients are 3-fold compared to those without AD

Adapted from Alzheimer's Association Report. 2023 Alzheimer's disease facts and figures. Alzheimer's Dement. 2023;19:1958-1695

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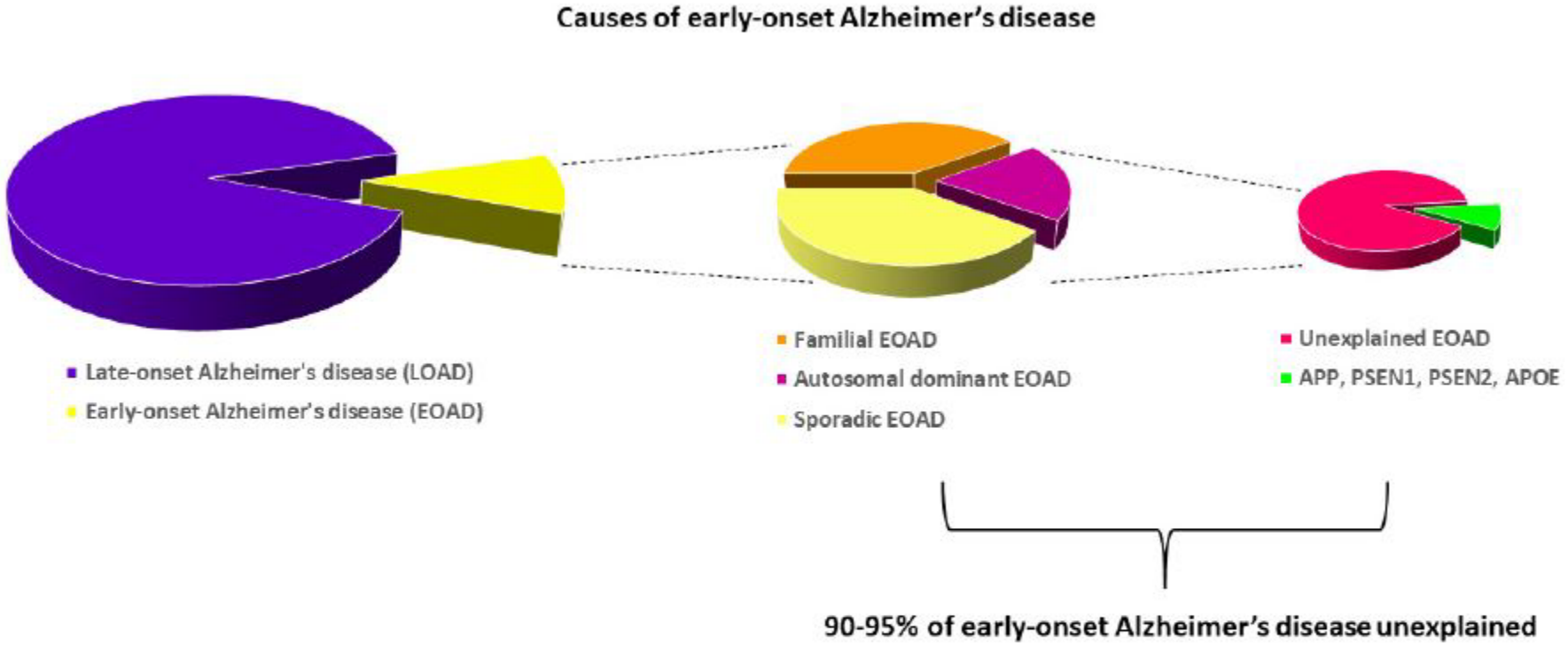

Figure 4. Causes of early-onset Alzheimer's disease. Early-onset Alzheimer's disease (EOAD) accounts for approximately 10% of Alzheimer's disease cases. Mutations in the amyloid precursor protein gene (*APP*), the presenilin 1 and 2 genes (*PSEN1* and -2), and the apolipoprotein E gene (*APOE*) explain only a small part of autosomal dominant early-onset Alzheimer's disease, leaving large parts of early-onset Alzheimer's disease unexplained. Adapted from Cacace et al., Alzheimer's Dement 2016.

Nordestgaard LT et al. Shared Risk Factors between Dementia and Atherosclerotic Cardiovascular Disease. International Journal of Molecular Sciences 2022;23:9777.

(Modifiable) Dementia Risk Factors

Diet
Exercise
Alcohol
Smoking

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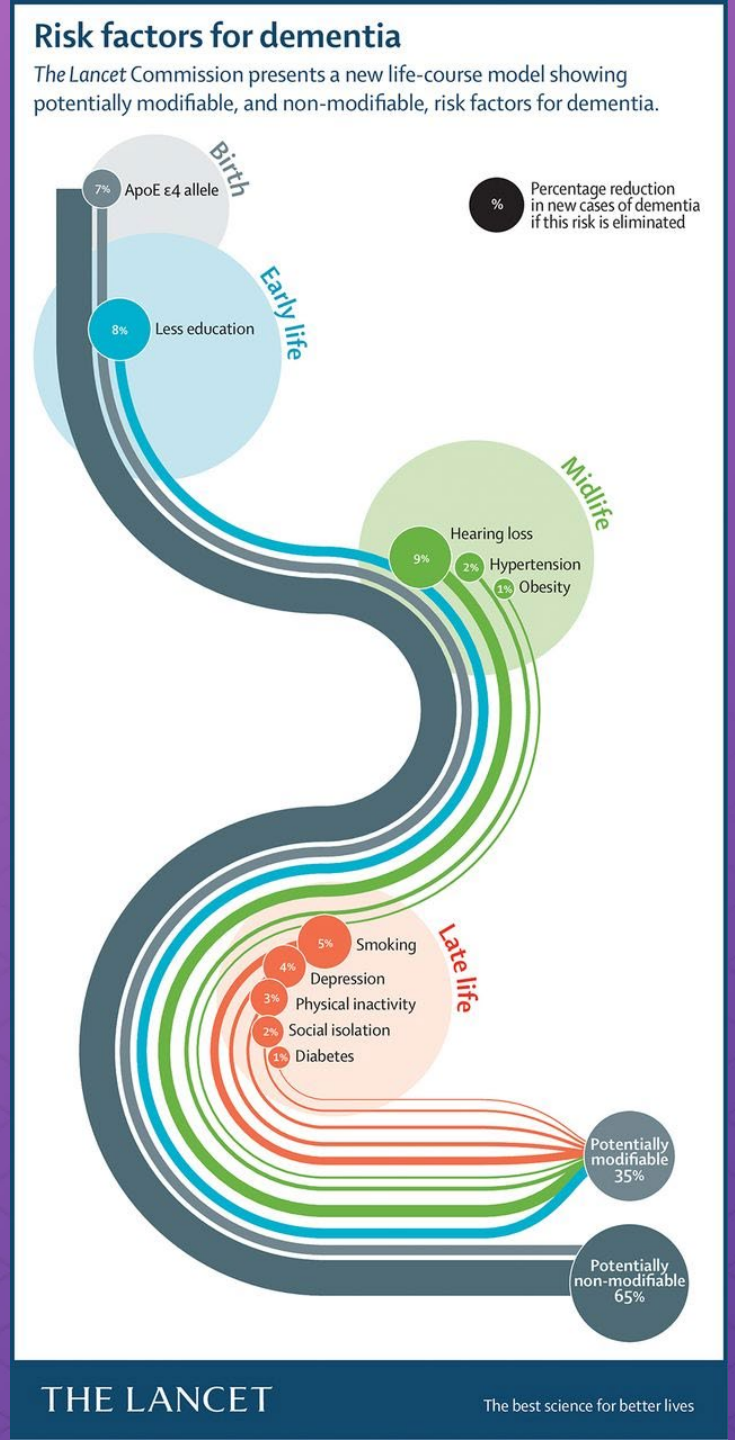

Alty J et al. Pract Neurol 2020;20:234-240.

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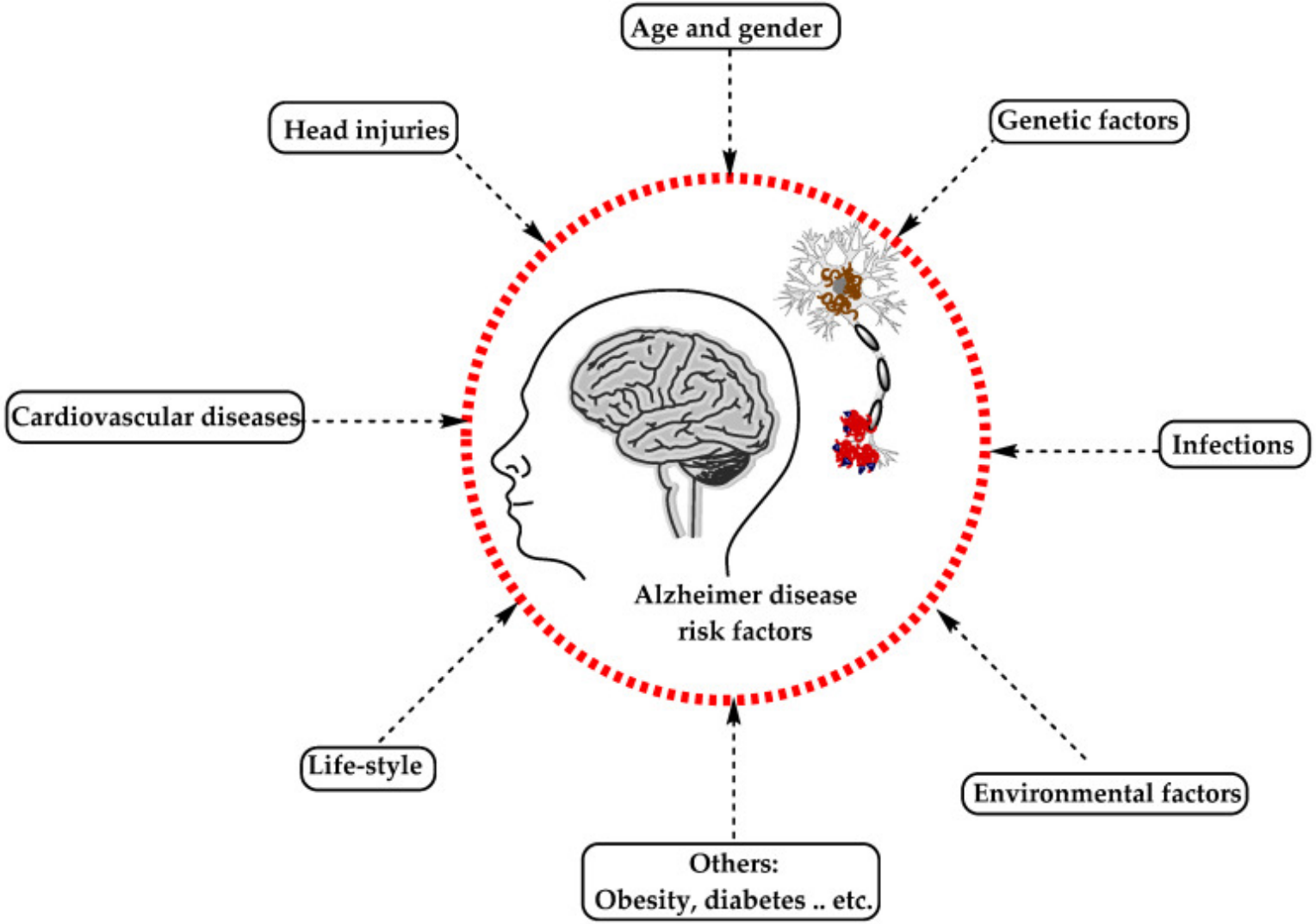

Breijyeh and Karman. Molecules 2020;25:2789.

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TABLE 1 Overview of the dietary components included in the Mediterranean, DASH, and MIND diets

	Mediterranean diet (16, 17)	DASH diet (10)	MIND diet (11)
High amounts	Olive oil	—	Olive oil
	Fish	—	Fish
	Breads and other forms of cereals	Grains	Whole grains
	Fruits	Fruits	Berries
	Vegetables	Vegetables	Green leafy vegetables
	—	—	Other vegetables
	Legumes	Legumes	—
	Nuts	Nuts	Nuts
	Beans	—	Beans
	Seeds	Seeds	—
	—	Low-fat dairy products	—
	—	—	Poultry
Moderate amounts	Dairy products	—	—
	Poultry	Poultry	—
	Alcohol	—	Alcohol/wine
	—	Fish	—
Restricted amounts	Red meat	Red meat	Red meat and products
	Processed meat	—	—
	Sweets	Sweets	Pastries and sweets
	—	Saturated fat	—
	—	Total fat	—
	—	Cholesterol	—
	—	Sodium	—
	—	—	Cheese
	—	—	Butter/margarine
	—	—	Fast fried foods

Van den Brink AC et al. Adv Nutr 2019;10:1040-1065.

Increased Adherence to Three Dietary Patterns are Associated with Less Cognitive Decline and Lower Alzheimer's Disease (AD) Risk

Mediterranean diet:

- Higher cognitive scores in
  - 9/12 cross-sectional studies
  - 17/25 longitudinal studies
  - 1/3 trials
- Lower AD risk
  - 1 case-control study
  - 6/8 longitudinal cohort studies

DASH diet:

- Higher cognitive scores
  - 1 cross-sectional study
  - 2/5 longitudinal studies
  - 1 trial

Adapted from Adv Nutr 2019;10:1040-1065.

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Increased Adherence to Three Dietary Patterns are Associated with Less Cognitive Decline and Lower Alzheimer's Disease (AD) Risk

MIND diet:

- Higher cognitive scores in
  - 1 cross-sectional studies
  - 2/3 longitudinal studies

MIND or DASH diet:

- Less cognitive decline
- Lower AD risk

Adapted from Adv Nutr 2019;10:1040-1065.

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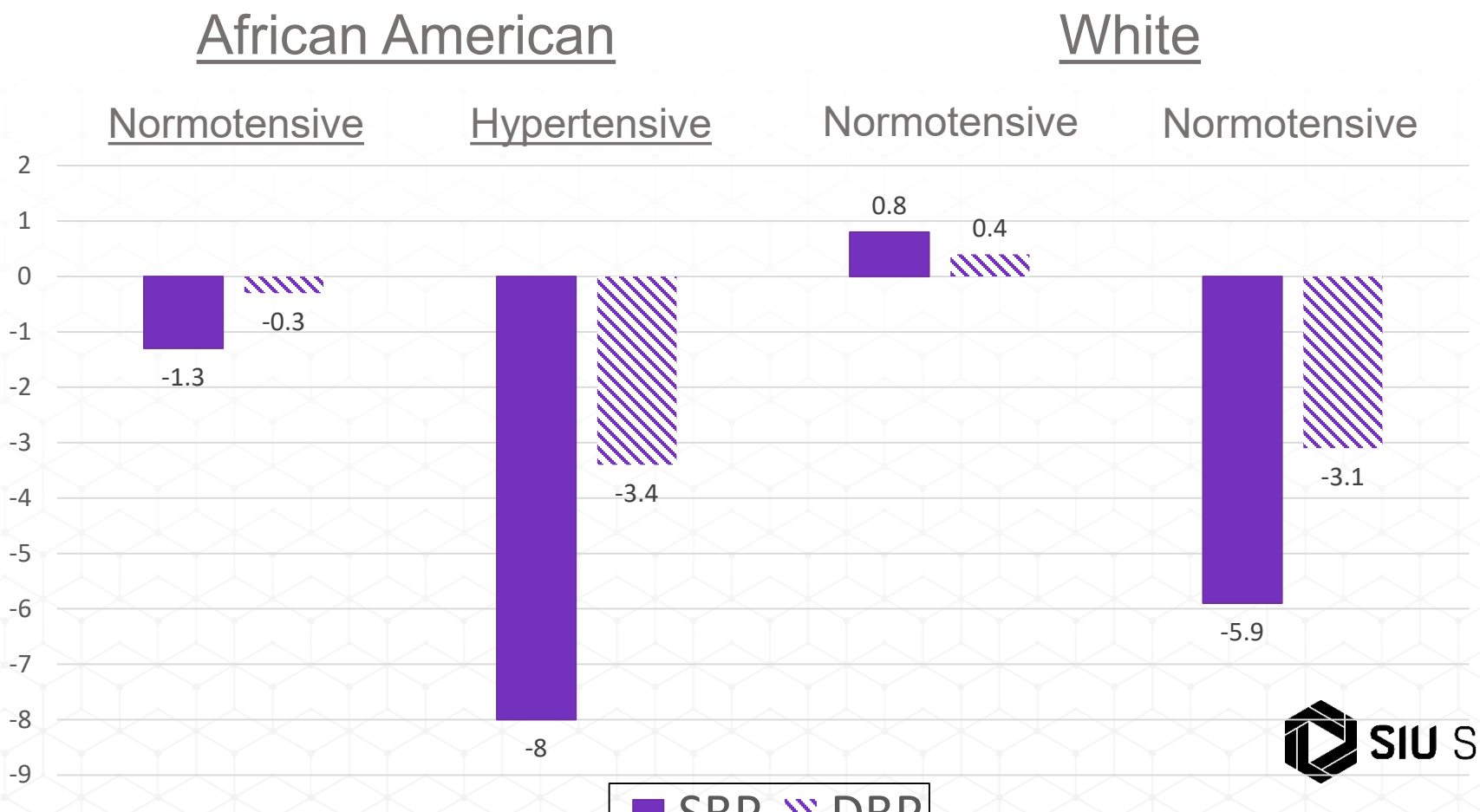
DASH Fruits and Vegetables Diet Effect on BP



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Alty J et al. Pract Neurol 2020;20:234-240.

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Alcohol Use and Dementia

- Light to moderate alcohol use (mid-to-late-adulthood) is associated with decreased risk for cognitive impairment and dementia

- Heavy alcohol use is associated with structural brain changes, cognitive impairment and all types of dementia

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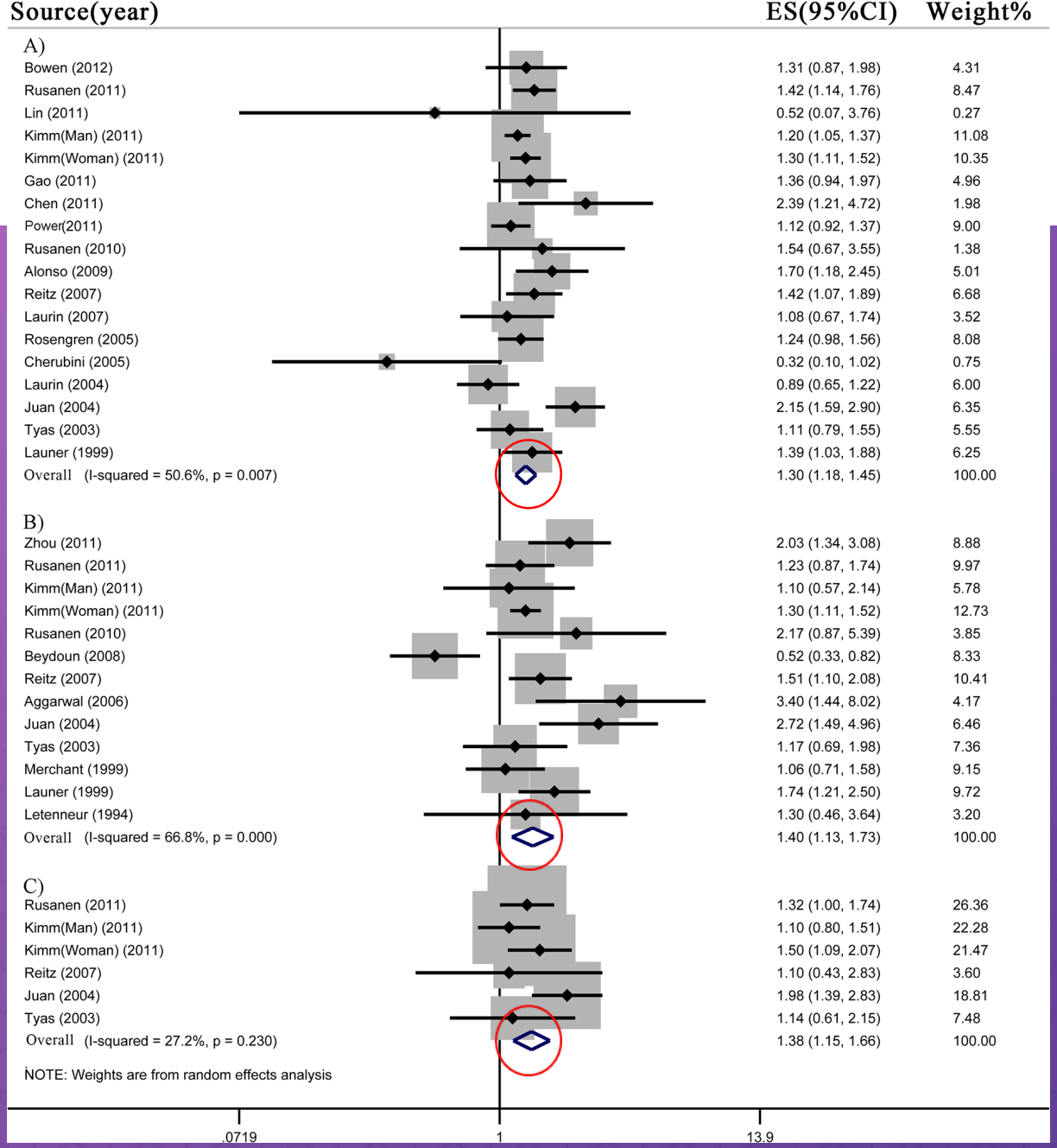
Rehm J et al. Alzheimer's Research and Therapy 2019;11:1.



Meta-analysis for current smoking and risk of A) all-cause dementia, B) Alzheimer's disease and C) vascular dementia.

Zhong G et al. PLOS ONE
DOI:
10.1371/journal.pone.0.118333.

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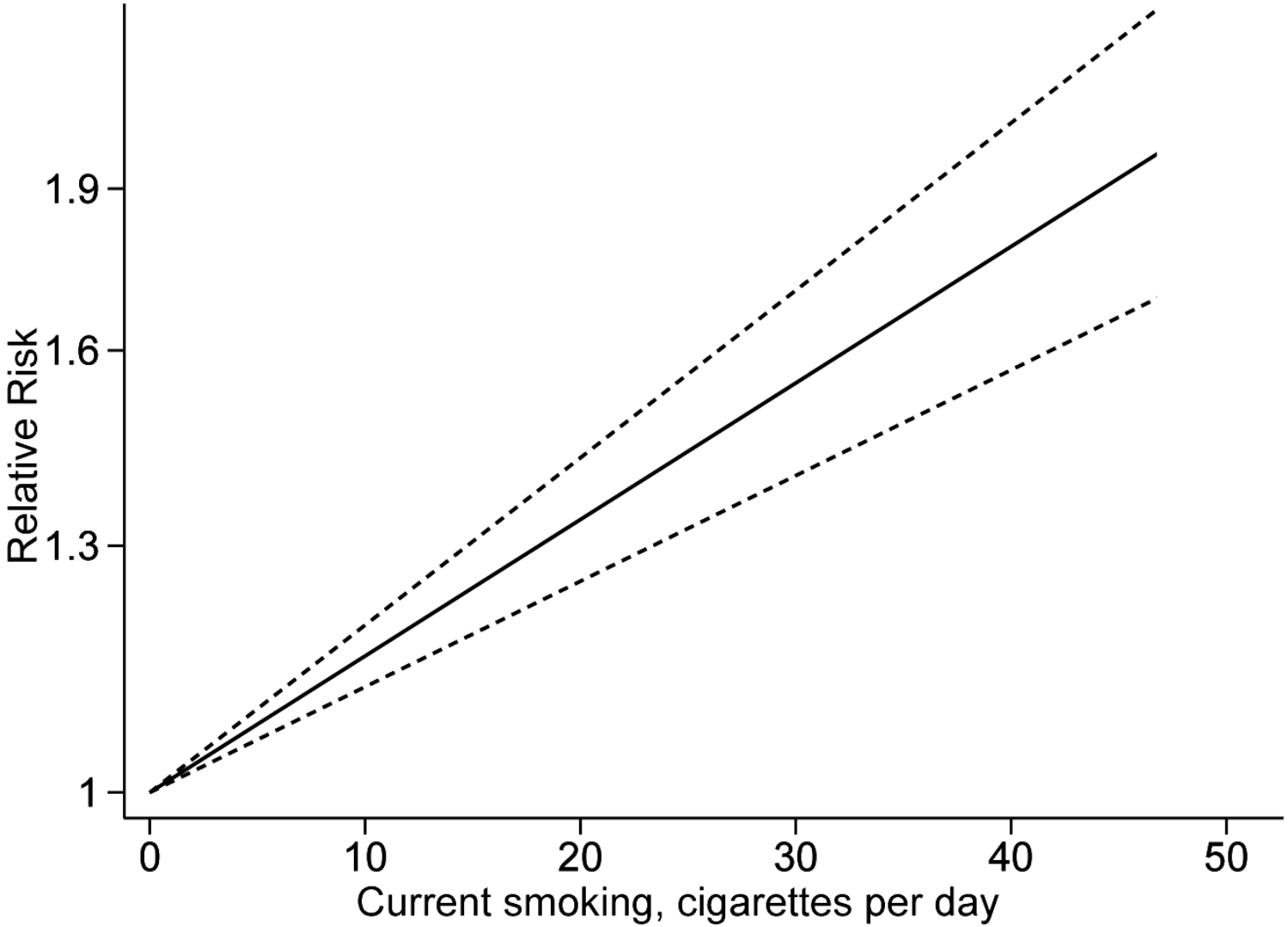

Zhong G et al. PLOS ONE
DOI:
10.1371/journal.pone.0.118333.

The solid line represents the linear trend and lines with short dashes represent its' 95% confidence interval.

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Table 3. (*Continued*)

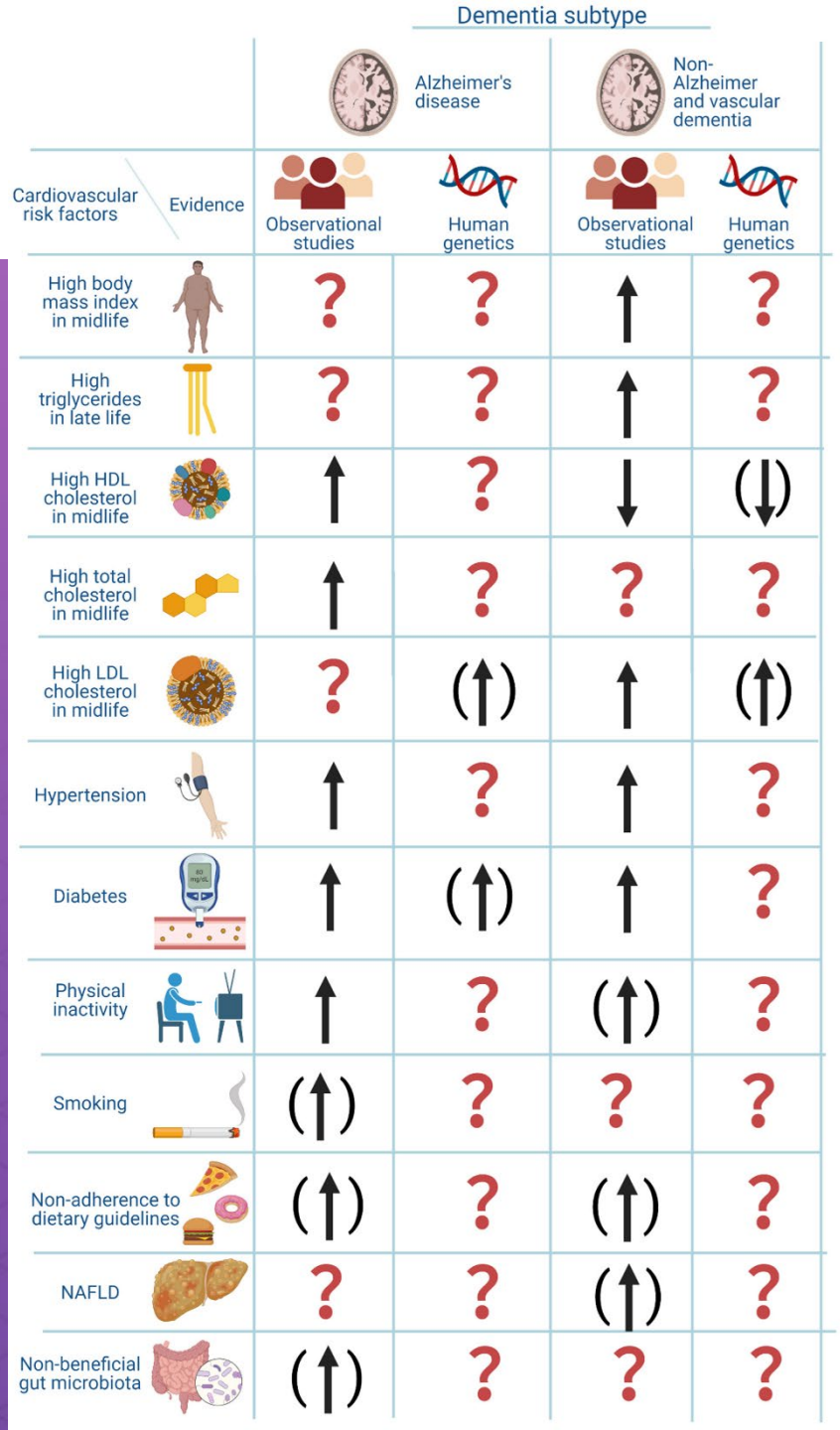
Subgroup	Ever versus never smoking				Current versus never smoking				Former versus never smoking			
	n	RR (95% CI)	I^2 (%)	p^1	n	RR (95% CI)	I^2 (%)	p^1	n	RR (95% CI)	I^2 (%)	p^1
No	15	1.06 (0.97–1.16)	48.8		10	1.19(1.06–1.34)	35.9		10	1.00 (0.93–1.07)	0.0	

CI, confidence interval; RR, risk ratio; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised.

[1] *P* for heterogeneity between subgroups with meta-regression.

[2] Note that among selected studies for body mass index and diabetes mellitus, researchers adjusted these two confounders in tandem. Thus, the results of subgroup analyses regarding body mass index and diabetes mellitus are identified.

Zhong G et al. PLOS ONE DOI: 10.1371/journal.pone.0.118333.



Nordestgaard LT et al. Int. J. Mol. Sci 2022;23:9777

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Shared Risk Factors between Dementia and CVD

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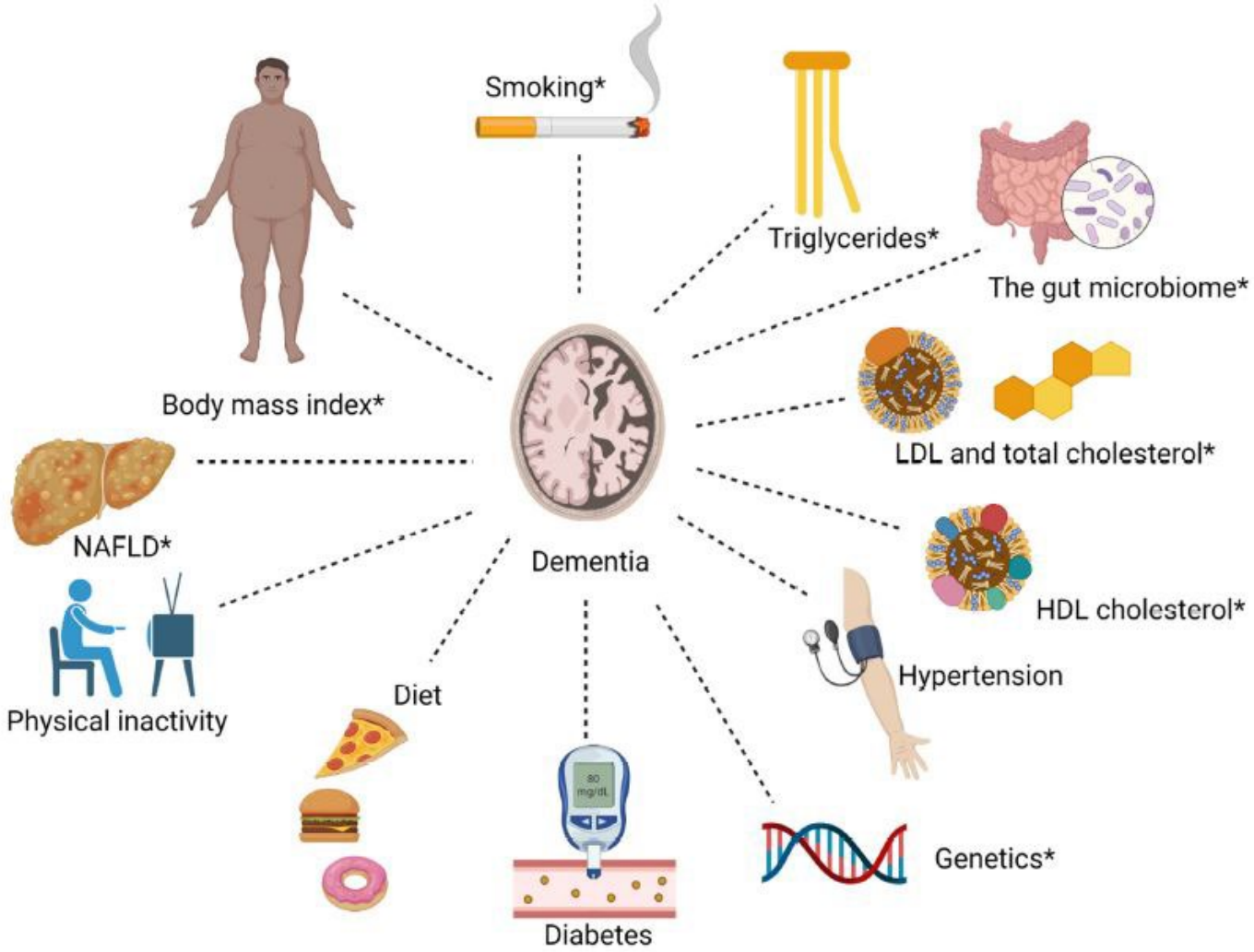

Figure 1. Overview of shared risk factors between dementia and atherosclerotic cardiovascular disease, discussed in this review. LDL, low-density lipoprotein; HDL, high-density lipoprotein; NAFLD, non-alcoholic fatty liver disease. The associations for some risk factors differ between Alzheimer's disease and non-Alzheimer dementia, specifically, body mass index, triglycerides, HDL cholesterol, NAFLD, the gut microbiome, smoking, and genetics (these are marked by *).

Nordestgaard LT et al. Shared Risk Factors between Dementia and Atherosclerotic Cardiovascular Disease. International Journal of Molecular Sciences 2022;23:9777.

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Transitioning from Normal/Mild Cognitive Impairment to Dementia

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Risk Factors for Progression of Mild Cognitive Impairment to Dementia

- ❑ Advanced age
- ❑ Amnestic MCI
- ❑ Atrophy of medial temporal lobe (MRI)
- ❑ Biomarkers
  - ❑ Parietal glucose metabolic rate
  - ❑ Total tau proteins
- ❑ Genetic factors
  - ❑ APOE E4
    - ❑ Allele carriers ~2X more likely to progress to AD
    - ❑ Allele homozygotes ~4X more likely to progress to AD
  - ❑ Clusterin (CLU) T-allele
    - ❑ Lower conversion to AD than non-carriers

Adapted from Campbell NL et al. Clin Geriatr Med 2013;29(4):873-893.

Predicting Progression to Dementia

Mayo Clinic Study of Aging (N=1598)

And

Framingham Heart Study (N=773)

- Older community dwelling adults without dementia
- Ages 70 to 89 years
- Baseline cognitive status determined by neuropsychological testing (similar but not identical across the two studies)
  - No cognitive impairment (ref)
  - 4 cognitive domains assessed: attention/executive, **memory domain**, language domain, visuospatial domain
  - Single or multiple amnestic or non-amnestic profiles at each cut-score
    - Normative mean SDs of ≤-0.5, -1, -1.5, and -2.
  - Incident dementia @6 years was determined

Knopman DS et al. Neurology 2015;85:1712-1721

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Table 1 Neuropsychological instruments[a] used in the FHS and MCSA

	FHS	MCSA
Attention/executive domain	Trail-Making Test, Part B	Trail-Making Test, Part B; WAIS-R Digit Symbol Substitution Test
Memory domain	WMS Logical Memory delayed recall; WMS Visual Reproduction delayed recall	WMS-R Logical Memory delayed recall; WMS-R Visual Reproduction delayed recall; Auditory Verbal Learning Test
Language domain	Boston Naming Test	Boston Naming Test; Category Fluency
Visuospatial domain	Hooper Visual Organization Test	WAIS-R Picture Completion Test; WAIS-R Block Design Test
Mental status examination	Mini-Mental State Examination	Short Test of Mental Status

Abbreviations: FHS = Framingham Heart Study; MCSA = Mayo Clinic Study of Aging; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMS = Wechsler Memory Scale; WMS-R = Wechsler Memory Scale-Revised.

[a] See appendix e-1 for references. For the FHS, the selected tests were chosen from a slightly larger battery to correspond to the tests and domains studied in the MCSA.

Knopman DS et al. Neurology 2015;85:1712-1721.

Table 2 Demographic and cognitive features of participants at baseline, grouped by dementia status: Mayo Clinic Study of Aging and Framingham Heart Study

	Framingham Heart Study		Mayo Clinic Study of Aging	
	Incident dementia (n = 113)	Remained dementia-free (n = 660)	Incident dementia (n = 162)	Remained dementia-free (n = 1,436)
Age at visit date, y, median (IQR)	81.2 (76.8, 85.1)	77.6 (72.9, 82.1)	82.7 (79.6, 86.0)	79.1 (74.8, 83.2)
Sex, male, n (%)	29 (38)	323 (46)	84 (52)	733 (51)
Duration of follow-up, y, median (IQR)	3.2 (1.9, 4.7)	5.3 (5.8, 6.0)	2.9 (1.9, 4.5)	5.7 (3.1, 6.6)
Educational attainment, n (%)				
<High school degree	18 (23)	69 (10)	28 (17)	148 (10)
High school degree	30 (39)	274 (39)	55 (34)	494 (34)
Some college	18 (23)	173 (25)	39 (24)	345 (24)
College degree	11 (14)	180 (26)	40 (25)	449 (31)
Short Test of Mental Status,[a] median score (IQR) (max 38 points)	—	—	31 (29, 33)	34 (32, 36)
Mini-Mental State Examination,[b] median score (IQR) (max 30 points)	28 (26, 29)	29 (28, 30)	—	—
Clinical Dementia Rating, global median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0.5)	0 (0, 0)
Functional Activities Questionnaire,[a] total (IQR)	—	—	1 (0, 3)	0 (0, 1)
Baseline cognitive domain, *z* scores, median (IQR)				
Memory	−0.91 (−1.67, 0.27)	0.10 (−0.62, 0.77)	−0.96 (−1.56, −0.31)	0.11 (−0.55, 0.75)
Language	−0.63 (−1.26, −0.19)	0.07 (−0.65, 0.50)	−0.80 (−1.42, −0.27)	0.14 (−0.44, 0.67)
Attention/executive	−0.87 (−1.69, −0.09)	0.10 (−0.36, 0.71)	−1.01 (−1.61, −0.28)	0.06 (−0.61, 0.64)
Visuospatial	−0.43 (−1.02, 0.19)	0.05 (−0.69, 0.65)	−0.60 (−1.29, 0.03)	0.13 (−0.55, 0.68)

Abbreviation: IQR = interquartile range.
[a] Performed only in the Mayo Clinic Study of Aging.
[b] Performed only in Framingham Heart Study.

Knopman DS et al. Neurology 2015;85:1712-1721.

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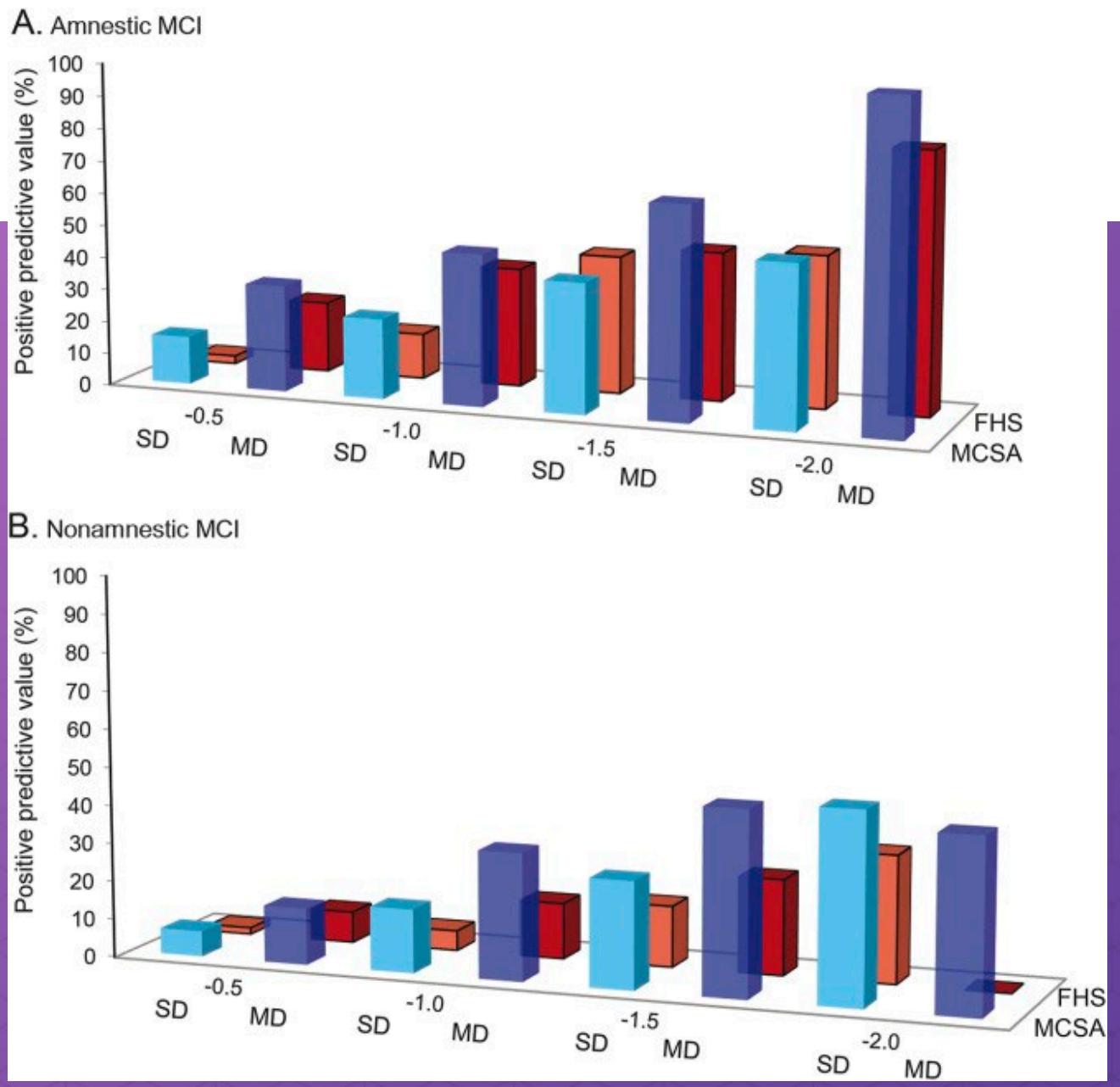

PPVs for incident dementia at 45 months post baseline PPVs (in percent) for incident dementia at 45 months post baseline for FHS (red bars) and MCSA (blue bars). PPVs are shown for amnestic MCI (A) and nonamnestic MCI (B) SD (lighter color) and MD (darker color) at the cutpoints of −0.5, −1.0, −1.5, and −2.0. FHS = Framingham Heart Study; MCI = mild cognitive impairment; MCSA = Mayo Clinic Study of Aging; MD = multidomain; PPV = positive predictive value; SD = single domain.

Knopman DS et al. Neurology 2015;85:1712-1721.

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Genetic Risk Factors for Dementia

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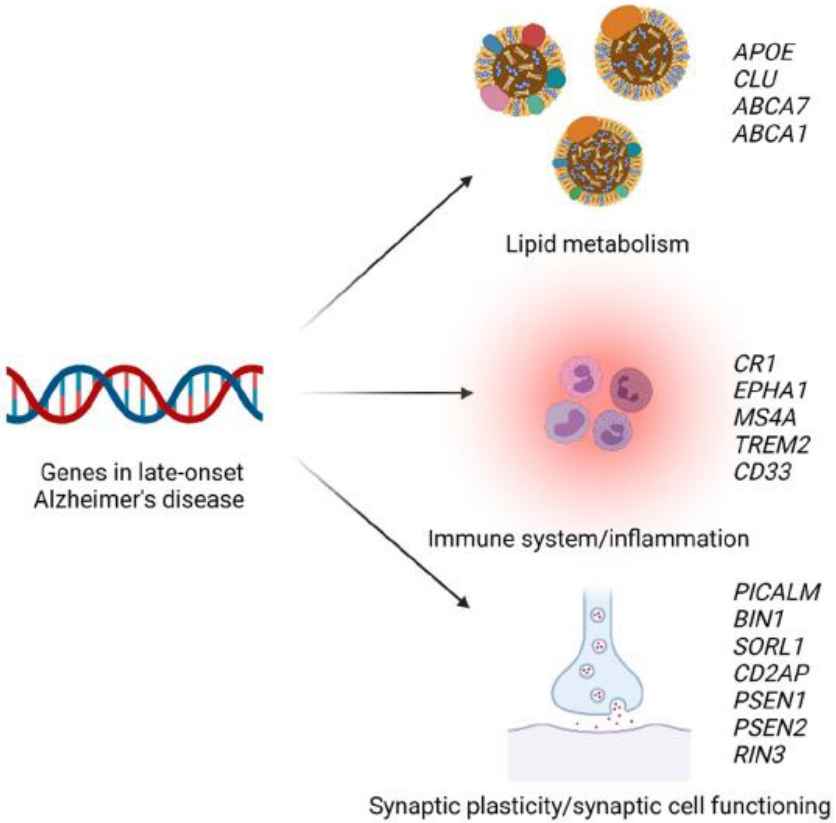

Figure 5. Selected genetic risk factors for late-onset Alzheimer's disease. Genes associated with a risk of Alzheimer's disease are involved in lipid metabolism, the immune system and inflammation, or synaptic plasticity and synaptic cell functioning. APOE, apolipoprotein E gene; CLU, clusterin gene; ABCA7, ATP-binding cassette transporter A7 gene; ABCA1, ATP-binding cassette transporter A1 gene; CR1, complement C3b/C4b receptor 1 gene; EPHA1, ephrin type-A receptor 1 gene; MS4A, membrane-spanning 4A gene; TREM2, triggering receptor expressed on myeloid cells 2 gene; PICALM, phosphatidylinositol binding clathrin assembly protein gene; BIN1, bridging integrator 1 gene; SORL1, sorting protein-related receptor gene; CDA2P, CD2-associated protein gene; PSEN1/2, presenilin 1 or 2 gene; RIN3, Ras and Rab interactor 3 gene; CD33, sialic acid binding Ig-like lectin 3 gene. Created with Biorender.com.

Nordestgaard LT et al. Shared Risk Factors between Dementia and Atherosclerotic Cardiovascular Disease. International Journal of Molecular Sciences 2022;23:9777.

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Proposed Mechanism(s) of Dementia Risk Factors

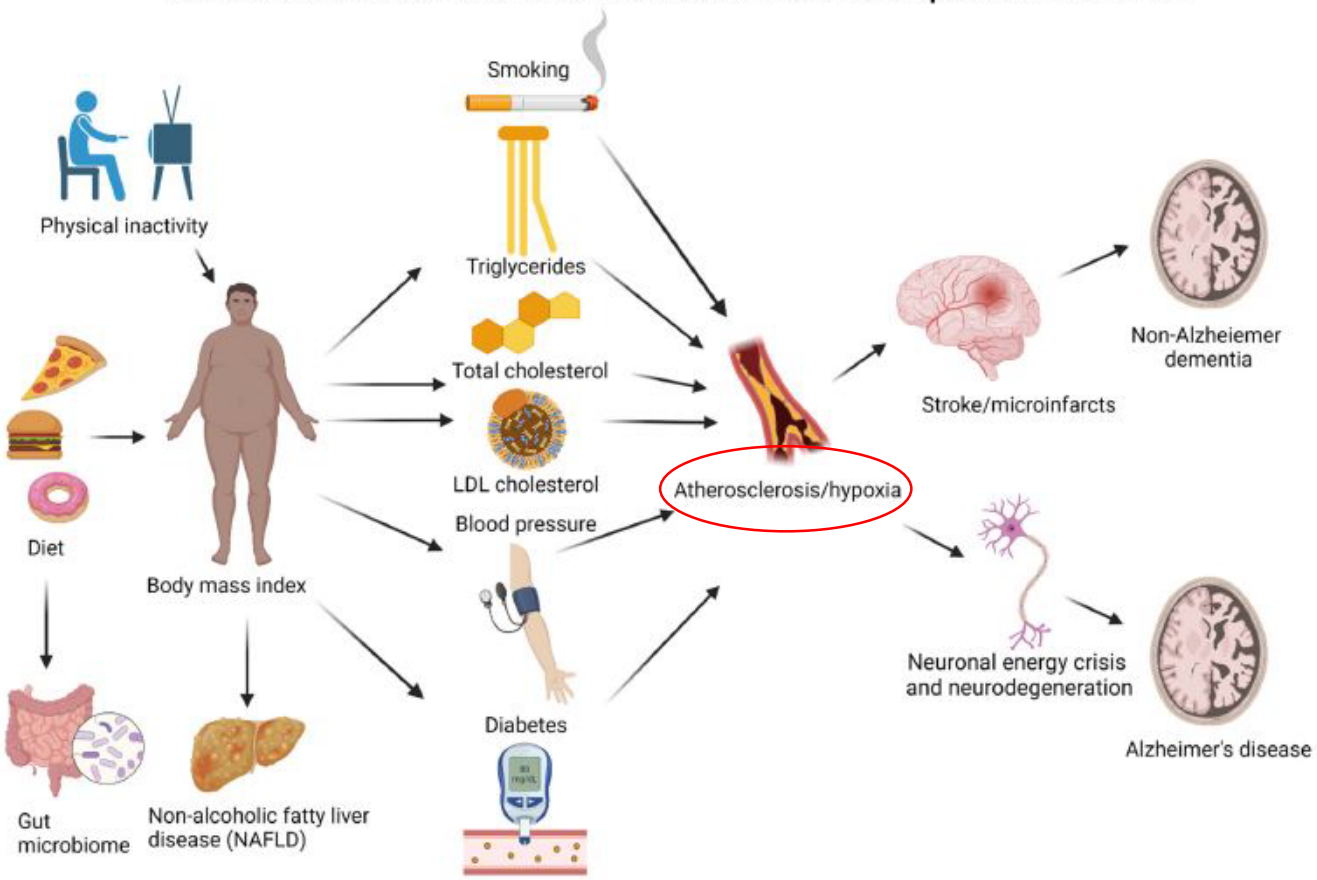

Figure 9. Proposed pathways from atherosclerotic cardiovascular risk factors for dementia to the development of disease. (1) The body mass index is influenced by the level of physical activity and diet, and the gut microbiome is influenced by diet composition. (2) The body mass index influences LDL cholesterol and triglyceride concentrations, blood pressure, and risk of diabetes and NAFLD. (3) Smoking, LDL cholesterol, triglycerides, blood pressure, and diabetes are all risk factors for developing atherosclerosis. (4) Atherosclerosis can cause long-term reduced cerebral blood flow and hypoxia if vessels are not completely blocked, leading to neuronal energy crisis, neurodegeneration, and eventually, Alzheimer's disease. Atherosclerosis can also cause acute hypoxia due to strokes, leading to vascular dementia. The association between high levels of HDL cholesterol and a high risk of dementia might be due to reverse causation caused by a low body mass index or due to high alcohol consumption. All risk factors can be influenced by genetics. Created with Biorender.com.

Nordestgaard LT et al. Shared Risk Factors between Dementia and Atherosclerotic Cardiovascular Disease. International Journal of Molecular Sciences 2022;23:9777.

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Mechanism(s) of Hypertension-Related Brain Injury

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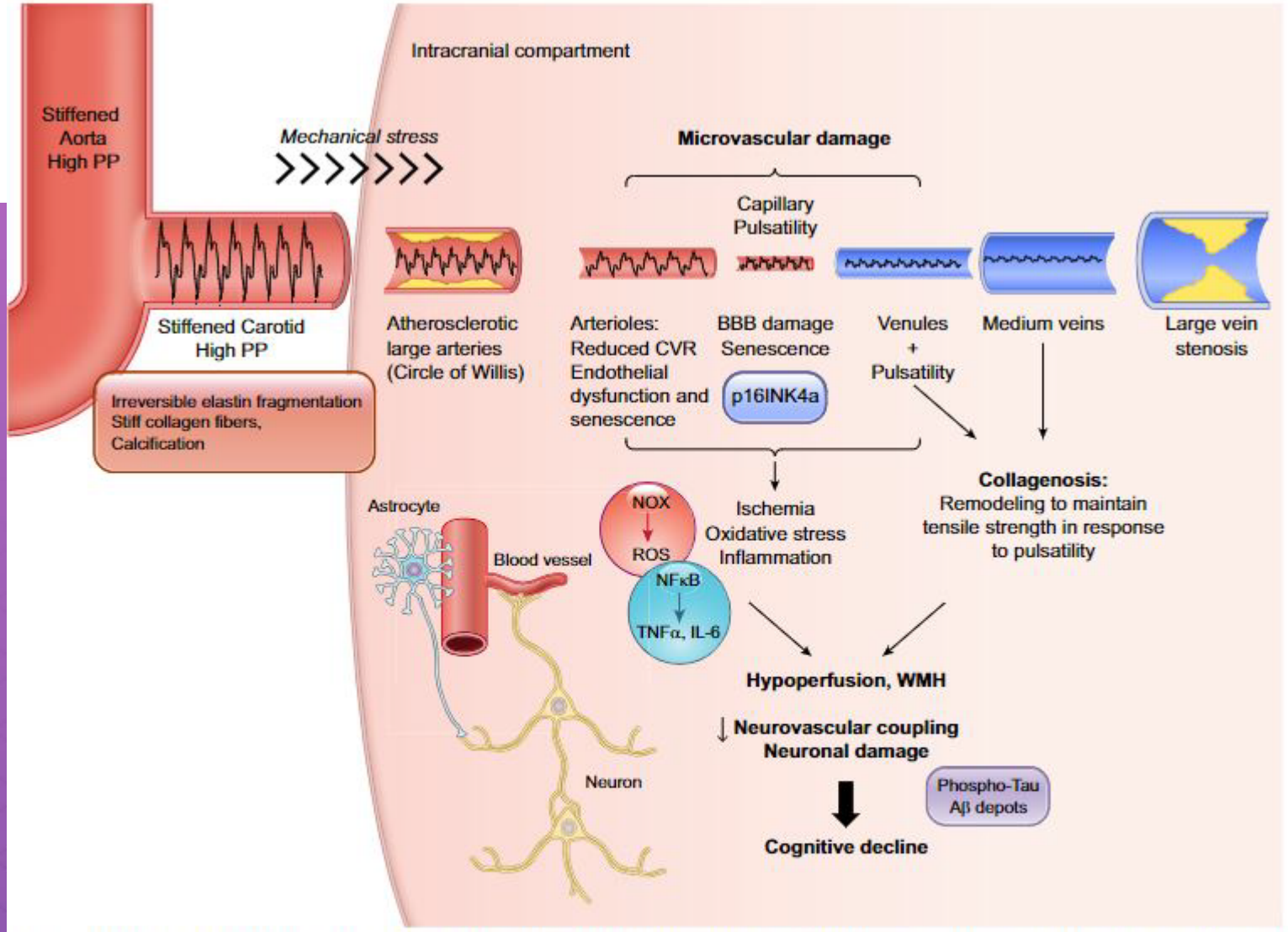

Fig. 2. Schematization of the putative cellular and molecular events linking pulse pressure penetration in the cerebral microcirculation and the development of cognitive decline. Age-associated stiffening of large elastic arteries such as the aorta and carotids is due to irreversible elastin fragmentation induced by the lifelong exposure of the vascular wall to the mechanical stress inherent to the heart beat. Stiff collagen, which replaces elastin, and calcification of the vascular wall significantly reduce arterial elasticity and augment the amplitude of the pulse pressure (PP) that penetrates into the fragile low-resistance cerebral microcirculation. Arteriolar, venular, and capillary pulsatility is associated with endothelial nitric oxide synthase dysfunction and possibly endothelial senescence (p16INK4a expression), reduced cerebrovascular reactivity (CVR), and blood-brain barrier (BBB) disruption. The latter permits the infiltration of inflammatory cells and toxic molecules, leading to inflammation (through NF-κB), oxidative stress [via NADPH oxidase (NOX) activation], and ischemia. In the venules and medium-size veins, pulsatility promotes collagenosis that contributes to cerebral hypoperfusion. Altogether, this deleterious ischemic and inflammatory environment favors parenchymal damage [including white matter hyperintensity (WMH)], neurovascular uncoupling, and neuronal damage [phospho-tau and amyloid-β (Aβ) depots], ultimately leading to cognitive decline and dementia. ROS, reactive oxygen species.

Thorin-Trescases N et al. Impact of pulse pressure on cerebrovascular events leading to age-related cognitive decline. Am J Physical Heart Circ Physiol 2018;314:H1214-H1224.

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Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

Outcomes	Treatment Group					
	Intensive		Standard			
	No. With Outcome/Person-Years	Cases per 1000 Person-Years	No. With Outcome/Person-Years	Cases per 1000 Person-Years	Hazard Ratio (95% CI)[a]	*P* Value
Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Mild cognitive impairment[b]	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
Composite of mild cognitive impairment or probable dementia	402/19 873	20.2	469/19 488	24.1	0.85 (0.74-0.97)	.01

[a] Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

[b] Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.

Taken from JAMA 2019;321(6):553-561.

Table 2. Changes in Cerebral Blood Flow by Treatment Group

Outcome	Cerebral blood flow, (95% CI), mL/100 g/min[a]						Difference in change (95% CI)	*P* value
	Intensive treatment			Standard treatment				
	Baseline	Follow-up	Change	Baseline	Follow-up	Change		
Whole brain	38.90 (36.64 to 41.17)	40.36 (37.95 to 42.77)	1.46 (0.08 to 2.83)	37.96 (35.67 to 40.26)	37.12 (34.66 to 39.58)	-0.84 (-2.30 to 0.61)	2.30 (0.30 to 4.30)	.02
Gray matter	50.76 (47.01 to 54.52)	52.91 (49.01 to 56.80)	2.14 (0.41 to 3.87)	49.40 (45.61 to 53.19)	49.06 (45.11 to 53.00)	-0.34 (-2.17 to 1.48)	2.49 (-0.03 to 5.00)	.05
White matter	19.86 (18.85 to 20.88)	20.51 (19.35 to 21.67)	0.65 (-0.32 to 1.61)	19.41 (18.36 to 20.46)	18.57 (17.36 to 19.79)	-0.83 (-1.85 to 0.18)	1.48 (0.08 to 2.88)	.04
Periventricular white matter	15.79 (14.81 to 16.78)	16.11 (15.01 to 17.21)	0.32 (-0.54 to 1.17)	15.48 (14.47 to 16.50)	14.60 (13.45 to 15.76)	-0.88 (-1.80 to 0.04)	1.20 (-0.06 to 2.45)	.06

[a] Estimates based on a linear mixed model, adjusting for age, sex, and days since randomization, with random effects for participant and magnetic resonance imaging facility. Estimates represent least-square means, with follow-up estimates computed at 1452 days (4.0 years) postrandomization, which was the median follow-up in both treatment groups. For change estimates, negative values denote decreases from baseline, while positive values indicate increases from baseline. Difference in change represents intensive treatment group minus standard treatment.

Dolui S et al. JAMA Neurol. 2022;79(4):380-389.

Brain Ischemia Likely Precedes the Onset of Alzheimer's and Vascular Dementia

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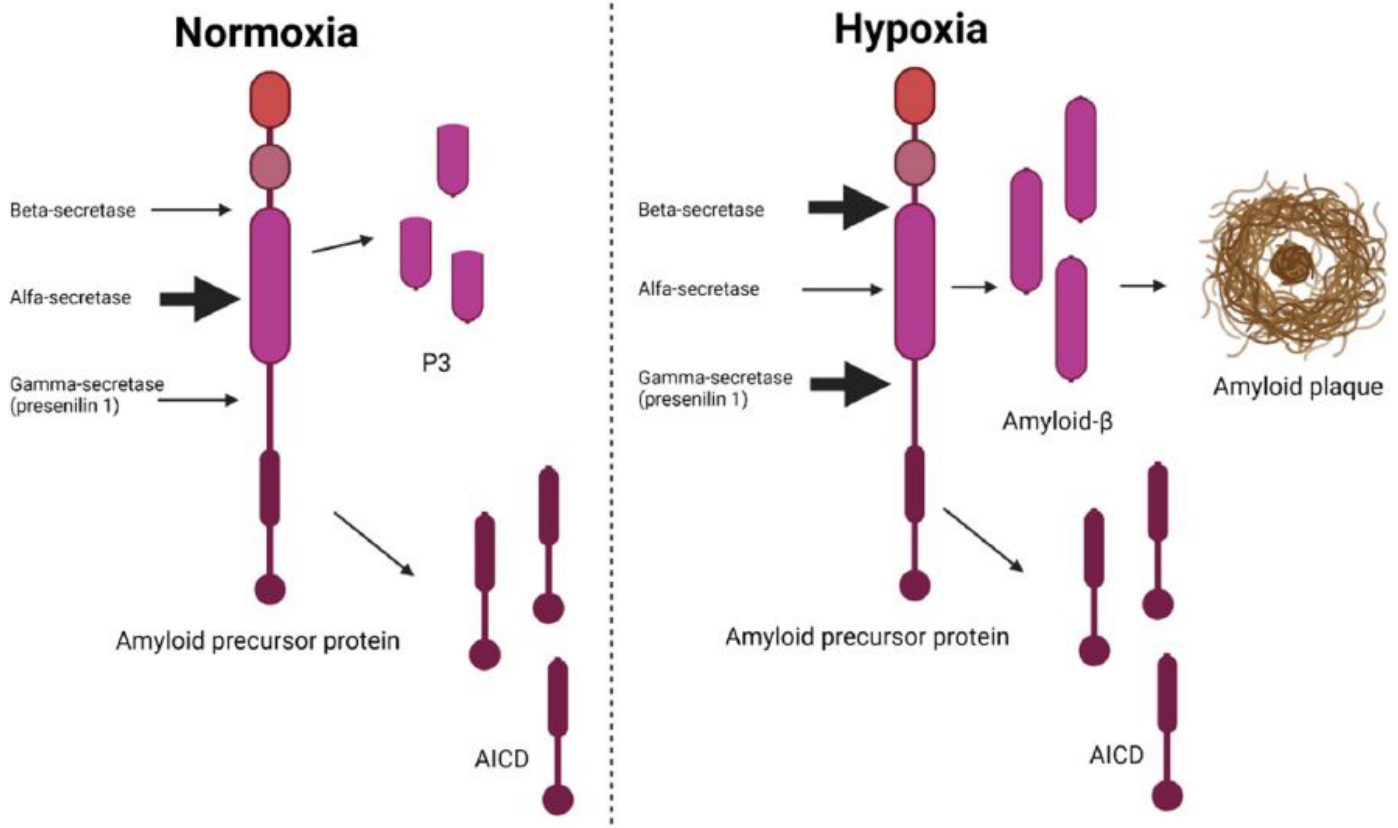

Figure 7. The impact of hypoxia/ischemia on the processing of amyloid precursor protein. During normoxia, the alfa-secretase is more active than the beta- and gamma-secretases resulting in very little production of β-amyloid. During hypoxia, the beta- and gamma-secretases are stimulated causing an excess production of β-amyloid leading to the formation of amyloid plaques—a pathological hallmark of Alzheimer's disease. AICD, amyloid precursor protein intracellular domain. Adapted from Salminen et al., J. Neurochem 2017 [23]. Created with Biorender.com.

Nordestgaard LT et al. Shared Risk Factors between Dementia and Atherosclerotic Cardiovascular Disease. International Journal of Molecular Sciences 2022;23:9777.

Summary

- Prevention, prevention and more prevention – at least by mid-life, though preferably sooner
- Brain health/dementia prevention strategies heavily overlap strategies known to prevent cardiovascular disease
- Brain ischemia appears to be a common early insult in both Alzheimer's and vascular dementias
- The population burden of dementia will likely triple by middle of this century – placing a considerable burden on unpaid caregivers, families, and the Medicare budget