Consideración del efecto de la edad en estudios observacionales examinando la relación entre factores de riesgo y demencia

Seminario del Centro Nacional de Epidemiología
18/06/2026

Marcos D. MACHADO-FRAGUA

CNIC - Cardiovascular Health and Imaging Lab

Cure Heart & Brain cnic

Co-funded by the European Union

Academic background and achievements

2010-2014

Bachelor of Science
Human Nutrition & Dietetics

2014-2015

Master of Science
Obesity

2015-2016

Master of Science
Epidemiology
1st out of 16 students

2017-2019

Ph.D
Epidemiology & Public Health
Excellence "cum laude"
International distinction
Extraordinary Ph.D award

2020-2025

Postdoctoral fellow
Epidemiology
Inserm U1153
EpiAgeing team

From 2025

MSCA Postdoctoral fellow
Epidemiology
CHI Lab

ADIPODEM
alternative measures of adiposity to define obesity and risk of dementia: a life-course approach

Co-funded by the European Union

INTRODUCTION

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Late-onset dementia

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Long preclinical phase.

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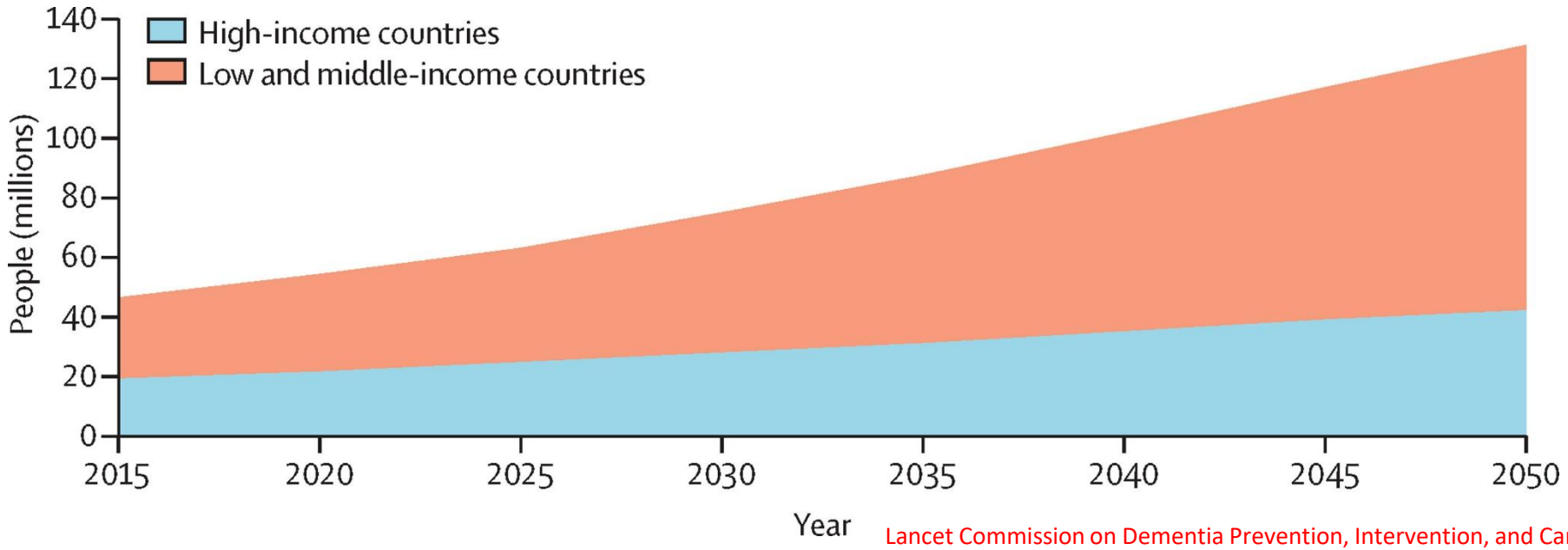
Late-onset dementia

Long preclinical phase.

No current curative solutions.

INTRODUCTION

Around 47 million people were living with dementia worldwide in 2015, affecting the individual, their family, and the wider society.

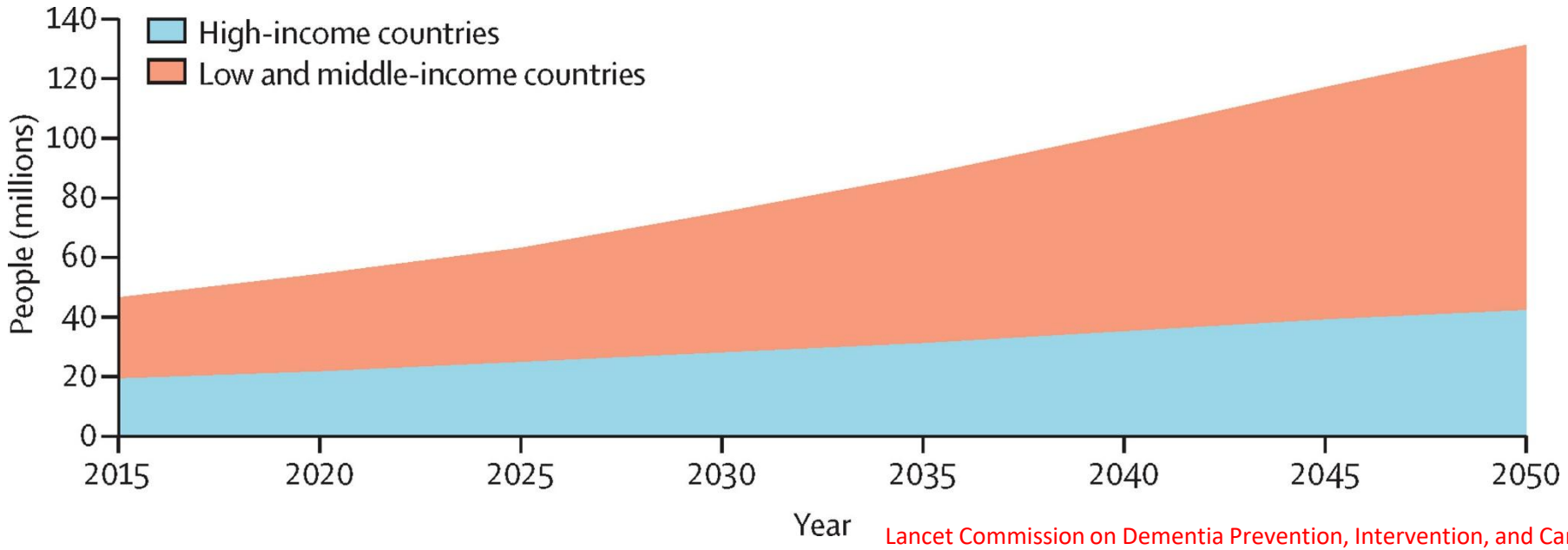


Lancet Commission on Dementia Prevention, Intervention, and Care 2017

INTRODUCTION

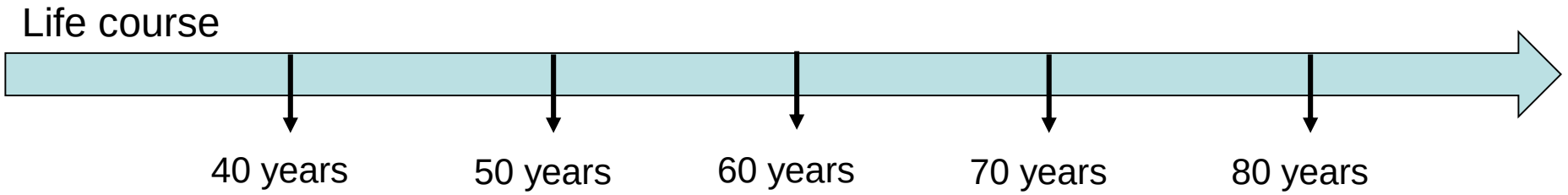
Around 47 million people were living with dementia worldwide in 2015, affecting the individual, their family, and the wider society.

As the world's population increases in age, the number of people living with dementia grows, and this figure is projected to continue to rise, especially in low and middle-income countries



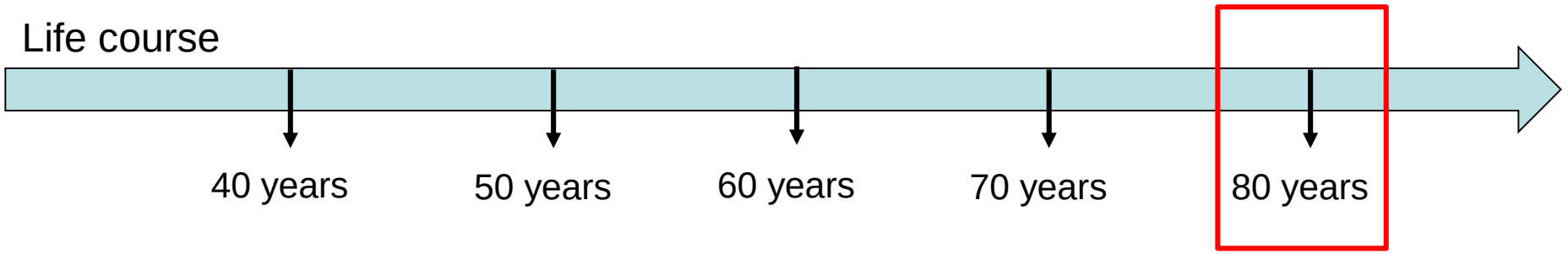
Lancet Commission on Dementia Prevention, Intervention, and Care 2017

The life-course approach to dementia



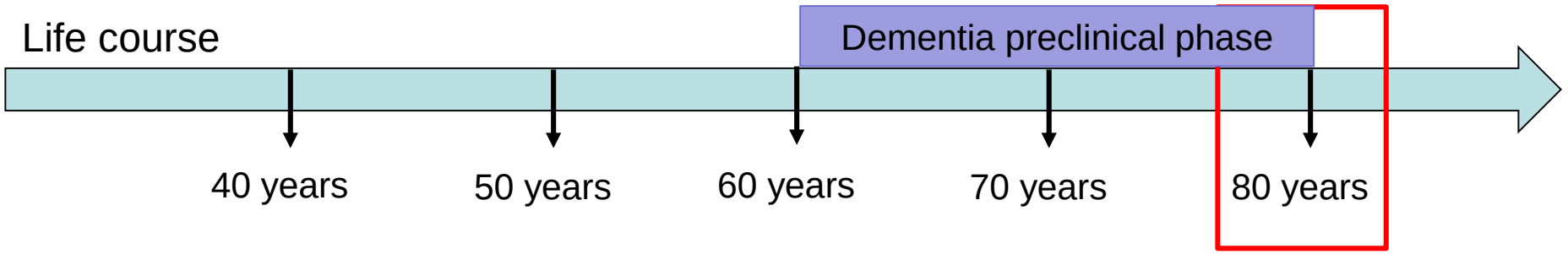
The life-course approach to dementia

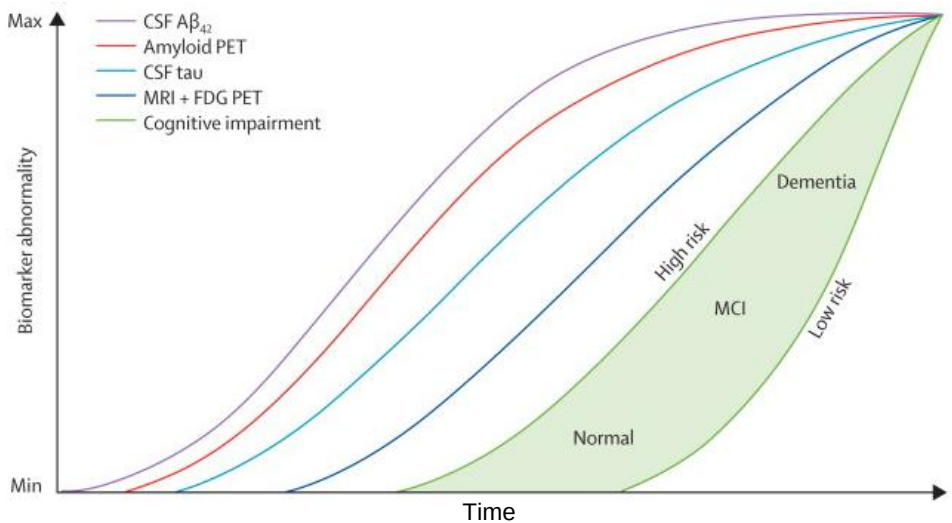
The average age at late-onset dementia diagnosis is around 80 years



The life-course approach to dementia

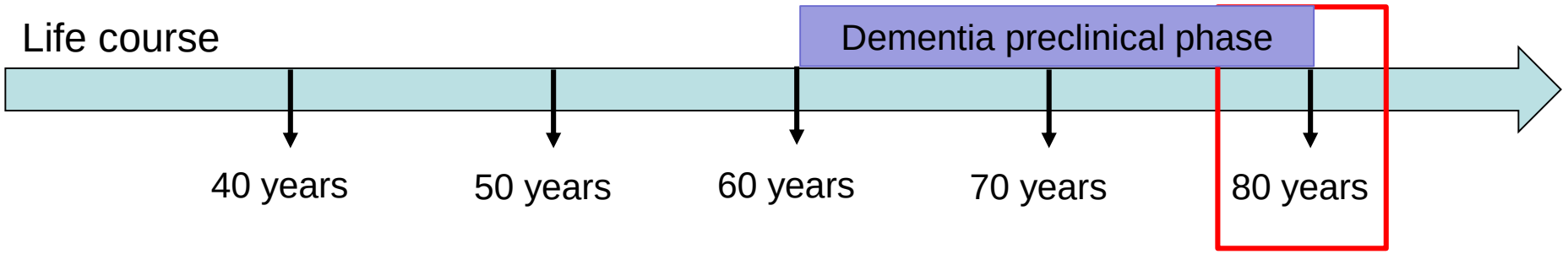
Dementia has a long preclinical phase (15 to 20 years)





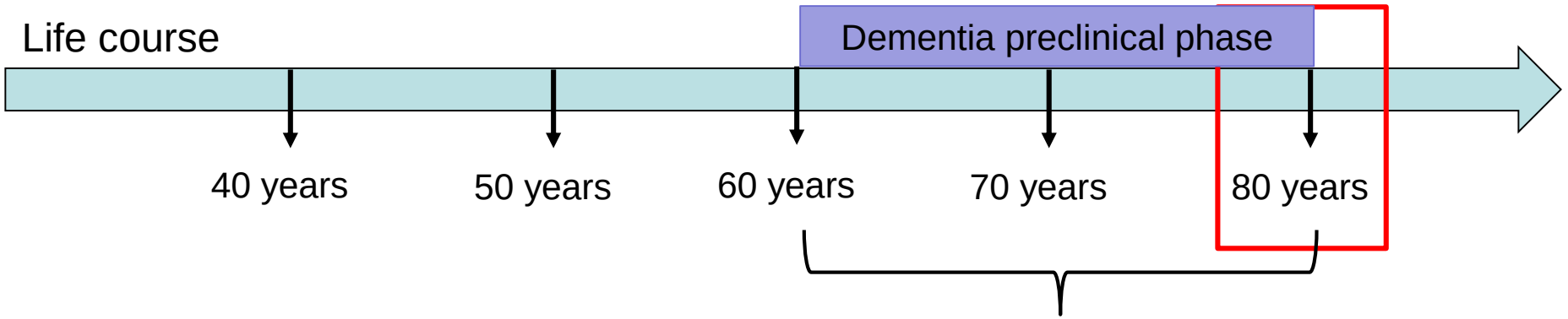
Jack Jr, CR. The Lancet Neurology, 2013.

The life-course approach to dementia



RISK FACTOR definition: should precede the onset of the outcome (dementia)

The life-course approach to dementia

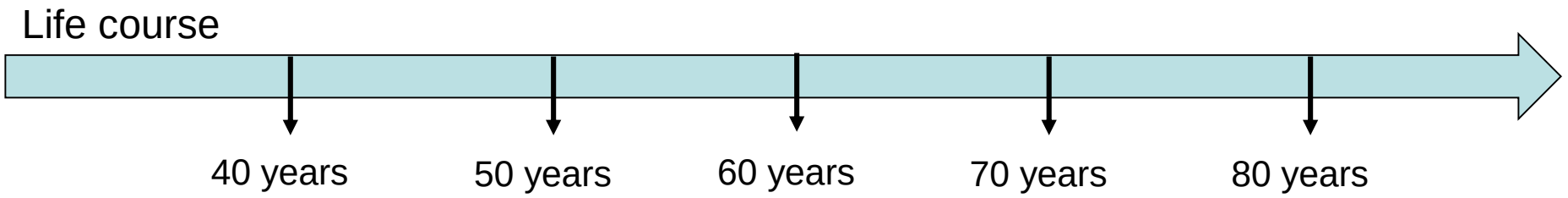


Exposures unlikely to be causal

Risk of reverse causation bias

The life-course approach to dementia

Observational studies are limited in their ability to establish causality



The life-course approach to dementia

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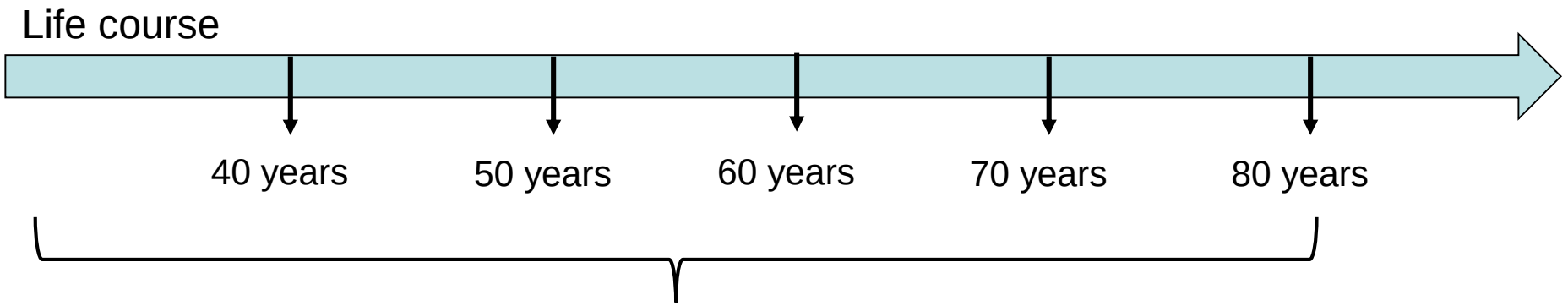
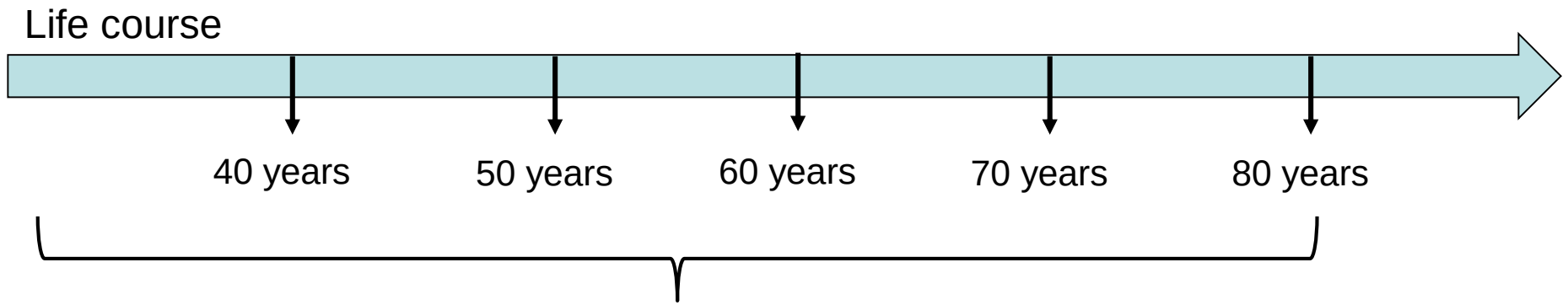


Clinical trials in such a time frame are unfeasible.

The life-course approach to dementia

Observational studies are limited in their ability to establish causality



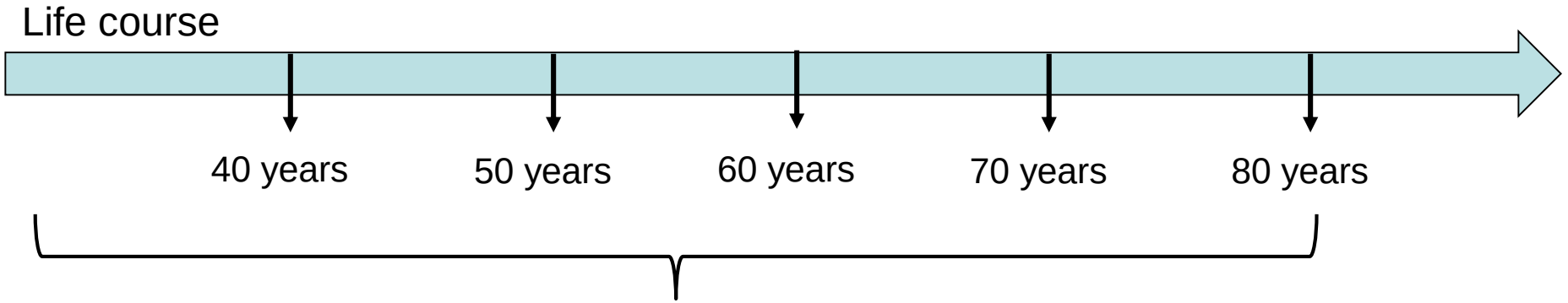
Clinical trials in such a time frame are unfeasible.

Lancet Commission on Dementia Prevention 2024

→ Most evidence comes from observational studies

The life-course approach to dementia

Observational studies are limited in their ability to establish causality



Clinical trials in such a time frame are unfeasible.

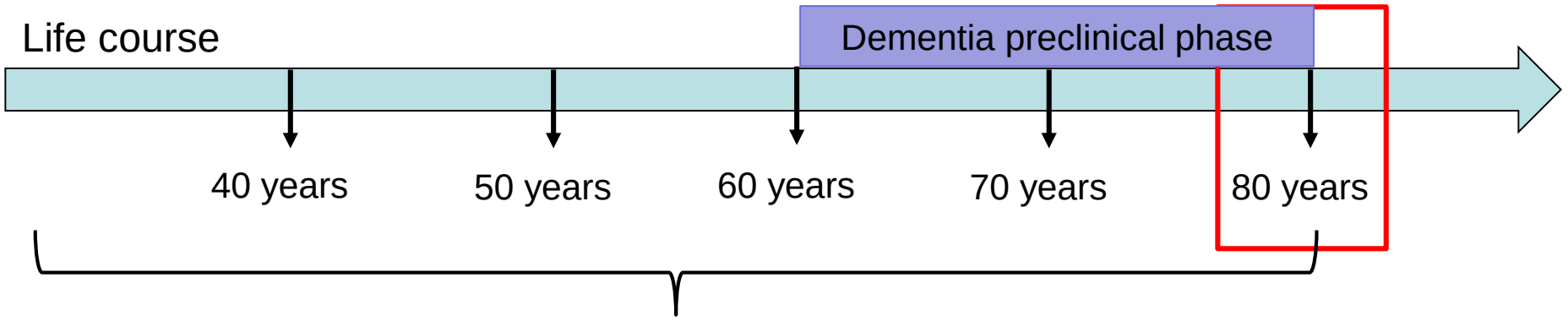
Lancet Commission on Dementia Prevention 2024

→ Most evidence comes from observational studies

Well-characterized observational studies: essential for dementia research

- Careful consideration of age at assessment of risk factors.
- Length of follow-up.
- Repeated measures on exposure.

The life-course approach to dementia

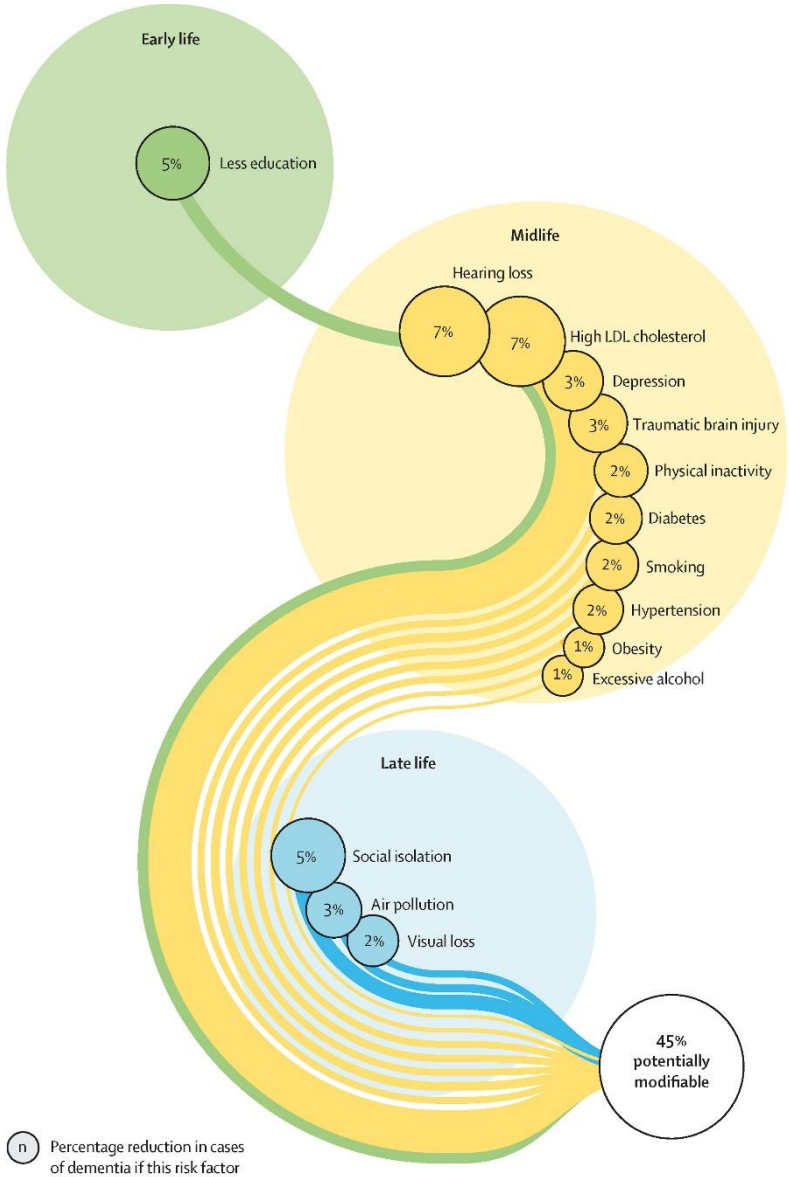


The life-course approach considers **timing** and **duration** of exposure

- Longitudinal studies
- Repeated measures over the life course

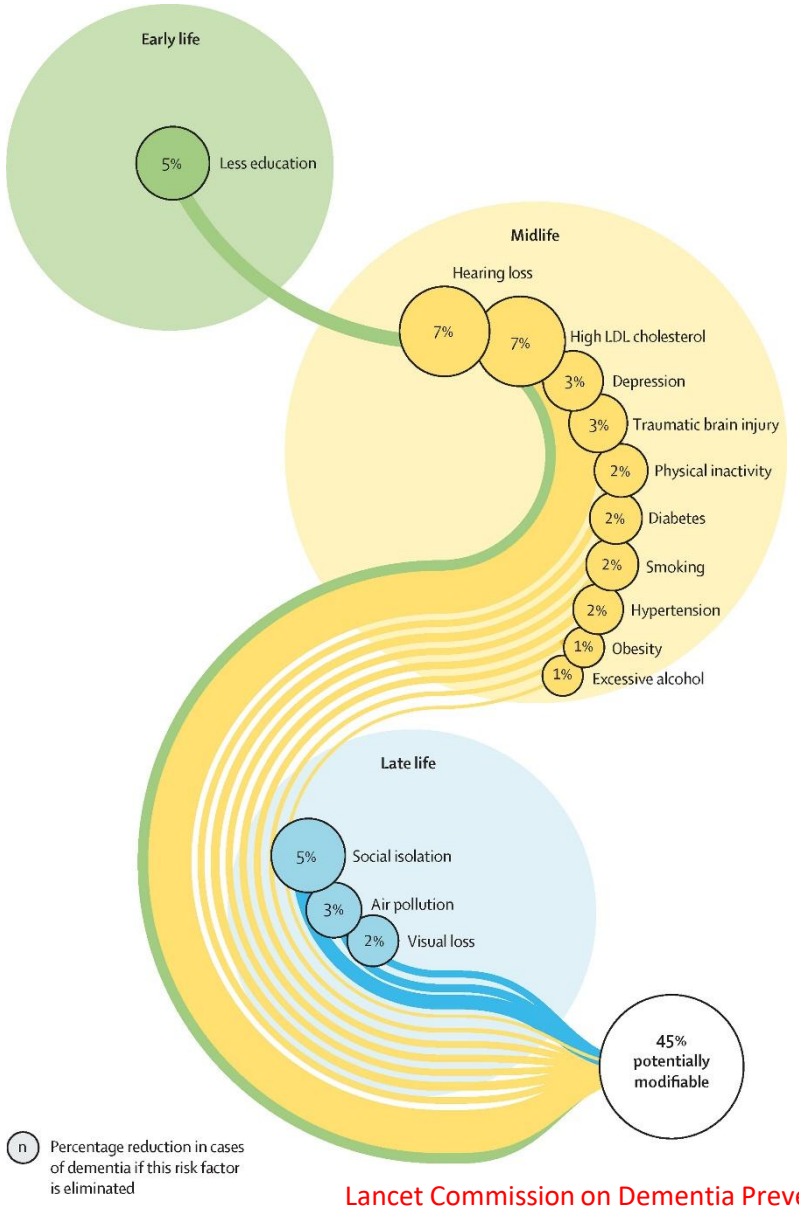
} Appropriate statistical methods

DEMENTIA RISK FACTORS



Lancet Commission on Dementia Prevention, Intervention, and Care 2024

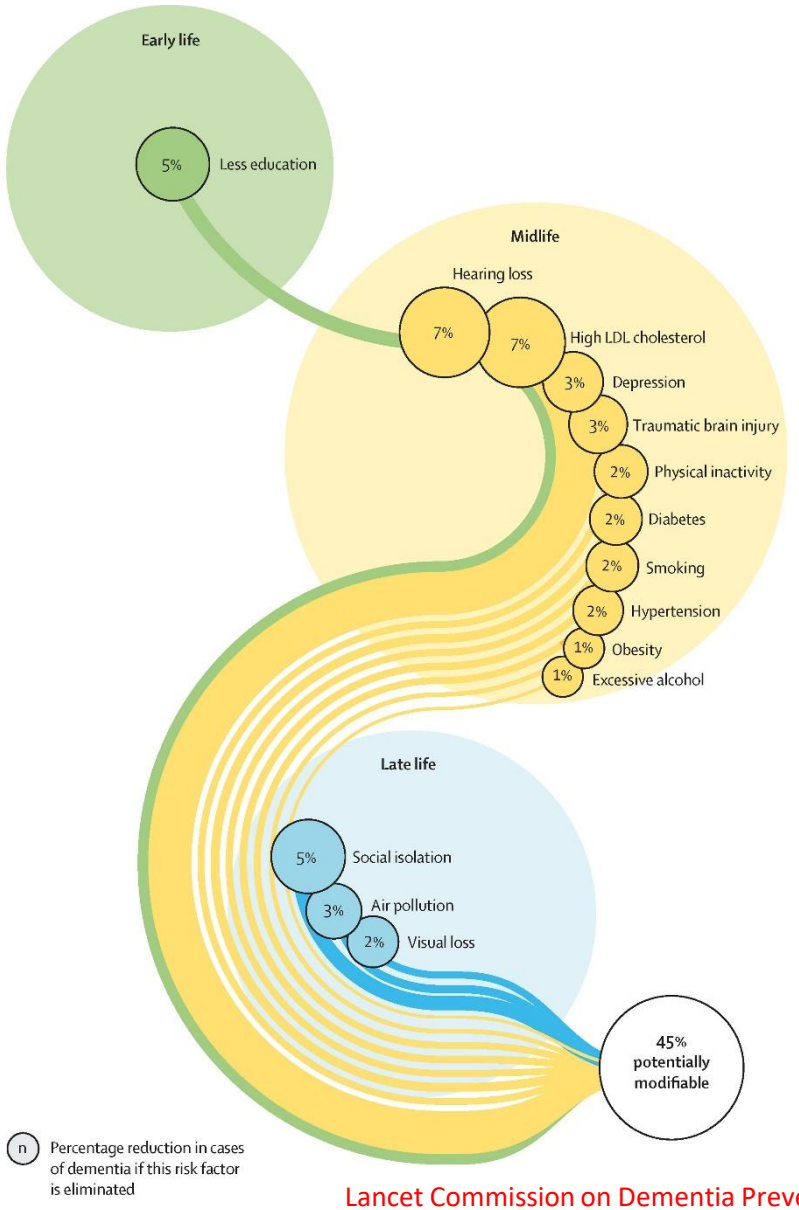
DEMENTIA RISK FACTORS



Age is the strongest (non-modifiable) risk factor for dementia

Lancet Commission on Dementia Prevention, Intervention, and Care 2024

DEMENTIA RISK FACTORS

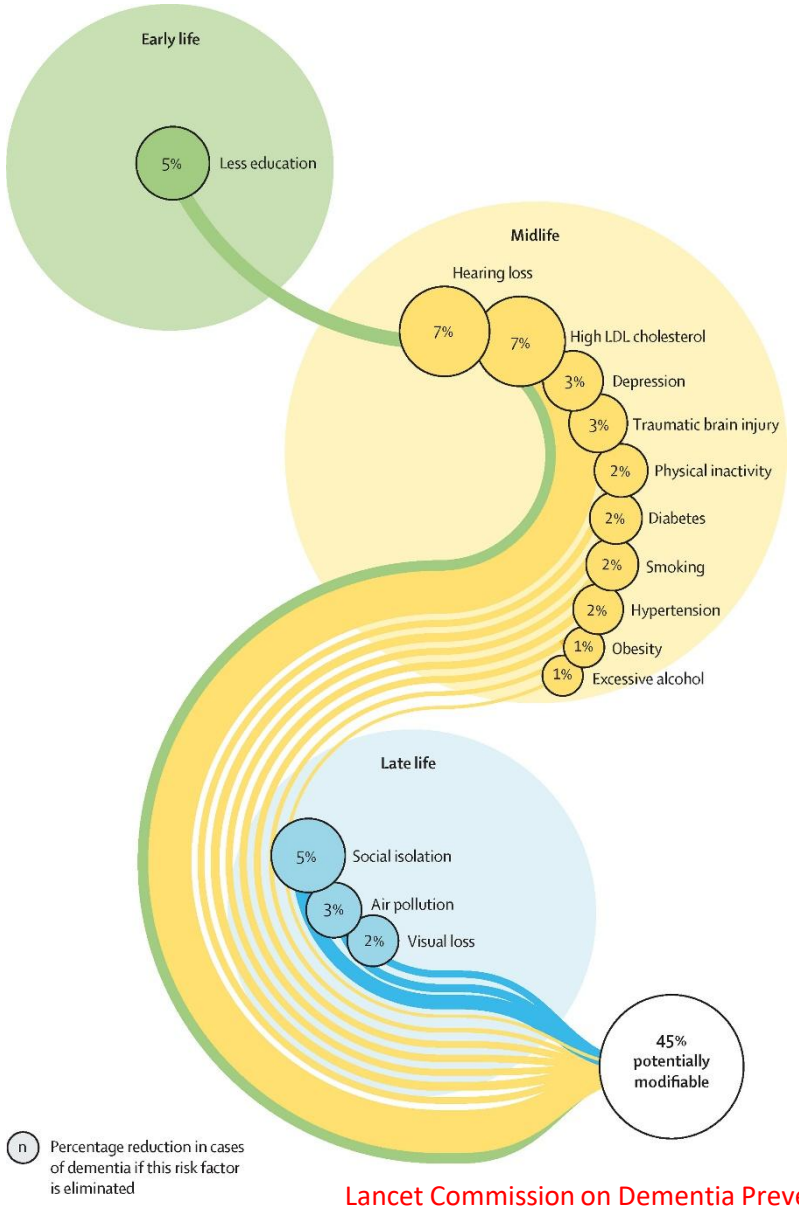


Age is the strongest (non-modifiable) risk factor for dementia

The risk of dementia doubles every five years after age 65

Lancet Commission on Dementia Prevention, Intervention, and Care 2024

DEMENTIA RISK FACTORS



Age is the strongest (non-modifiable) risk factor for dementia

The risk of dementia doubles every five years after age 65

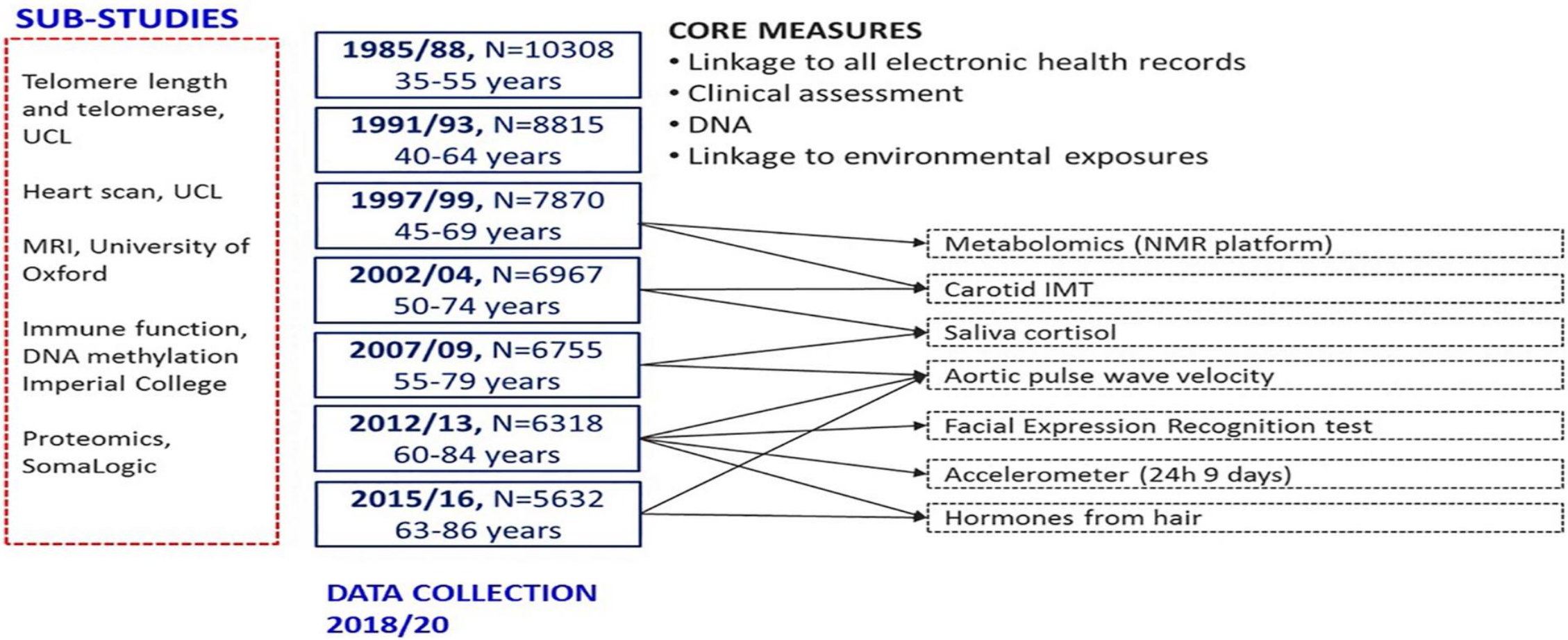
Observational studies must explicitly account for age to disentangle its impact from the actual effect of the risk factor on dementia

Lancet Commission on Dementia Prevention, Intervention, and Care 2024

Major studies on ageing start data collection at age 65

Study	Country	Start	N	Age
Iceland Birth Cohort Study	Iceland	1957	**3704**	61-64
Gothenburg Study	Sweden	1971	**1148**	70
PAQUID	France	1987	**3777**	65+
Kungsholmen Project	Sweden	1987	**1810**	75+
Rotterdam	Netherlands	1990	**7983**	55+
Cognitive Function & Ageing Study (CFAS)	UK	1991	**13004**	65+
Etude du Vieillissement Artériel (EVA)	France	1991	**1389**	60-70
Italian Longitudinal Study on Aging (ILSA)	Italy	1992	**5632**	65-84
Longitudinal Aging Study Amsterdam (LASA)	Netherlands	1992	**3017**	55-85
Maastricht Aging Study (MAAS)	Netherlands	1992	**2043**	24-81
Longitudinal Study of Aging Danish Twins	Denmark	1995	**2401**	75+
The German Aging Survey	Germany	1996	**5000**	40-85
In Chianti Study	Italy	1998	**1453**	20-102
3-City Study	France	1999	**9294**	65+
The Swedish National study of Aging & Care	Sweden	2001	**3089**	60+
Newcastle 85+ Study	UK	2006	**1042**	85+
UK Biobank	**UK**	**2006/2010**	**500,000**	**40-69**
CONSTANCES	**France**	**2012/2018**	**200,000**	**45-69**
NAKO	**Germany**	**2014/2019**	**200,000**	**20-69**

The Whitehall study: unique data to study ageing outcomes



BLOOD METABOLITES AND DEMENTIA

Machado-Fragua *et al. BMC Medicine* (2022) 20:334
https://doi.org/10.1186/s12916-022-02519-6

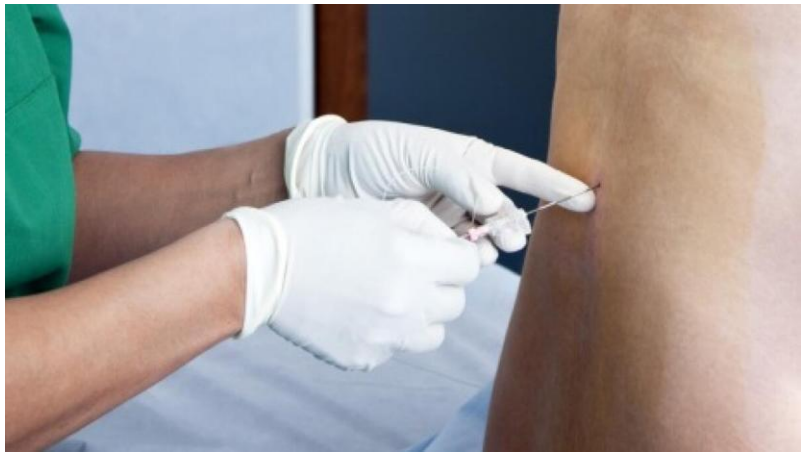
BMC Medicine

RESEARCH ARTICLE Open Access

Circulating serum metabolites as predictors of dementia: a machine learning approach in a 21-year follow-up of the Whitehall II cohort study

Marcos D. Machado-Fragua[1*], Benjamin Landré[1], Mathilde Chen[1], Aurore Fayosse[1], Aline Dugravot[1], Mika Kivimaki[2], Séverine Sabia[1,2] and Archana Singh-Manoux[1,2]

BLOOD METABOLITES AND DEMENTIA



CSF BIOMARKERS

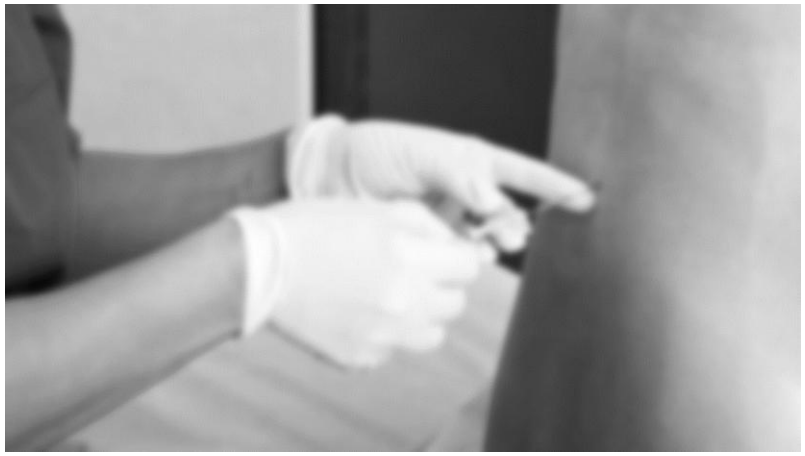
Invasive Spinal Tap

Diagnosis of AD

- CSF Aβ (amyloid beta)
- CSF P-Tau (phosphorylated tau)
- CSF NFL (neurofilament light chain)

BLOOD METABOLITES AND DEMENTIA

From CSF to blood-based biomarkers



Blood-based biomarkers

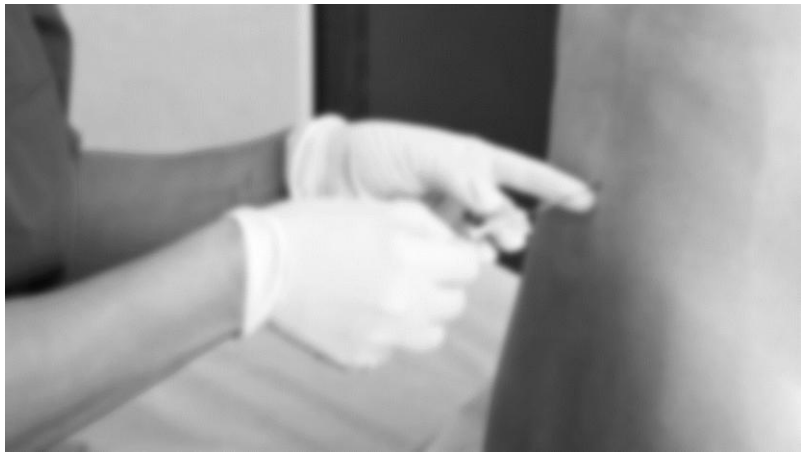
Venipuncture: less invasive

Healthcare and research settings

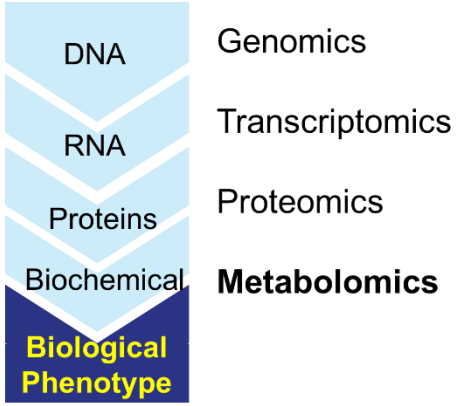
Are blood-based biomarkers useful in identifying prevention targets?

BLOOD METABOLITES AND DEMENTIA

From CSF to blood-based biomarkers



Metabolites in blood assessed late in life: not meaningful for prevention

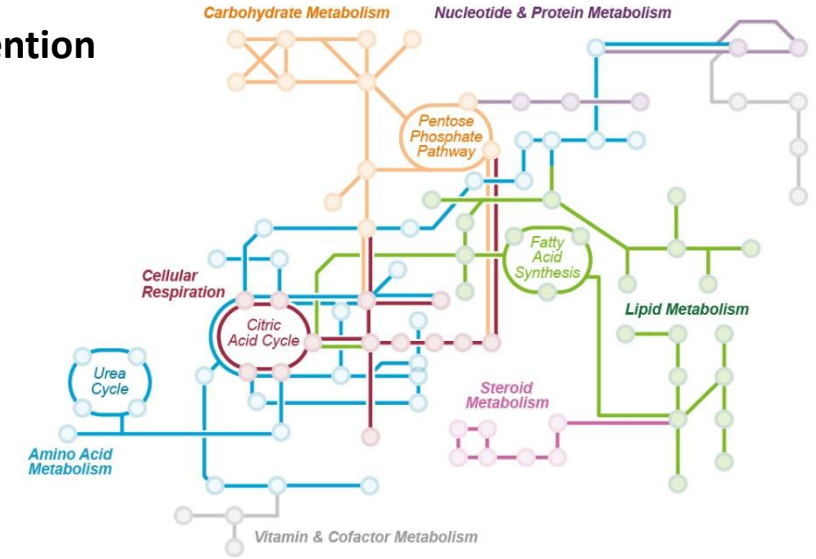


Genomics

Transcriptomics

Proteomics

Metabolomics



BLOOD METABOLITES AND DEMENTIA

Limitations of previous studies on the association between metabolite panels and the risk of dementia

1. Correction for multiple testing

Bonferroni correction, FDR, PCA

- Too conservative
- Metabolites with a very large effect

BLOOD METABOLITES AND DEMENTIA

Limitations of previous studies on the association between metabolite panels and the risk of dementia

2. Age included in the predictive model

- Prediction due to age
- Prediction due to the biomarkers

BLOOD METABOLITES AND DEMENTIA

Limitations of previous studies on the association between metabolite panels and the risk of dementia

RANDOM PARTITIONING OF THE DATASET TO GENERATE CROSS-VALIDATION FOLDS

Krstajic *et al. Journal of Cheminformatics* 2014, **6**:10
http://www.jcheminf.com/content/6/1/10

Journal of Cheminformatics

METHODOLOGY Open Access

Cross-validation pitfalls when selecting and assessing regression and classification models

Damjan Krstajic[1,2,3*], Ljubomir J Buturovic[3], David E Leahy[4] and Simon Thomas[5]

RESEARCH ARTICLE
Metabolomics

Molecular Nutrition & Food Research
www.mnf-journal.com

Diet-Related Metabolites Associated with Cognitive Decline Revealed by Untargeted Metabolomics in a Prospective Cohort

Dorrain Yanwen Low, Sophie Lefèvre-Arbogast, Raúl González-Domínguez, Mireia Urpi-Sarda, Pierre Micheau, Melanie Petera, Delphine Centeno, Stephanie Durand, Estelle Pujos-Guillot, Aniko Korosi, Paul J Lucassen, Ludwig Aigner, Cécile Proust-Lima, Boris P Hejblum, Catherine Helmer, Cristina Andres-Lacueva, Sandrine Thuret, Cécilia Samieri,* and Claudine Manach*

ELSEVIER

CrossMark

Alzheimer's & Dementia 12 (2016) 815-822

Alzheimer's & Dementia

Featured Article

Blood metabolite markers of preclinical Alzheimer's disease in two longitudinally followed cohorts of older individuals

Ramon Casanova[a], Sudhir Varma[b], Brittany Simpson[c,d], Min Kim[e], Yang An[f], Santiago Saldana[a], Carlos Riveros[g], Pablo Moscato[g], Michael Griswold[h], Denise Sonntag[i], Judith Wahrheit[i], Kristaps Klavins[i], Palmi V. Jonsson[j], Gudny Eiriksdottir[k], Thor Aspelund[j,k], Lenore J. Launer[l], Vilmundur Gudnason[j,k], Cristina Legido Quigley[e], Madhav Thambisetty[c,*]

BLOOD METABOLITES AND DEMENTIA

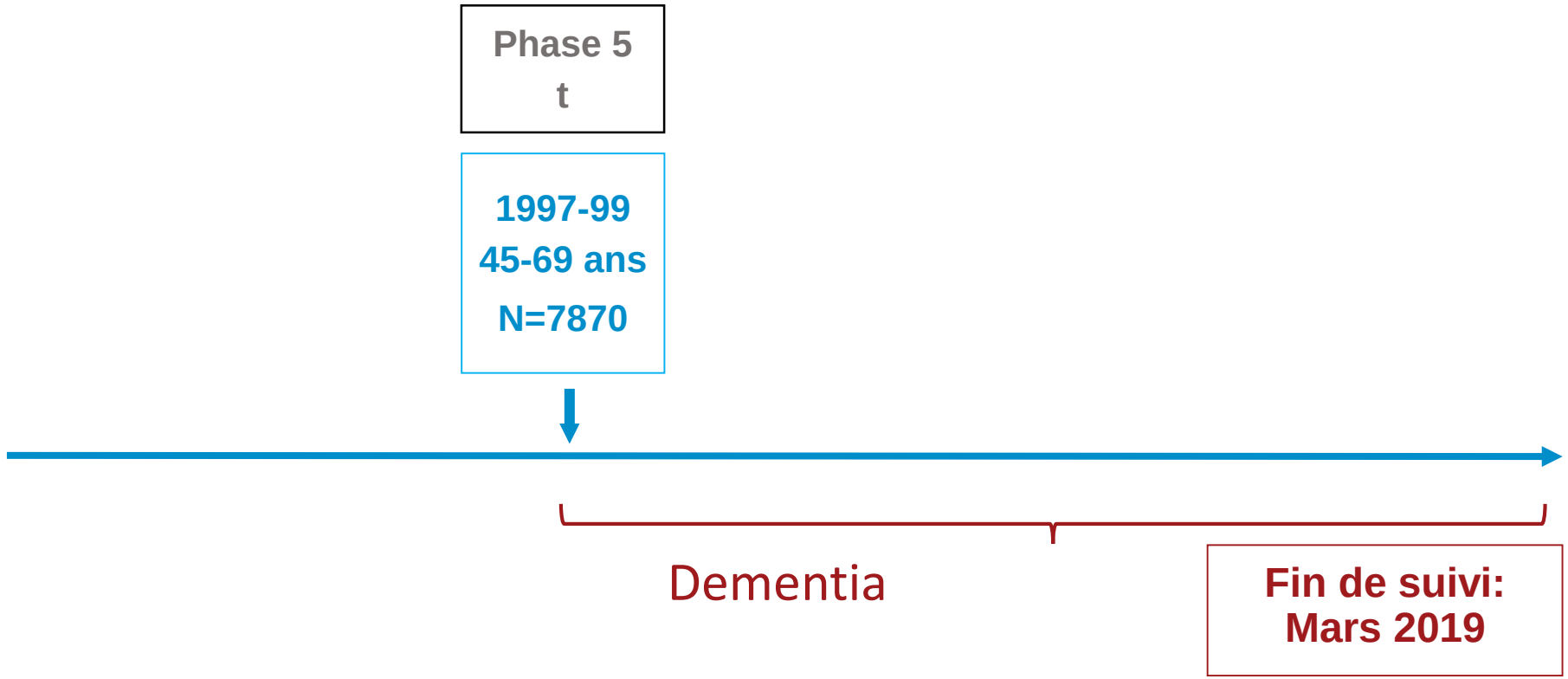
AIM

Our aim was to identify metabolites predicting incident dementia independently of age over 21-year follow-up, using machine learning for survival analysis, namely elastic net penalized Cox regression.

BLOOD METABOLITES AND DEMENTIA

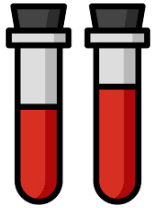
STUDY DESIGN

La cohorte Whitehall II



BLOOD METABOLITES AND DEMENTIA

Metabolite panel (1997-1999)



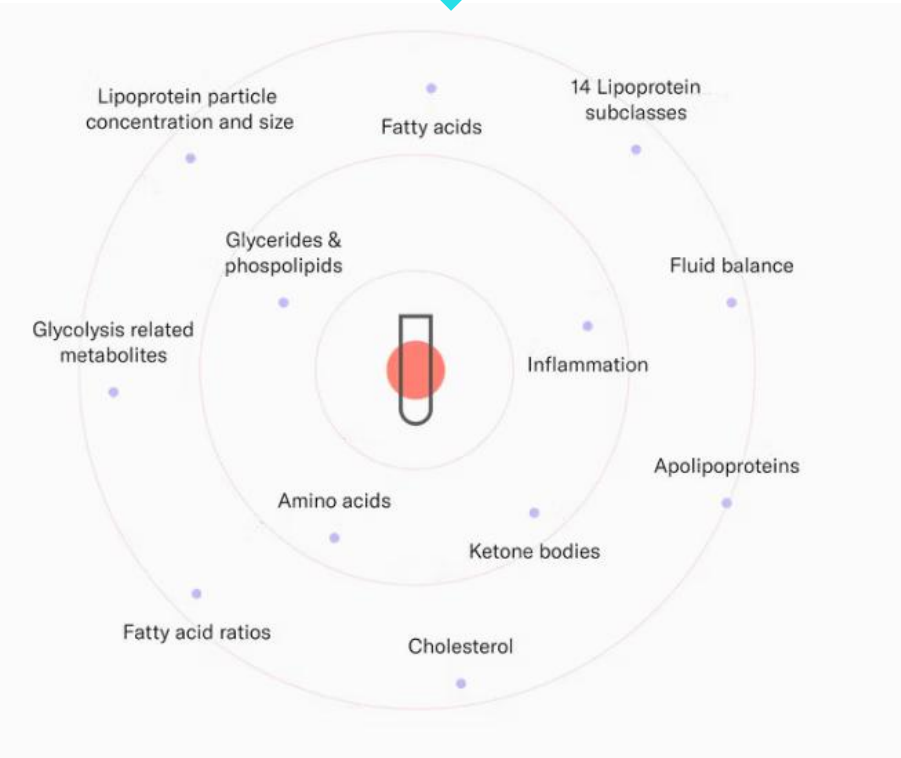
Fasting serum (1997-1999)

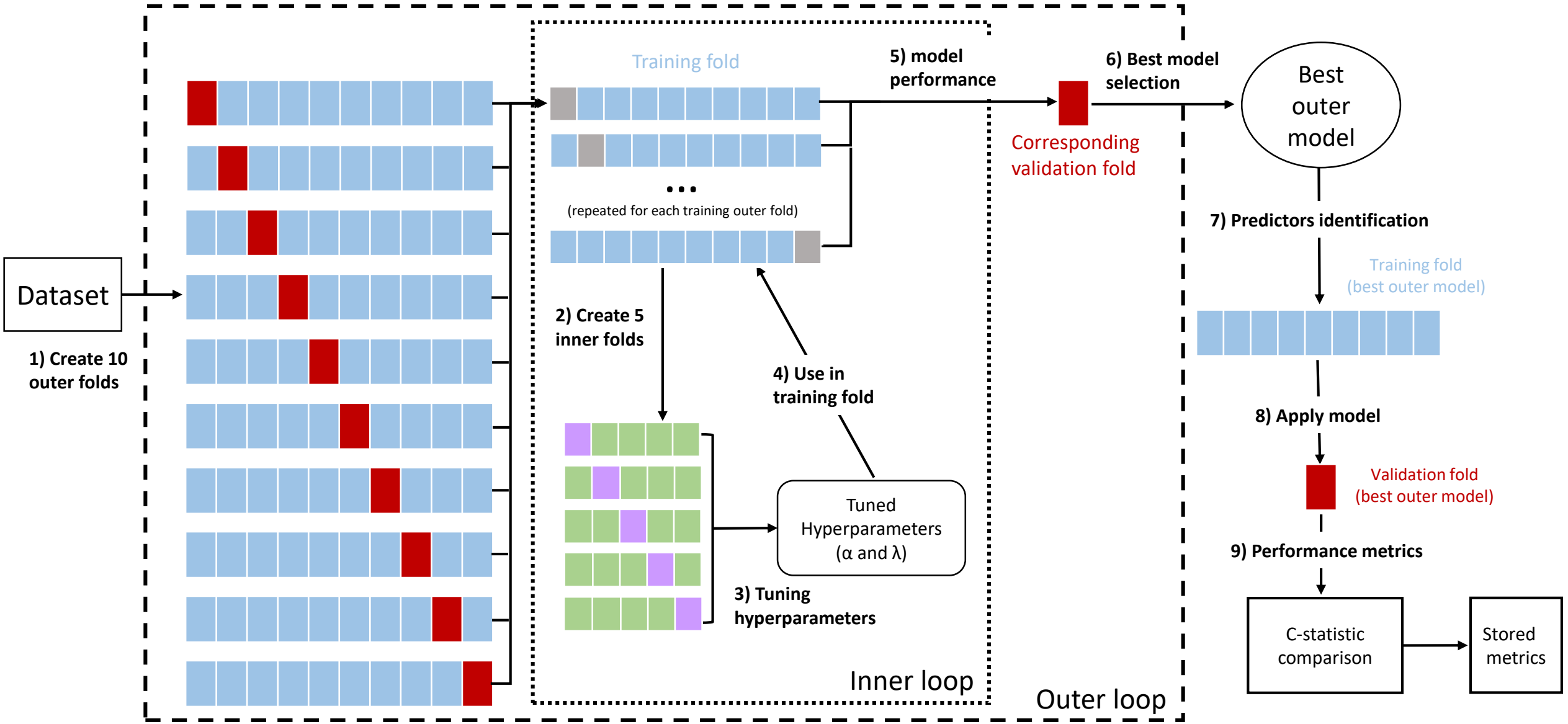
233 metabolites

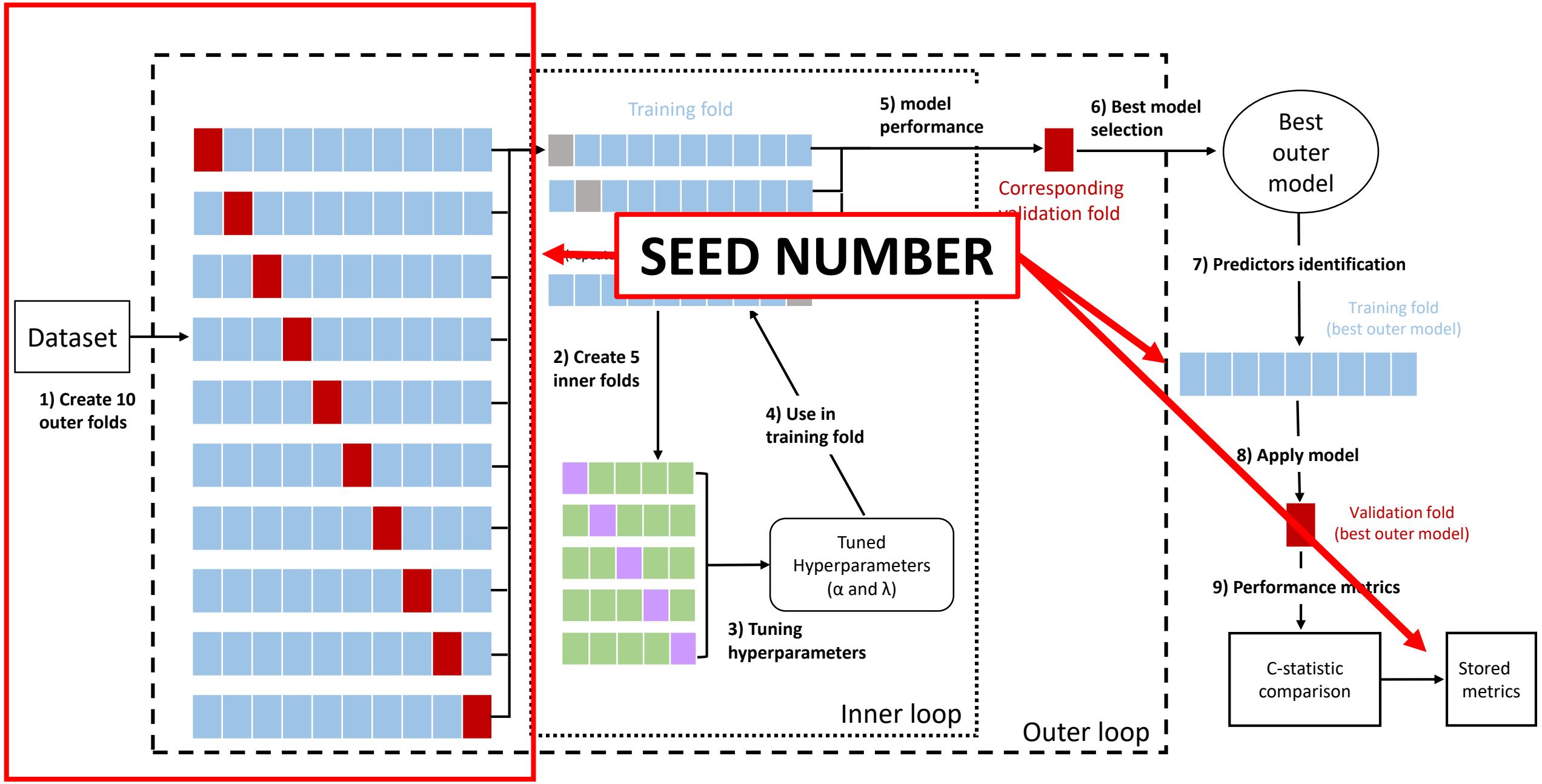
Consortium of Metabolomics Studies (2014)

NMR metabolomics

Nightingale platform




Dataset
1) Create 10 outer folds
Training fold
5) model performance
6) Best model selection
Best outer model
Corresponding validation fold
(repeated for each training outer fold)
2) Create 5 inner folds
4) Use in training fold
Tuned Hyperparameters (α and λ)
3) Tuning hyperparameters
Inner loop
Outer loop
7) Predictors identification
Training fold (best outer model)
8) Apply model
Validation fold (best outer model)
9) Performance metrics
C-statistic comparison
Stored metrics


Dataset
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Training fold
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6) Best model selection
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SEED NUMBER
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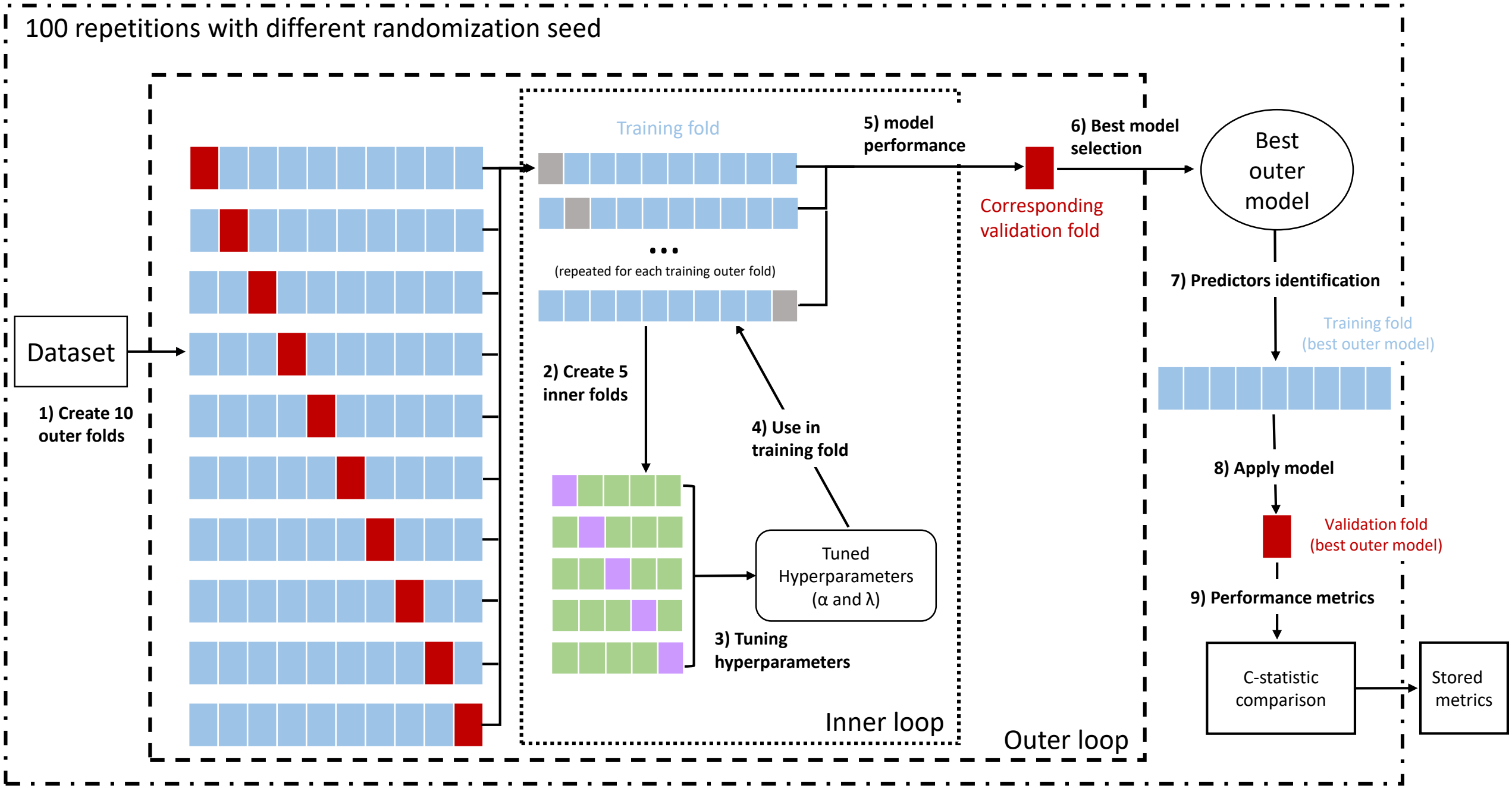
Inner loop
Outer loop


100 repetitions with different randomization seed
Dataset
1) Create 10 outer folds
Training fold
(repeated for each training outer fold)
2) Create 5 inner folds
3) Tuning hyperparameters
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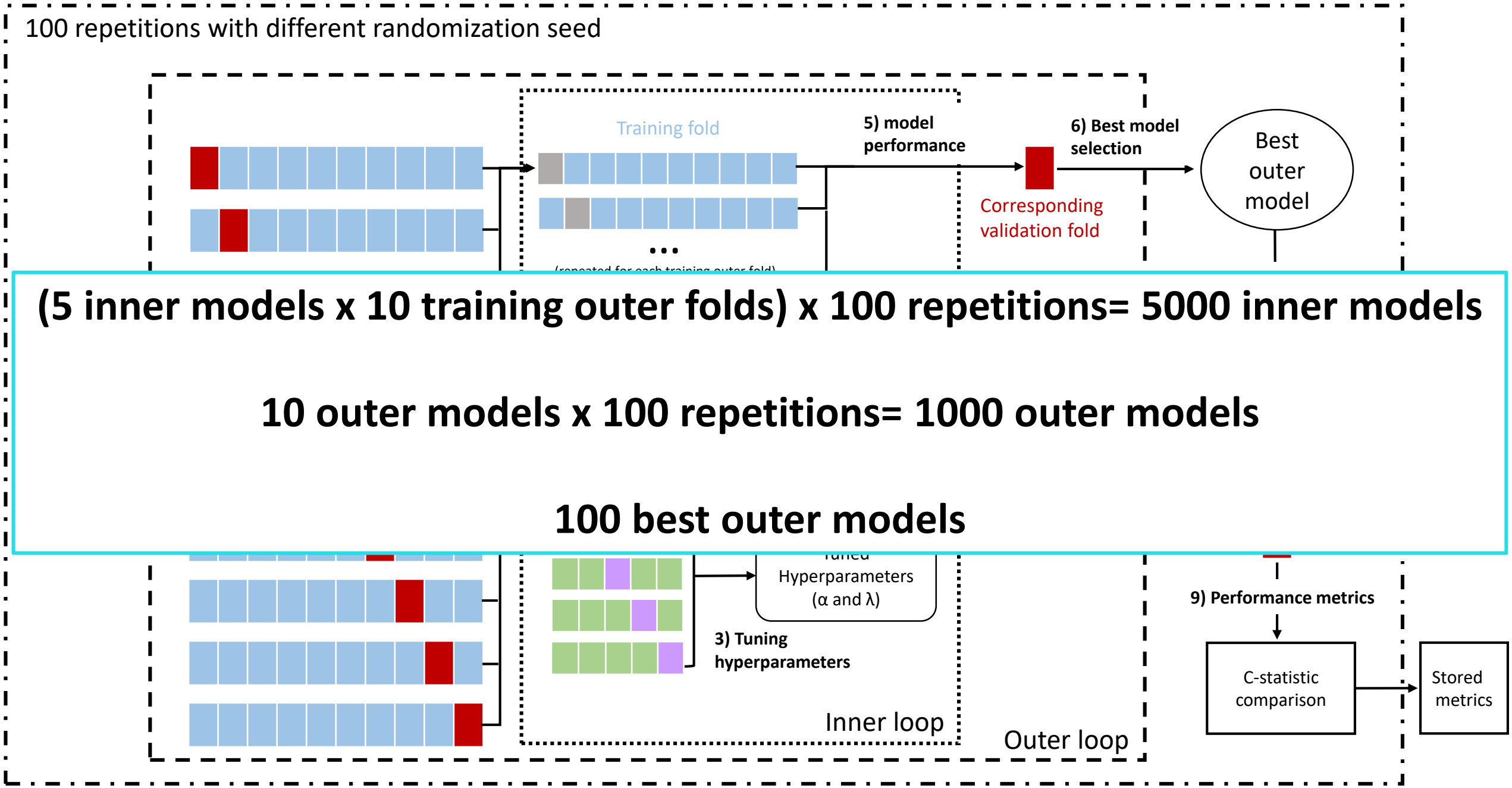
100 repetitions with different randomization seed
Training fold
5) model performance
6) Best model selection
Best outer model
Corresponding validation fold
(5 inner models x 10 training outer folds) x 100 repetitions= 5000 inner models
10 outer models x 100 repetitions= 1000 outer models
100 best outer models
Hyperparameters (α and λ)
3) Tuning hyperparameters
Inner loop
Outer loop
9) Performance metrics
C-statistic comparison
Stored metrics

BLOOD METABOLITES AND DEMENTIA

Models retained: p-value for difference in C-statistic <0.05 (compared to an age-only model)

6 risk scores

1. Age
2. Age + Metabolites present in 100%
3. Age + Metabolites present in ≥90%
4. Age + Metabolites present in ≥60%
5. Age + Metabolites present in ≥50%
6. Age + Metabolites selected at least once

Standardization
(Z-scores)

BLOOD METABOLITES AND DEMENTIA

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→ Standardization (Z-scores)

Analyses

1. Association 1SD increment in risk score with incident dementia: Cox regression
2. Predictive accuracy: R^2, AIC, sensitivity, specificity, C-statistic

BLOOD METABOLITES AND DEMENTIA

Results: Cox regression with Bonferroni correction

5 metabolites associated with dementia at $p<0.05$

1. Total cholesterol to total lipids ratio in chrylomicrons and extremely large VLDL, HR (95% CI): 0.84 (0.73-0.96)
2. Free colesterol to total lipids ratio in chrylomicrons and extremely large VLDL, HR (95% CI): 0.86 (0.74-0.99)
3. Triglycerides to total lipids ratio in chrylomicrons and extremely large VLDL, HR (95% CI): 1.17 (1.04-1.33)
4. Phospholipids to total lipids ratio in médium HDL, HR (95% CI): 1.15 (1.03-1.29)
5. Glucose, HR (95% CI): 1.24 (1.13-1.36)

BLOOD METABOLITES AND DEMENTIA

Results: Cox regression with Bonferroni correction

5 metabolites associated with dementia at $p<0.05$

1. Total cholesterol to total lipids ratio in chrylomicrons and extremely large VLDL, HR (95% CI): 0.84 (0.73-0.96)
2. Free colesterol to total lipids ratio in chrylomicrons and extremely large VLDL, HR (95% CI): 0.86 (0.74-0.99)
3. Triglycerides to total lipids ratio in chrylomicrons and extremely large VLDL, HR (95% CI): 1.17 (1.04-1.33)
4. Phospholipids to total lipids ratio in médium HDL, HR (95% CI): 1.15 (1.03-1.29)
5. Glucose, HR (95% CI): 1.24 (1.13-1.36)

Glucose was the only metabolite associated with dementia after Bonferroni correction:

p for glucose=0.00001

BLOOD METABOLITES AND DEMENTIA

Results: Selected models from the machine learning algorithm

Table 2 Elastic net penalized Cox regression with repeated nested cross-validation: models (out of 100 repetitions) that improved prediction accuracy for incident dementia compared to an age-only model

Repetition number	α*	λ*	c-statistic of the best model†	c-statistic age-only model‡	*p*-value§	Number of predictors in the selected model¶
2	0.9	0.00617437	0.760	0.749	0.01	4
4	1	0.00617437	0.724	0.715	0.007	4
10	1	0.00677636	0.747	0.741	0.04	4
16	1	0.00512607	0.775	0.765	0.02	7
18	0.7	0.01299645	0.742	0.738	0.007	3
22	1	0.00816215	0.703	0.696	0.02	2
23	1	0.00425575	0.779	0.763	0.001	8
30	1	0.00617437	0.746	0.736	0.009	5
38	1	0.00617437	0.718	0.711	0.04	4
50	1	0.00562585	0.745	0.734	0.01	5
57	1	0.00467068	0.747	0.731	0.0006	9
67	0.5	0.00983134	0.755	0.743	0.004	6
74	0.8	0.00816215	0.735	0.726	0.02	3
91	1	0.00677636	0.724	0.714	0.008	3
94	0.7	0.00677636	0.762	0.751	0.03	9
96	0.5	0.00743705	0.735	0.722	0.04	12

* These are hyperparameters, allowing selection of the model with the lowest partial likelihood deviance in the inner loop; α ranges from 0 to 1 and when it is 0 all predictors are retained in the model, λ controls the coefficient shrinkage

† c-statistic, in the validation fold of the outer loop, of the best model (lowest partial likelihood deviance in the training folds of the outer loop)

‡ c-statistic of the age-only model in the validation fold of the best outer loop model

§ *p*-value for difference in C-statistic between the best model and the age-only model

¶ Age was forced to be selected in all models.

BLOOD METABOLITES AND DEMENTIA

Results: Frequency of metabolites in the selected models

Table 3 Frequency of metabolites identified by elastic net penalized Cox regression in the sixteen selected models

Name of metabolite	*N* (%)
Glucose (mmol/l)	16/16 (100)
Phospholipids to total lipids ratio in medium HDL (%)	15/16 (93.8)
Creatinine (mmol/l)	10/16 (62.5)
Triglycerides to total lipids ratio in very large VLDL (%)	8/16 (50.0)
Phospholipids to total lipids ratio in medium VLDL (%)	5/16 (31.3)
Alanine (mmol/l)	5/16 (31.3)
β-hydroxybutyrate (mmol/l)	3/16 (18.8)
Free cholesterol to total lipids ratio in small HDL (%)	2/16 (12.5)
Citrate (mmol/l)	2/16 (12.5)
Free cholesterol to total lipids ratio in very large VLDL (%)	1/16 (6.3)
Free cholesterol to total lipids ratio in large HDL (%)	1/16 (6.3)
Triglycerides to total lipids ratio in medium HDL (%)	1/16 (6.3)
Phospholipids to total lipids ratio in small HDL (%)	1/16 (6.3)
Sphingomyelins (mmol/l)	1/16 (6.3)
Albumin (signal area)	1/16 (6.3)

VLDL very low-density lipoproteins, *HDL* high-density lipoprotein

15 metabolites identified in 16 selected models

BLOOD METABOLITES AND DEMENTIA

Results: Association and predictive accuracy of risk scores

Table 4 Predictive performance of risk scores for incident dementia (*N*=5374)

Risk scores	HR (95% confidence interval)	R^2 (95% confidence interval)	AIC	Δ AIC	Sensitivity %	Specificity %	c-statistic (95% confidence interval)	*p*-value*
Age-only model	3.04 (2.66, 3.47)	0.525 (0.450, 0.593)	5198.2	Ref.	75.5	70.3	0.780 (0.757, 0.802)	Ref.
Risk score 1†	3.13 (2.75, 3.57)	0.545 (0.468, 0.636)	5181.2	− 17.0	80.9	64.7	0.786 (0.763, 0.808)	0.05
Risk score 2‡	3.16 (2.77, 3.60)	0.551 (0.475, 0.620)	5176.1	− 22.1	81.5	64.2	0.787 (0.764, 0.809)	0.05
Risk score 3§	3.17 (2.78, 3.61)	0.557 (0.482, 0.630)	5170.8	− 27.4	77.0	69.1	0.788 (0.766, 0.811)	0.03
Risk score 4¶	3.19 (2.80, 3.63)	0.565 (0.492, 0.636)	5163.6	− 34.6	72.4	72.7	0.790 (0.767, 0.813)	0.02
Risk score 5#	3.26 (2.87, 3.71)	0.582 (0.511, 0.649)	5147.7	− 50.5	74.0	72.0	0.796 (0.774, 0.819)	<0.001

R^2 Royston's R^2, *AIC* Akaike information criterion, *c-statistic* Harrell's C-index, *VLDL* very low-density lipoproteins, *HDL* high-density lipoprotein

* *p*-value for difference in c-statistic using age-only model as reference

† Risk score 1 includes age and glucose

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§ Risk score 3 includes age, glucose, phospholipids to total lipids ratio in medium HDL (%) and creatinine (mmol/l)

¶ Risk score 4 includes age, glucose, phospholipids to total lipids ratio in medium HDL (%), creatinine (mmol/l) and triglycerides to total lipids ratio in very large VLDL (%)

Risk score 5 includes age, glucose, phospholipids to total lipids ratio in medium HDL (%), creatinine (mmol/l), triglycerides to total lipids ratio in very large VLDL (%), phospholipids to total lipids ratio in medium VLDL (%), alanine (mmol/l), 3-hydroxybutyrate (mmol/l), free cholesterol to total lipids ratio in small HDL (%), citrate (mmol/l), free cholesterol to total lipids ratio in very large VLDL (%), free cholesterol to total lipids ratio in large HDL (%), triglycerides to total lipids ratio in medium HDL (%), phospholipids to total lipids ratio in small HDL (%), sphingomyelins (mmol/l) and albumin (signal area)

Youden index cutoff points for the calculation of the sensitivity and specificity are as follows: 0.541 for the age-only model; 0.310 for risk score 1; 0.296 for risk score 2; 0.468 for risk score 3; 0.604 for risk score 4; and 0.564 for risk score 5

BLOOD METABOLITES AND DEMENTIA

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BLOOD METABOLITES AND DEMENTIA

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BLOOD METABOLITES AND DEMENTIA

What our study adds

Explicit consideration of age in our analyses

1. Machine learning algorithm
2. Predictive performance analyses

BLOOD METABOLITES AND DEMENTIA

What our study adds

Explicit consideration of age in our analyses

1. Machine learning algorithm
2. Predictive performance analyses

Use of a machine learning algorithm

1. Highly correlated data
2. Nested-cross validation procedure
3. Random partitioning

BLOOD METABOLITES AND DEMENTIA

Conclusions

- The results for glucose are robust: glucose was identified using Cox regression with Bonferroni correction and in all machine learning models.
- Our results highlight the role of age; there was only a modest increase in predictive accuracy when metabolites selected using a machine learning appoach were added to the predictive model containing age (C-statistic for age: 0.780 vs C-statistic for risk score 5: 0.796).
- Although the contribution of the 15 metabolites to dementia prediction was small, it is woth noting that our approach required all metabolites to improve predictive accuracy of a model containing age.
- It is urgent to identify other biomarkers for better prediction.

METABOLIC SYNDROME AND DEMENTIA

Diabetes Care Volume 45, September 2022

Association of Metabolic Syndrome With Incident Dementia: Role of Number and Age at Measurement of Components in a 28-Year Follow-up of the Whitehall II Cohort Study

Marcos D. Machado-Fragua,[1] Aurore Fayosse,[1] Manasa Shanta Yerramalla,[1] Thomas T. van Sloten,[2] Adam G. Tabak,[3,4,5] Mika Kivimaki,[3] Séverine Sabia,[1,3] and Archana Singh-Manoux[1,3]

Diabetes Care 2022;45:2127–2135 | https://doi.org/10.2337/dc22-0206

METABOLIC SYNDROME AND DEMENTIA

METABOLIC SYNDROME
(MetS)

Central obesity
Low HDL-C
Hypertriglyceridemia
Hypertension
Elevated fasting glucose

→ DEMENTIA ??

Increased risk of coronary artery disease and stroke

Obesity
Hypertension
Diabetes

→ Risk factors for late-onset dementia
(Lancet commission on dementia prevention)

METABOLIC SYNDROME AND DEMENTIA

Meta-analysis of longitudinal studies: Atti AR. Am J Geriatr psychiatry 2019;27:625-37

- Studies with short follow-up (<10 years)
- Wide age range at baseline
- Most studies on older people

No association between MetS and dementia or AD
Significant positive association of MetS with vascular dementia (VaD)

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2 studies with follow-up >20 years (only men):

Study 1: Kaljmin S. Arterioscler Thromb Vasc Biol 2000;20:2255-60

- No standardized definition of MetS.
- MetS and dementia were measured at 1 point with a 25-year interval.
- No consideration of competing risk of death in the analyses.
- Increased risk of dementia among participants with “MetS”

Study 2: Creavin ST. J Alzheimers Dis 2012;28:931-9

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- Small number of dementia cases (n < 100)
- No association between MetS and dementia

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Recent research on Asian populations

Higher risk of all-cause dementia (follow-up < 10 years)

Lee JE. J Clin Med 2020;9
Cho Y. Endocrinol Metab 2021;36:424-35
Kim YJ. Diabetol Metab Syndr 2021;13:4

METABOLIC SYNDROME AND DEMENTIA

OBJECTIVE

The aim of our study, using data spanning nearly 30 years, was to examine the role of age at measurement of MetS and its components for incident dementia.

METABOLIC SYNDROME AND DEMENTIA

Metabolic syndrome (exposure)

Criteria	AHA/NHBLI (2009)
	Any 3 of the following criteria
Anthropometry	**Central obesity (population- and country-specific measures)** WC ≥ 102 cm male, WC ≥ 88 cm female (EUROPE)
Triglycerides	**Elevated triglycerides** ≥ 150 mg/dL (1.7 mmol/L) or specific treatment
HDL cholesterol	**Low HDL-cholesterol** < 40 mg/dL (1.03 mmol/L) male < 50 mg/dL (1.29 mmol/L) female or under specific treatment
Blood pressure	**Elevated Blood Pressure** systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg or under specific treatment
Glucose	**Elevated fasting glucose** FG ≥ 100 mg/dL (5.6 mmol/L) or under specific treatment

Alberti KG. Circulation 2009;120:1640-5.

METABOLIC SYNDROME AND DEMENTIA

Dementia (outcome)

Dementia

Electronic health records:

- Hospital Episode Statistics (HES)
- Mental Health services dataset
- Mortality register using ICD-10 codes F00-03, F05.1, G30 and G31

Date of dementia was set at the first record of dementia diagnosis in any of these three databases.

METABOLIC SYNDROME AND DEMENTIA

Covariates

Sociodemographic:

- Age
- Sex
- Educational level
- Ethnicity
- Birth cohort (5-year range)

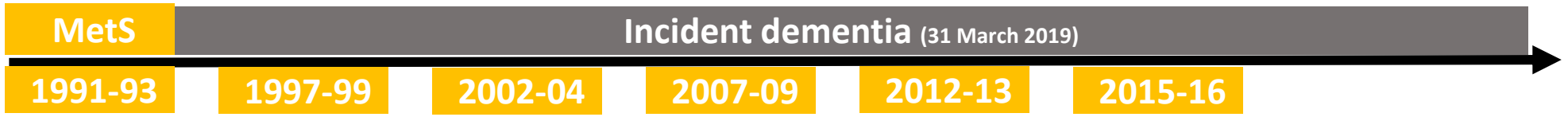
Health-related behaviors:

- Smoking (never, former and current smoker)
- Alcohol consumption (no consumption, 1-14 units/wk, >14 units/wk)
- Fruits and vegetables consumption (les tan daily, once a day, twice or more a day)
- Moderate and vigorous physical activity (hours per week).

METABOLIC SYNDROME AND DEMENTIA

Study design

WHITEHALL II COHORT STUDY



METABOLIC SYNDROME AND DEMENTIA

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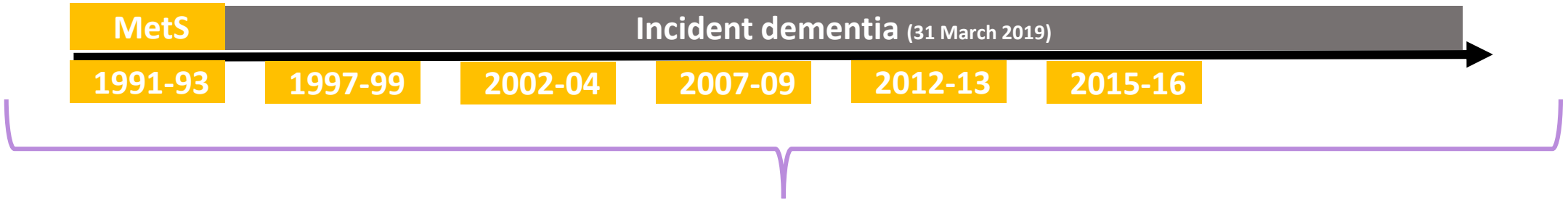
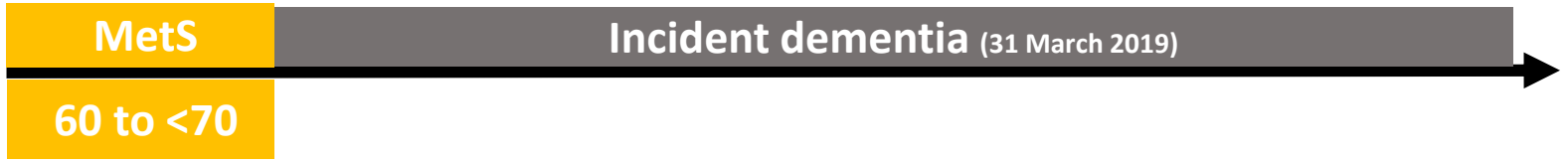


MetS components and covariates at age <60 (Range 40-59.9)

MetS components and covariates at age ≥60 to <70 (Range 60-69.9)



MetS components and covariates at age ≥70 (Range 70-84)

METABOLIC SYNDROME AND DEMENTIA

Study design

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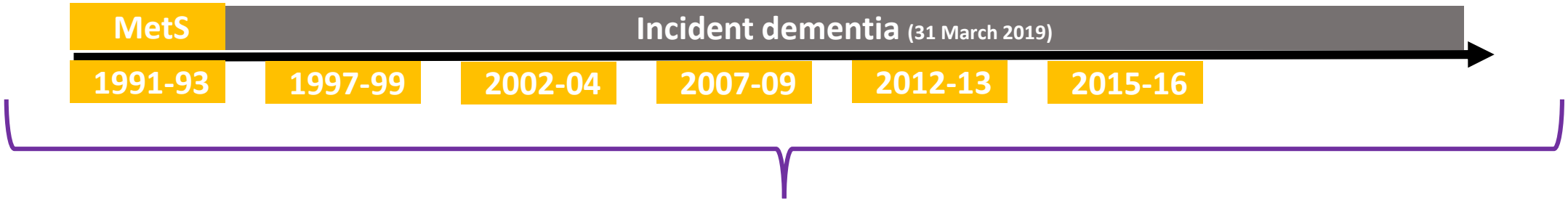

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METABOLIC SYNDROME AND DEMENTIA

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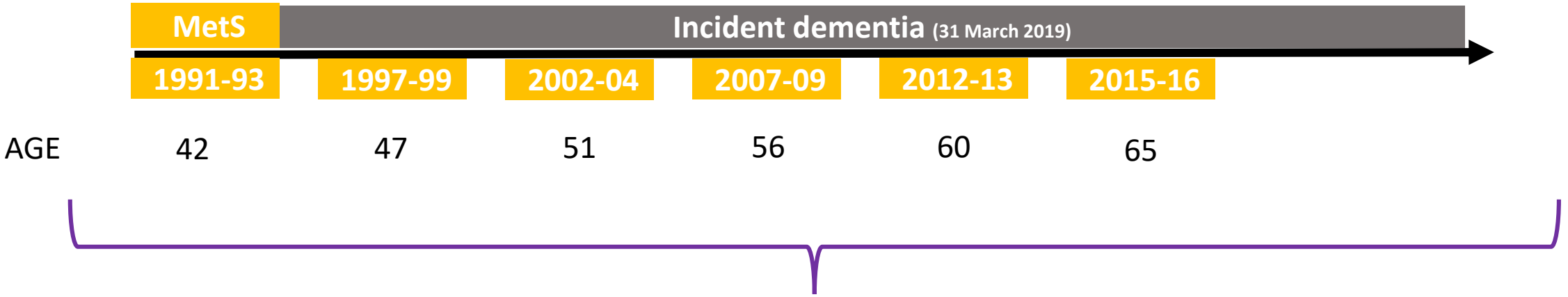

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METABOLIC SYNDROME AND DEMENTIA

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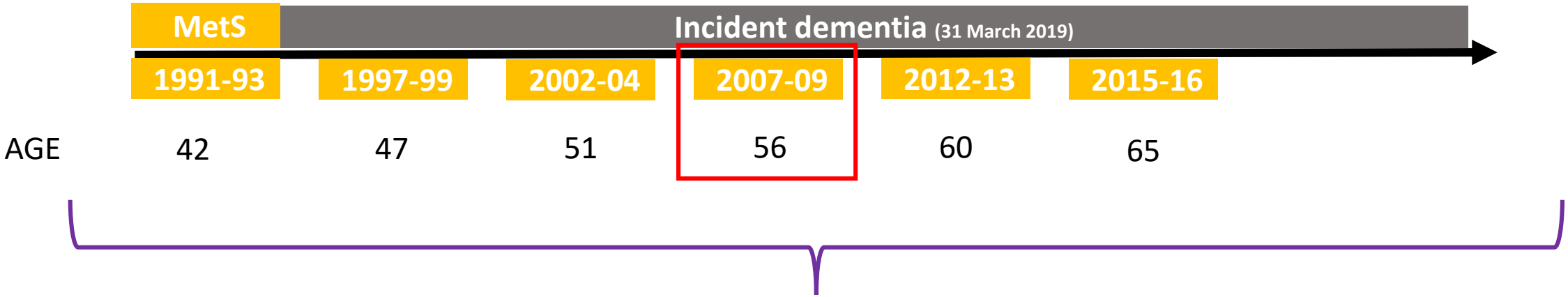

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METABOLIC SYNDROME AND DEMENTIA

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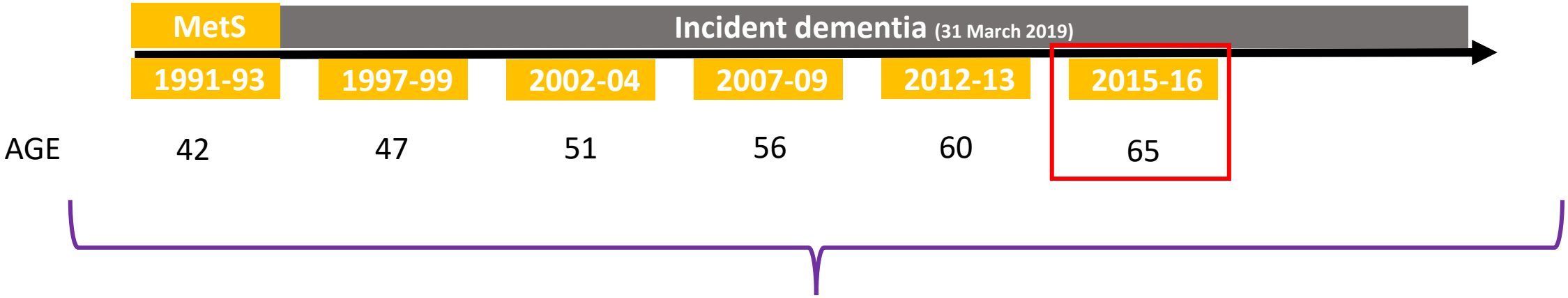

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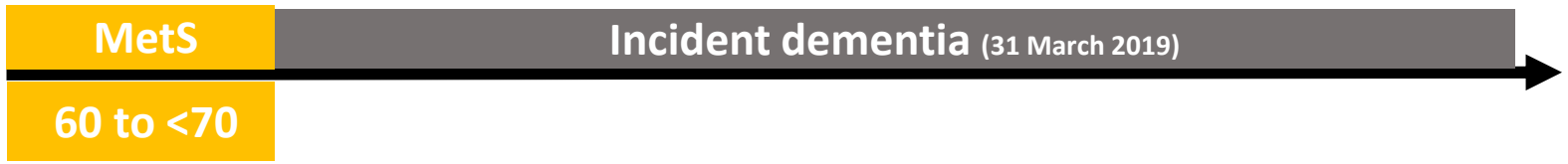

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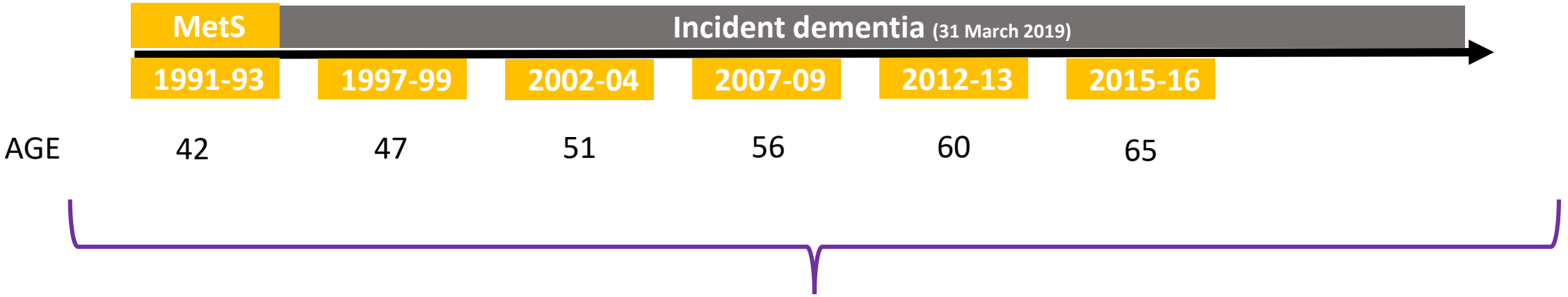
Study design

WHITEHALL II COHORT STUDY

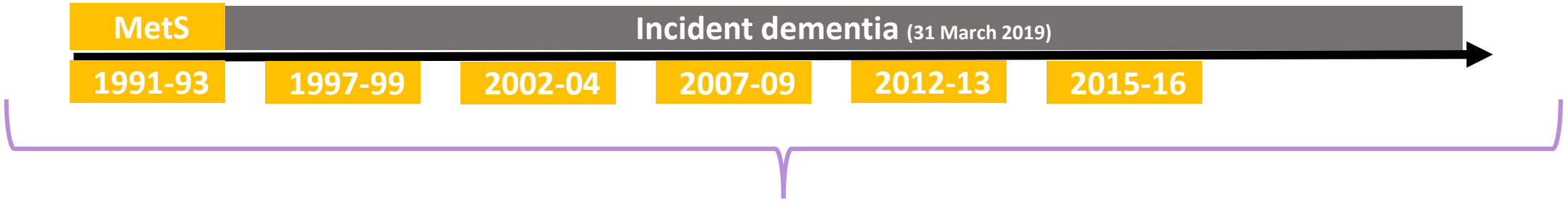


MetS components and covariates at age ≥70 (Range 70-84)

METABOLIC SYNDROME AND DEMENTIA

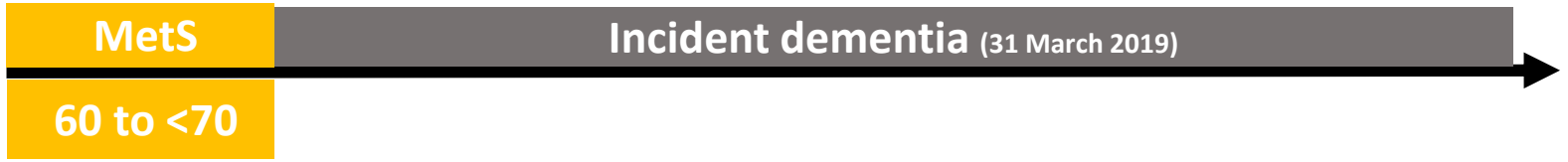
Study design

WHITEHALL II COHORT STUDY



MetS components and covariates at age <60 (Range 40-59.9)

MetS components and covariates at age ≥60 to <70 (Range 60-69.9)



MetS components and covariates at age ≥70 (Range 70-84)

METABOLIC SYNDROME AND DEMENTIA

Table 2. Association between individual metabolic syndrome components at <60, 60 to <70, and ≥70 years and incidence of dementia.

	Elevated WC		Elevated triglycerides		Low HDL-C		Elevated blood pressure		Elevated fasting glucose	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
At age <60 years[a], Median (IQR) follow-up 20.8 (15.5, 26.2) years										
Dementia cases/total, N	322/5979	71/1286	270/5102	123/2163	306/5954	87/1311	184/4072	209/3193	293/5603	100/1662
Rate/1000 person-years	2.69	3.11	2.68	2.95	2.60	3.47	2.28	3.37	2.65	3.13
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.45 (1.12, 1.89)	1 (Ref.)	1.10 (0.89, 1.36)	1 (Ref.)	1.33 (1.04, 1.68)	1 (Ref.)	1.36 (1.11, 1.66)	1 (Ref.)	1.18 (0.94, 1.49)
Model 2[e]	1 (Ref.)	1.39 (1.07, 1.81)	1 (Ref.)	1.04 (0.84, 1.29)	1 (Ref.)	1.30 (1.02, 1.66)	1 (Ref.)	1.34 (1.09, 1.63)	1 (Ref.)	1.18 (0.94, 1.49)
At age 60 to <70 years[b], Median (IQR) follow-up 10.4 (6.4, 15.6) years										
Dementia cases/total, N	318/4760	99/1900	269/4052	148/2608	295/4551	122/2109	172/2784	245/3876	298/4945	119/1715
Rate/1000 person-years	5.87	5.31	5.75	5.68	5.60	6.05	5.67	5.77	5.41	6.71
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.06 (0.84, 1.33)	1 (Ref.)	1.20 (0.98, 1.47)	1 (Ref.)	1.32 (1.07, 1.64)	1 (Ref.)	0.99 (0.81, 1.20)	1 (Ref.)	1.41 (1.14, 1.76)
Model 2[e]	1 (Ref.)	1.00 (0.79, 1.26)	1 (Ref.)	1.16 (0.95, 1.42)	1 (Ref.)	1.26 (1.02, 1.57)	1 (Ref.)	0.97 (0.80, 1.18)	1 (Ref.)	1.40 (1.12, 1.74)
At age ≥70 years[c], Median (IQR) follow-up 4.2 (3.1, 7.1) years										
Dementia cases/total, N	177/2327	87/1281	122/1685	142/1923	133/1798	131/1810	69/1006	195/2602	172/2631	92/977
Rate/1000 person-years	12.95	12.35	12.38	13.08	12.52	12.99	12.31	12.91	11.41	16.33
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.01 (0.77, 1.32)	1 (Ref.)	1.08 (0.85, 1.38)	1 (Ref.)	1.08 (0.85, 1.38)	1 (Ref.)	0.99 (0.75, 1.31)	1 (Ref.)	1.39 (1.08, 1.80)
Model 2[e]	1 (Ref.)	1.00 (0.76, 1.30)	1 (Ref.)	1.06 (0.83, 1.35)	1 (Ref.)	1.06 (0.83, 1.30)	1 (Ref.)	0.96 (0.73, 1.27)	1 (Ref.)	1.38 (1.07, 1.79)

IQR: interquartile range; WC: waist circumference; HDL-C: high density lipoprotein-cholesterol

[a] Mean (SD) age at assessment=55.1 (2.9) years

[b] Mean (SD) age at assessment=65.0 (1.5) years

[c] Mean (SD) age at assessment=73.9 (1.9) years

[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)

[e] Model 2: Model 1 plus adjustment for health behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Table 2. Association between individual metabolic syndrome components at <60, 60 to <70, and ≥70 years and incidence of dementia.

	Elevated WC		Elevated triglycerides		Low HDL-C		Elevated blood pressure		Elevated fasting glucose	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
At age <60 years[a], Median (IQR) follow-up 20.8 (15.5, 26.2) years										
Dementia cases/total, N	322/5979	71/1286	270/5102	123/2163	306/5954	87/1311	184/4072	209/3193	293/5603	100/1662
Rate/1000 person-years	2.69	3.11	2.68	2.95	2.60	3.47	2.28	3.37	2.65	3.13
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.45 (1.12, 1.89)	1 (Ref.)	1.10 (0.89, 1.36)	1 (Ref.)	1.33 (1.04, 1.68)	1 (Ref.)	1.36 (1.11, 1.66)	1 (Ref.)	1.18 (0.94, 1.49)
Model 2[e]	1 (Ref.)	1.39 (1.07, 1.81)	1 (Ref.)	1.04 (0.84, 1.29)	1 (Ref.)	1.30 (1.02, 1.66)	1 (Ref.)	1.34 (1.09, 1.63)	1 (Ref.)	1.18 (0.94, 1.49)
At age 60 to <70 years[b], Median (IQR) follow-up 10.4 (6.4, 15.6) years										
Dementia cases/total, N	318/4760	99/1900	269/4052	148/2608	295/4551	122/2109	172/2784	245/3876	298/4945	119/1715
Rate/1000 person-years	5.87	5.31	5.75	5.68	5.60	6.05	5.67	5.77	5.41	6.71
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.06 (0.84, 1.33)	1 (Ref.)	1.20 (0.98, 1.47)	1 (Ref.)	1.32 (1.07, 1.64)	1 (Ref.)	0.99 (0.81, 1.20)	1 (Ref.)	1.41 (1.14, 1.76)
Model 2[e]	1 (Ref.)	1.00 (0.79, 1.26)	1 (Ref.)	1.16 (0.95, 1.42)	1 (Ref.)	1.26 (1.02, 1.57)	1 (Ref.)	0.97 (0.80, 1.18)	1 (Ref.)	1.40 (1.12, 1.74)
At age ≥70 years[c], Median (IQR) follow-up 4.2 (3.1, 7.1) years										
Dementia cases/total, N	177/2327	87/1281	122/1685	142/1923	133/1798	131/1810	69/1006	195/2602	172/2631	92/977
Rate/1000 person-years	12.95	12.35	12.38	13.08	12.52	12.99	12.31	12.91	11.41	16.33
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.01 (0.77, 1.32)	1 (Ref.)	1.08 (0.85, 1.38)	1 (Ref.)	1.08 (0.85, 1.38)	1 (Ref.)	0.99 (0.75, 1.31)	1 (Ref.)	1.39 (1.08, 1.80)
Model 2[e]	1 (Ref.)	1.00 (0.76, 1.30)	1 (Ref.)	1.06 (0.83, 1.35)	1 (Ref.)	1.06 (0.83, 1.30)	1 (Ref.)	0.96 (0.73, 1.27)	1 (Ref.)	1.38 (1.07, 1.79)

IQR: interquartile range; WC: waist circumference; HDL-C: high density lipoprotein-cholesterol
[a] Mean (SD) age at assessment=55.1 (2.9) years
[b] Mean (SD) age at assessment=65.0 (1.5) years
[c] Mean (SD) age at assessment=73.9 (1.9) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Table 2. Association between individual metabolic syndrome components at <60, 60 to <70, and ≥70 years and incidence of dementia.

	Elevated WC		Elevated triglycerides		Low HDL-C		Elevated blood pressure		Elevated fasting glucose	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
At age <60 years[a], Median (IQR) follow-up 20.8 (15.5, 26.2) years										
Dementia cases/total, N	322/5979	71/1286	270/5102	123/2163	306/5954	87/1311	184/4072	209/3193	293/5603	100/1662
Rate/1000 person-years	2.69	3.11	2.68	2.95	2.60	3.47	2.28	3.37	2.65	3.13
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.45 (1.12, 1.89)	1 (Ref.)	1.10 (0.89, 1.36)	1 (Ref.)	1.33 (1.04, 1.68)	1 (Ref.)	1.36 (1.11, 1.66)	1 (Ref.)	1.18 (0.94, 1.49)
Model 2[e]	1 (Ref.)	1.39 (1.07, 1.81)	1 (Ref.)	1.04 (0.84, 1.29)	1 (Ref.)	1.30 (1.02, 1.66)	1 (Ref.)	1.34 (1.09, 1.63)	1 (Ref.)	1.18 (0.94, 1.49)
At age 60 to <70 years[b], Median (IQR) follow-up 10.4 (6.4, 15.6) years										
Dementia cases/total, N	318/4760	99/1900	269/4052	148/2608	295/4551	122/2109	172/2784	245/3876	298/4945	119/1715
Rate/1000 person-years	5.87	5.31	5.75	5.68	5.60	6.05	5.67	5.77	5.41	6.71
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.06 (0.84, 1.33)	1 (Ref.)	1.20 (0.98, 1.47)	1 (Ref.)	1.32 (1.07, 1.64)	1 (Ref.)	0.99 (0.81, 1.20)	1 (Ref.)	1.41 (1.14, 1.76)
Model 2[e]	1 (Ref.)	1.00 (0.79, 1.26)	1 (Ref.)	1.16 (0.95, 1.42)	1 (Ref.)	1.26 (1.02, 1.57)	1 (Ref.)	0.97 (0.80, 1.18)	1 (Ref.)	1.40 (1.12, 1.74)
At age ≥70 years[c], Median (IQR) follow-up 4.2 (3.1, 7.1) years										
Dementia cases/total, N	177/2327	87/1281	122/1685	142/1923	133/1798	131/1810	69/1006	195/2602	172/2631	92/977
Rate/1000 person-years	12.95	12.35	12.38	13.08	12.52	12.99	12.31	12.91	11.41	16.33
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.01 (0.77, 1.32)	1 (Ref.)	1.08 (0.85, 1.38)	1 (Ref.)	1.08 (0.85, 1.38)	1 (Ref.)	0.99 (0.75, 1.31)	1 (Ref.)	1.39 (1.08, 1.80)
Model 2[e]	1 (Ref.)	1.00 (0.76, 1.30)	1 (Ref.)	1.06 (0.83, 1.35)	1 (Ref.)	1.06 (0.83, 1.30)	1 (Ref.)	0.96 (0.73, 1.27)	1 (Ref.)	1.38 (1.07, 1.79)

IQR: interquartile range; WC: waist circumference; HDL-C: high density lipoprotein-cholesterol
[a] Mean (SD) age at assessment=55.1 (2.9) years
[b] Mean (SD) age at assessment=65.0 (1.5) years
[c] Mean (SD) age at assessment=73.9 (1.9) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Table 2. Association between individual metabolic syndrome components at <60, 60 to <70, and ≥70 years and incidence of dementia.

	Elevated WC		Elevated triglycerides		Low HDL-C		Elevated blood pressure		Elevated fasting glucose	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
At age <60 years[a], Median (IQR) follow-up 20.8 (15.5, 26.2) years										
Dementia cases/total, N	322/5979	71/1286	270/5102	123/2163	306/5954	87/1311	184/4072	209/3193	293/5603	100/1662
Rate/1000 person-years	2.69	3.11	2.68	2.95	2.60	3.47	2.28	3.37	2.65	3.13
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.45 (1.12, 1.89)	1 (Ref.)	1.10 (0.89, 1.36)	1 (Ref.)	1.33 (1.04, 1.68)	1 (Ref.)	1.36 (1.11, 1.66)	1 (Ref.)	1.18 (0.94, 1.49)
Model 2[e]	1 (Ref.)	1.39 (1.07, 1.81)	1 (Ref.)	1.04 (0.84, 1.29)	1 (Ref.)	1.30 (1.02, 1.66)	1 (Ref.)	1.34 (1.09, 1.63)	1 (Ref.)	1.18 (0.94, 1.49)
At age 60 to <70 years[b], Median (IQR) follow-up 10.4 (6.4, 15.6) years										
Dementia cases/total, N	318/4760	99/1900	269/4052	148/2608	295/4551	122/2109	172/2784	245/3876	298/4945	119/1715
Rate/1000 person-years	5.87	5.31	5.75	5.68	5.60	6.05	5.67	5.77	5.41	6.71
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.06 (0.84, 1.33)	1 (Ref.)	1.20 (0.98, 1.47)	1 (Ref.)	1.32 (1.07, 1.64)	1 (Ref.)	0.99 (0.81, 1.20)	1 (Ref.)	1.41 (1.14, 1.76)
Model 2[e]	1 (Ref.)	1.00 (0.79, 1.26)	1 (Ref.)	1.16 (0.95, 1.42)	1 (Ref.)	1.26 (1.02, 1.57)	1 (Ref.)	0.97 (0.80, 1.18)	1 (Ref.)	1.40 (1.12, 1.74)
At age ≥70 years[c], Median (IQR) follow-up 4.2 (3.1, 7.1) years										
Dementia cases/total, N	177/2327	87/1281	122/1685	142/1923	133/1798	131/1810	69/1006	195/2602	172/2631	92/977
Rate/1000 person-years	12.95	12.35	12.38	13.08	12.52	12.99	12.31	12.91	11.41	16.33
Cox regression, HR (95% CI)										
Model 1[d]	1 (Ref.)	1.01 (0.77, 1.32)	1 (Ref.)	1.08 (0.85, 1.38)	1 (Ref.)	1.08 (0.85, 1.38)	1 (Ref.)	0.99 (0.75, 1.31)	1 (Ref.)	1.39 (1.08, 1.80)
Model 2[e]	1 (Ref.)	1.00 (0.76, 1.30)	1 (Ref.)	1.06 (0.83, 1.35)	1 (Ref.)	1.06 (0.83, 1.30)	1 (Ref.)	0.96 (0.73, 1.27)	1 (Ref.)	1.38 (1.07, 1.79)

IQR: interquartile range; WC: waist circumference; HDL-C: high density lipoprotein-cholesterol

[a] Mean (SD) age at assessment=55.1 (2.9) years

[b] Mean (SD) age at assessment=65.0 (1.5) years

[c] Mean (SD) age at assessment=73.9 (1.9) years

[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)

[e] Model 2: Model 1 plus adjustment for health behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Table 3. Association between the number of MetS components at <60, 60 to <70, and ≥70 years and incidence of dementia.

Number of components	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)		HR (95% CI) per component increment	
			Model 1[d]	Model 2[e]	Model 1[d]	Model 2[e]
At age <60 years[a], Median follow-up 20.8 (IQR 15.5, 26.2) years						
0	97/2325	2.08	1 (Ref.)	1 (Ref.)		
1	123/2145	2.85	1.28 (0.99, 1.68)	1.25 (0.96, 1.63)		
2	92/1493	3.21	1.57 (1.18, 2.09)	1.48 (1.11, 1.98)	1.15 (1.06, 1.24)	1.13 (1.05, 1.23)
3	47/823	2.98	1.38 (0.97, 1.96)	1.31 (0.92, 1.85)		
4	28/380	4.12	1.99 (1.30, 3.04)	1.92 (1.25, 2.93)		
5	6/99	3.48	1.90 (0.83, 4.35)	1.73 (0.76, 3.97)		
At age 60 to <70 years[b], Median follow-up 10.4 (IQR 6.4, 15.6) years						
0	75/1409	4.65	1 (Ref.)	1 (Ref.)		
1	127/1753	6.20	1.30 (0.98, 1.73)	1.28 (0.96, 1.71)		
2	100/1387	6.31	1.42 (1.05, 1.92)	1.38 (1.02, 1.86)	1.10 (1.02, 1.18)	1.08 (1.00, 1.16)
3	68/1089	6.03	1.46 (1.05, 2.03)	1.39 (1.00, 1.94)		
4	33/696	5.20	1.51 (0.99, 2.29)	1.38 (0.91, 2.10)		
5	14/326	5.12	1.64 (0.92, 2.93)	1.54 (0.86, 2.76)		
At age ≥70 years[c], Median follow-up 4.2 (IQR 3.1, 7.1) years						
0	23/442	8.90	1 (Ref.)	1 (Ref.)		
1	57/729	13.26	1.50 (0.92, 2.42)	1.44 (0.88, 2.34)		
2	48/650	12.81	1.50 (0.91, 2.47)	1.45 (0.88, 2.39)	1.05 (0.97, 1.14)	1.04 (0.96, 1.13)
3	68/844	13.95	1.56 (0.97, 2.50)	1.49 (0.93, 2.40)		
4	50/683	13.45	1.57 (0.96, 2.59)	1.53 (0.93, 2.51)		
5	18/260	12.12	1.38 (0.75, 2.57)	1.27 (0.68, 2.37)		

IQR: interquartile range; [a] Mean (SD) age at assessment=55.1 (2.9) years
[b] Mean (SD) age at assessment=65.0 (1.5) years
[c] Mean (SD) age at assessment=73.9 (1.9) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Table 3. Association between the number of MetS components at <60, 60 to <70, and ≥70 years and incidence of dementia.

Number of components	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)		HR (95% CI) per component increment	
			Model 1[d]	Model 2[e]	Model 1[d]	Model 2[e]
At age <60 years[a], Median follow-up 20.8 (IQR 15.5, 26.2) years						
0	97/2325	2.08	1 (Ref.)	1 (Ref.)		
1	123/2145	2.85	1.28 (0.99, 1.68)	1.25 (0.96, 1.63)		
2	92/1493	3.21	1.57 (1.18, 2.09)	1.48 (1.11, 1.98)		
3	47/823	2.98	1.38 (0.97, 1.96)	1.31 (0.92, 1.85)	1.15 (1.06, 1.24)	1.13 (1.05, 1.23)
4	28/380	4.12	1.99 (1.30, 3.04)	1.92 (1.25, 2.93)		
5	6/99	3.48	1.90 (0.83, 4.35)	1.73 (0.76, 3.97)		
At age 60 to <70 years[b], Median follow-up 10.4 (IQR 6.4, 15.6) years						
0	75/1409	4.65	1 (Ref.)	1 (Ref.)		
1	127/1753	6.20	1.30 (0.98, 1.73)	1.28 (0.96, 1.71)		
2	100/1387	6.31	1.42 (1.05, 1.92)	1.38 (1.02, 1.86)		
3	68/1089	6.03	1.46 (1.05, 2.03)	1.39 (1.00, 1.94)	1.10 (1.02, 1.18)	1.08 (1.00, 1.16)
4	33/696	5.20	1.51 (0.99, 2.29)	1.38 (0.91, 2.10)		
5	14/326	5.12	1.64 (0.92, 2.93)	1.54 (0.86, 2.76)		
At age ≥70 years[c], Median follow-up 4.2 (IQR 3.1, 7.1) years						
0	23/442	8.90	1 (Ref.)	1 (Ref.)		
1	57/729	13.26	1.50 (0.92, 2.42)	1.44 (0.88, 2.34)		
2	48/650	12.81	1.50 (0.91, 2.47)	1.45 (0.88, 2.39)		
3	68/844	13.95	1.56 (0.97, 2.50)	1.49 (0.93, 2.40)	1.05 (0.97, 1.14)	1.04 (0.96, 1.13)
4	50/683	13.45	1.57 (0.96, 2.59)	1.53 (0.93, 2.51)		
5	18/260	12.12	1.38 (0.75, 2.57)	1.27 (0.68, 2.37)		

IQR: interquartile range; [a] Mean (SD) age at assessment=55.1 (2.9) years
[b] Mean (SD) age at assessment=65.0 (1.5) years
[c] Mean (SD) age at assessment=73.9 (1.9) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Table 3. Association between the number of MetS components at <60, 60 to <70, and ≥70 years and incidence of dementia.

Number of components	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)		HR (95% CI) per component increment	
			Model 1[d]	Model 2[e]	Model 1[d]	Model 2[e]
At age <60 years[a], Median follow-up 20.8 (IQR 15.5, 26.2) years						
0	97/2325	2.08	1 (Ref.)	1 (Ref.)		
1	123/2145	2.85	1.28 (0.99, 1.68)	1.25 (0.96, 1.63)		
2	92/1493	3.21	1.57 (1.18, 2.09)	1.48 (1.11, 1.98)	1.15 (1.06, 1.24)	1.13 (1.05, 1.23)
3	47/823	2.98	1.38 (0.97, 1.96)	1.31 (0.92, 1.85)		
4	28/380	4.12	1.99 (1.30, 3.04)	1.92 (1.25, 2.93)		
5	6/99	3.48	1.90 (0.83, 4.35)	1.73 (0.76, 3.97)		
At age 60 to <70 years[b], Median follow-up 10.4 (IQR 6.4, 15.6) years						
0	75/1409	4.65	1 (Ref.)	1 (Ref.)		
1	127/1753	6.20	1.30 (0.98, 1.73)	1.28 (0.96, 1.71)		
2	100/1387	6.31	1.42 (1.05, 1.92)	1.38 (1.02, 1.86)	1.10 (1.02, 1.18)	1.08 (1.00, 1.16)
3	68/1089	6.03	1.46 (1.05, 2.03)	1.39 (1.00, 1.94)		
4	33/696	5.20	1.51 (0.99, 2.29)	1.38 (0.91, 2.10)		
5	14/326	5.12	1.64 (0.92, 2.93)	1.54 (0.86, 2.76)		
At age ≥70 years[c], Median follow-up 4.2 (IQR 3.1, 7.1) years						
0	23/442	8.90	1 (Ref.)	1 (Ref.)		
1	57/729	13.26	1.50 (0.92, 2.42)	1.44 (0.88, 2.34)		
2	48/650	12.81	1.50 (0.91, 2.47)	1.45 (0.88, 2.39)	1.05 (0.97, 1.14)	1.04 (0.96, 1.13)
3	68/844	13.95	1.56 (0.97, 2.50)	1.49 (0.93, 2.40)		
4	50/683	13.45	1.57 (0.96, 2.59)	1.53 (0.93, 2.51)		
5	18/260	12.12	1.38 (0.75, 2.57)	1.27 (0.68, 2.37)		

IQR: interquartile range; [a] Mean (SD) age at assessment=55.1 (2.9) years
[b] Mean (SD) age at assessment=65.0 (1.5) years
[c] Mean (SD) age at assessment=73.9 (1.9) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Table 3. Association between the number of MetS components at <60, 60 to <70, and ≥70 years and incidence of dementia.

Number of components	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)		HR (95% CI) per component increment	
			Model 1[d]	Model 2[e]	Model 1[d]	Model 2[e]
At age <60 years[a], Median follow-up 20.8 (IQR 15.5, 26.2) years						
0	97/2325	2.08	1 (Ref.)	1 (Ref.)		
1	123/2145	2.85	1.28 (0.99, 1.68)	1.25 (0.96, 1.63)		
2	92/1493	3.21	1.57 (1.18, 2.09)	1.48 (1.11, 1.98)	1.15 (1.06, 1.24)	1.13 (1.05, 1.23)
3	47/823	2.98	1.38 (0.97, 1.96)	1.31 (0.92, 1.85)		
4	28/380	4.12	1.99 (1.30, 3.04)	1.92 (1.25, 2.93)		
5	6/99	3.48	1.90 (0.83, 4.35)	1.73 (0.76, 3.97)		
At age 60 to <70 years[b], Median follow-up 10.4 (IQR 6.4, 15.6) years						
0	75/1409	4.65	1 (Ref.)	1 (Ref.)		
1	127/1753	6.20	1.30 (0.98, 1.73)	1.28 (0.96, 1.71)		
2	100/1387	6.31	1.42 (1.05, 1.92)	1.38 (1.02, 1.86)	1.10 (1.02, 1.18)	1.08 (1.00, 1.16)
3	68/1089	6.03	1.46 (1.05, 2.03)	1.39 (1.00, 1.94)		
4	33/696	5.20	1.51 (0.99, 2.29)	1.38 (0.91, 2.10)		
5	14/326	5.12	1.64 (0.92, 2.93)	1.54 (0.86, 2.76)		
At age ≥70 years[c], Median follow-up 4.2 (IQR 3.1, 7.1) years						
0	23/442	8.90	1 (Ref.)	1 (Ref.)		
1	57/729	13.26	1.50 (0.92, 2.42)	1.44 (0.88, 2.34)		
2	48/650	12.81	1.50 (0.91, 2.47)	1.45 (0.88, 2.39)	1.05 (0.97, 1.14)	1.04 (0.96, 1.13)
3	68/844	13.95	1.56 (0.97, 2.50)	1.49 (0.93, 2.40)		
4	50/683	13.45	1.57 (0.96, 2.59)	1.53 (0.93, 2.51)		
5	18/260	12.12	1.38 (0.75, 2.57)	1.27 (0.68, 2.37)		

IQR: interquartile range; [a] Mean (SD) age at assessment=55.1 (2.9) years
[b] Mean (SD) age at assessment=65.0 (1.5) years
[c] Mean (SD) age at assessment=73.9 (1.9) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Table 4. Alternate cut-off points to define "high metabolic risk" at <60, 60 to <70, and ≥70 years and incidence of dementia.

Metabolic risk	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)	
			Model 1[d]	Model 2[e]
High metabolic risk defined as presence of ≥1 MetS component				
At age <60 years[a]				
No risk	97/2325	2.08	Ref.	Ref.
High risk	296/4940	3.08	1.44 (1.14, 1.81)	1.38 (1.09, 1.74)
At age 60 to <70 years[b]				
No risk	75/1409	4.65	Ref.	Ref.
High risk	342/5251	6.03	1.39 (1.08, 1.79)	1.35 (1.05, 1.73)
At age ≥70 years[c]				
No risk	23/442	8.90	Ref.	Ref.
High risk	241/3166	13.30	1.52 (0.99, 2.33)	1.46 (0.95, 2.24)
High metabolic risk defined as presence of ≥2 MetS components				
At age <60 years[a]				
No risk	220/4470	2.45	Ref.	Ref.
High risk	173/2795	3.27	1.37 (1.12, 1.68)	1.32 (1.08, 1.62)
At age 60 to <70 years[b]				
No risk	202/3162	5.52	Ref.	Ref.
High risk	215/3498	5.94	1.26 (1.03, 1.52)	1.19 (0.98, 1.46)
At age ≥70 years[c]				
No risk	80/1171	11.62	Ref.	Ref.
High risk	184/2437	13.31	1.17 (0.90, 1.52)	1.15 (0.88, 1.49)
High metabolic risk defined as presence of ≥3 MetS components (current clinical MetS definition)				
At age <60 years[a]				
No risk (non-MetS)	312/5963	2.64	Ref.	Ref.
High risk (MetS)	81/1302	3.34	1.27 (0.99, 1.62)	1.23 (0.96, 1.57)
At age 60 to <70 years[b]				
No risk (non-MetS)	302/4549	5.76	Ref.	Ref.
High risk (MetS)	115/2111	5.65	1.20 (0.96, 1.49)	1.14 (0.91, 1.42)
At age ≥70 years[c]				
No risk (non-MetS)	128/1821	12.04	Ref.	Ref.
High risk (MetS)	136/1787	13.49	1.12 (0.88, 1.43)	1.10 (0.86, 1.40)

MetS: Metabolic syndrome.
[a] Mean (SD) age at assessment=55.1 (2.9) years; median (IQR) follow-up 20.8 (15.5, 26.2) years
[b] Mean (SD) age at assessment=65.0 (1.5) years; median (IQR) follow-up 10.4 (6.4, 15.6) years
[c] Mean (SD) age at assessment=73.9 (1.9) years) years; median (IQR) follow-up 4.2 (3.1, 7.1) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Table 4. Alternate cut-off points to define "high metabolic risk" at <60, 60 to <70, and ≥70 years and incidence of dementia.

Metabolic risk	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)	
			Model 1[d]	Model 2[e]
High metabolic risk defined as presence of ≥1 MetS component				
At age <60 years[a]				
No risk	97/2325	2.08	Ref.	Ref.
High risk	296/4940	3.08	1.44 (1.14, 1.81)	1.38 (1.09, 1.74)
At age 60 to <70 years[b]				
No risk	75/1409	4.65	Ref.	Ref.
High risk	342/5251	6.03	1.39 (1.08, 1.79)	1.35 (1.05, 1.73)
At age ≥70 years[c]				
No risk	23/442	8.90	Ref.	Ref.
High risk	241/3166	13.30	1.52 (0.99, 2.33)	1.46 (0.95, 2.24)
High metabolic risk defined as presence of ≥2 MetS components				
At age <60 years[a]				
No risk	220/4470	2.45	Ref.	Ref.
High risk	173/2795	3.27	1.37 (1.12, 1.68)	1.32 (1.08, 1.62)
At age 60 to <70 years[b]				
No risk	202/3162	5.52	Ref.	Ref.
High risk	215/3498	5.94	1.26 (1.03, 1.52)	1.19 (0.98, 1.46)
At age ≥70 years[c]				
No risk	80/1171	11.62	Ref.	Ref.
High risk	184/2437	13.31	1.17 (0.90, 1.52)	1.15 (0.88, 1.49)
High metabolic risk defined as presence of ≥3 MetS components (current clinical MetS definition)				
At age <60 years[a]				
No risk (non-MetS)	312/5963	2.64	Ref.	Ref.
High risk (MetS)	81/1302	3.34	1.27 (0.99, 1.62)	1.23 (0.96, 1.57)
At age 60 to <70 years[b]				
No risk (non-MetS)	302/4549	5.76	Ref.	Ref.
High risk (MetS)	115/2111	5.65	1.20 (0.96, 1.49)	1.14 (0.91, 1.42)
At age ≥70 years[c]				
No risk (non-MetS)	128/1821	12.04	Ref.	Ref.
High risk (MetS)	136/1787	13.49	1.12 (0.88, 1.43)	1.10 (0.86, 1.40)

MetS: Metabolic syndrome.
[a] Mean (SD) age at assessment=55.1 (2.9) years; median (IQR) follow-up 20.8 (15.5, 26.2) years
[b] Mean (SD) age at assessment=65.0 (1.5) years; median (IQR) follow-up 10.4 (6.4, 15.6) years
[c] Mean (SD) age at assessment=73.9 (1.9) years) years; median (IQR) follow-up 4.2 (3.1, 7.1) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Table 4. Alternate cut-off points to define "high metabolic risk" at <60, 60 to <70, and ≥70 years and incidence of dementia.

Metabolic risk	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)	
			Model 1[d]	Model 2[e]
High metabolic risk defined as presence of ≥1 MetS component				
At age <60 years[a]				
No risk	97/2325	2.08	Ref.	Ref.
High risk	296/4940	3.08	1.44 (1.14, 1.81)	1.38 (1.09, 1.74)
At age 60 to <70 years[b]				
No risk	75/1409	4.65	Ref.	Ref.
High risk	342/5251	6.03	1.39 (1.08, 1.79)	1.35 (1.05, 1.73)
At age ≥70 years[c]				
No risk	23/442	8.90	Ref.	Ref.
High risk	241/3166	13.30	1.52 (0.99, 2.33)	1.46 (0.95, 2.24)
High metabolic risk defined as presence of ≥2 MetS components				
At age <60 years[a]				
No risk	220/4470	2.45	Ref.	Ref.
High risk	173/2795	3.27	1.37 (1.12, 1.68)	1.32 (1.08, 1.62)
At age 60 to <70 years[b]				
No risk	202/3162	5.52	Ref.	Ref.
High risk	215/3498	5.94	1.26 (1.03, 1.52)	1.19 (0.98, 1.46)
At age ≥70 years[c]				
No risk	80/1171	11.62	Ref.	Ref.
High risk	184/2437	13.31	1.17 (0.90, 1.52)	1.15 (0.88, 1.49)
High metabolic risk defined as presence of ≥3 MetS components (current clinical MetS definition)				
At age <60 years[a]				
No risk (non-MetS)	312/5963	2.64	Ref.	Ref.
High risk (MetS)	81/1302	3.34	1.27 (0.99, 1.62)	1.23 (0.96, 1.57)
At age 60 to <70 years[b]				
No risk (non-MetS)	302/4549	5.76	Ref.	Ref.
High risk (MetS)	115/2111	5.65	1.20 (0.96, 1.49)	1.14 (0.91, 1.42)
At age ≥70 years[c]				
No risk (non-MetS)	128/1821	12.04	Ref.	Ref.
High risk (MetS)	136/1787	13.49	1.12 (0.88, 1.43)	1.10 (0.86, 1.40)

MetS: Metabolic syndrome.
[a] Mean (SD) age at assessment=55.1 (2.9) years; median (IQR) follow-up 20.8 (15.5, 26.2) years
[b] Mean (SD) age at assessment=65.0 (1.5) years; median (IQR) follow-up 10.4 (6.4, 15.6) years
[c] Mean (SD) age at assessment=73.9 (1.9) years) years; median (IQR) follow-up 4.2 (3.1, 7.1) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Table 4. Alternate cut-off points to define "high metabolic risk" at <60, 60 to <70, and ≥70 years and incidence of dementia.

Metabolic risk	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)	
			Model 1[d]	Model 2[e]
High metabolic risk defined as presence of ≥1 MetS component				
At age <60 years[a]				
No risk	97/2325	2.08	Ref.	Ref.
High risk	296/4940	3.08	1.44 (1.14, 1.81)	1.38 (1.09, 1.74)
At age 60 to <70 years[b]				
No risk	75/1409	4.65	Ref.	Ref.
High risk	342/5251	6.03	1.39 (1.08, 1.79)	1.35 (1.05, 1.73)
At age ≥70 years[c]				
No risk	23/442	8.90	Ref.	Ref.
High risk	241/3166	13.30	1.52 (0.99, 2.33)	1.46 (0.95, 2.24)
High metabolic risk defined as presence of ≥2 MetS components				
At age <60 years[a]				
No risk	220/4470	2.45	Ref.	Ref.
High risk	173/2795	3.27	1.37 (1.12, 1.68)	1.32 (1.08, 1.62)
At age 60 to <70 years[b]				
No risk	202/3162	5.52	Ref.	Ref.
High risk	215/3498	5.94	1.26 (1.03, 1.52)	1.19 (0.98, 1.46)
At age ≥70 years[c]				
No risk	80/1171	11.62	Ref.	Ref.
High risk	184/2437	13.31	1.17 (0.90, 1.52)	1.15 (0.88, 1.49)
High metabolic risk defined as presence of ≥3 MetS components (current clinical MetS definition)				
At age <60 years[a]				
No risk (non-MetS)	312/5963	2.64	Ref.	Ref.
High risk (MetS)	81/1302	3.34	1.27 (0.99, 1.62)	1.23 (0.96, 1.57)
At age 60 to <70 years[b]				
No risk (non-MetS)	302/4549	5.76	Ref.	Ref.
High risk (MetS)	115/2111	5.65	1.20 (0.96, 1.49)	1.14 (0.91, 1.42)
At age ≥70 years[c]				
No risk (non-MetS)	128/1821	12.04	Ref.	Ref.
High risk (MetS)	136/1787	13.49	1.12 (0.88, 1.43)	1.10 (0.86, 1.40)

MetS: Metabolic syndrome.
[a] Mean (SD) age at assessment=55.1 (2.9) years; median (IQR) follow-up 20.8 (15.5, 26.2) years
[b] Mean (SD) age at assessment=65.0 (1.5) years; median (IQR) follow-up 10.4 (6.4, 15.6) years
[c] Mean (SD) age at assessment=73.9 (1.9) years) years; median (IQR) follow-up 4.2 (3.1, 7.1) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

eTable 1. Role of the number of metabolic components at <60, 60 to <70, and ≥70 years on the association between metabolic syndrome and incidence of dementia.

Number of MetS components	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)	
			Model 1[d]	Model 2[e]
At age <60 years[a], Median (IQR) follow-up 20.8 (15·5, 26·2) years				
0	97/2325	2·08	1 (Ref.)	1 (Ref.)
1	123/2145	2·85	1·29 (0·99, 1·68)	1·25 (0·96, 1·63)
2	92/1493	3·21	1·57 (1·17, 2·09)	1·48 (1·11, 1·98)
MetS (3-5)	81/1302	3·34	1·58 (1·17, 2·13)	1·50 (1·11, 2·02)
At age 60 years to <70 years[b], Median (IQR) follow-up 10·4 (6·4, 15·6) years				
0	75/1409	4·65	1 (Ref.)	1 (Ref.)
1	127/1753	6·20	1·30 (0·98, 1·73)	1·28 (0·96, 1·71)
2	100/1387	6·31	1·42 (1·05, 1·92)	1·38 (1·02, 1·86)
MetS (3-5)	115/2111	5·65	1·49 (1·11, 2·01)	1·40 (1·04, 1·89)
At age ≥70 years[c], Median (IQR) follow-up 4·2 (3·1, 7·1) years				
0	23/442	8·90	1 (Ref.)	1 (Ref.)
1	57/729	13·26	1·49 (0·92, 2·42)	1·44 (0·88, 2·34)
2	48/650	12·81	1·50 (0·91, 2·47)	1·45 (0·88, 2·39)
MetS (3-5)	136/1787	13·49	1·54 (0·99, 2·40)	1·47 (0·94, 2·30)

MetS: Metabolic syndrome
[a] Mean (SD) age at assessment=55·1 (2·9) years
[b] Mean (SD) age at assessment=65·0 (1·5) years
[c] Mean (SD) age at assessment=73·9 (1·9) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
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METABOLIC SYNDROME AND DEMENTIA

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Number of MetS components	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)	
			Model 1[d]	Model 2[e]
At age <60 years[a], Median (IQR) follow-up 20.8 (15·5, 26·2) years				
0	97/2325	2·08	1 (Ref.)	1 (Ref.)
1	123/2145	2·85	1·29 (0·99, 1·68)	1·25 (0·96, 1·63)
2	92/1493	3·21	1·57 (1·17, 2·09)	1·48 (1·11, 1·98)
MetS (3-5)	81/1302	3·34	1·58 (1·17, 2·13)	1·50 (1·11, 2·02)
At age 60 years to <70 years[b], Median (IQR) follow-up 10·4 (6·4, 15·6) years				
0	75/1409	4·65	1 (Ref.)	1 (Ref.)
1	127/1753	6·20	1·30 (0·98, 1·73)	1·28 (0·96, 1·71)
2	100/1387	6·31	1·42 (1·05, 1·92)	1·38 (1·02, 1·86)
MetS (3-5)	115/2111	5·65	1·49 (1·11, 2·01)	1·40 (1·04, 1·89)
At age ≥70 years[c], Median (IQR) follow-up 4·2 (3·1, 7·1) years				
0	23/442	8·90	1 (Ref.)	1 (Ref.)
1	57/729	13·26	1·49 (0·92, 2·42)	1·44 (0·88, 2·34)
2	48/650	12·81	1·50 (0·91, 2·47)	1·45 (0·88, 2·39)
MetS (3-5)	136/1787	13·49	1·54 (0·99, 2·40)	1·47 (0·94, 2·30)

MetS: Metabolic syndrome
[a] Mean (SD) age at assessment=55·1 (2·9) years
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[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
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METABOLIC SYNDROME AND DEMENTIA

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Number of MetS components	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)	
			Model 1[d]	Model 2[e]
At age <60 years[a], Median (IQR) follow-up 20.8 (15·5, 26·2) years				
0	97/2325	2·08	1 (Ref.)	1 (Ref.)
1	123/2145	2·85	1·29 (0·99, 1·68)	1·25 (0·96, 1·63)
2	92/1493	3·21	1·57 (1·17, 2·09)	1·48 (1·11, 1·98)
MetS (3-5)	81/1302	3·34	1·58 (1·17, 2·13)	1·50 (1·11, 2·02)
At age 60 years to <70 years[b], Median (IQR) follow-up 10·4 (6·4, 15·6) years				
0	75/1409	4·65	1 (Ref.)	1 (Ref.)
1	127/1753	6·20	1·30 (0·98, 1·73)	1·28 (0·96, 1·71)
2	100/1387	6·31	1·42 (1·05, 1·92)	1·38 (1·02, 1·86)
MetS (3-5)	115/2111	5·65	1·49 (1·11, 2·01)	1·40 (1·04, 1·89)
At age ≥70 years[c], Median (IQR) follow-up 4·2 (3·1, 7·1) years				
0	23/442	8·90	1 (Ref.)	1 (Ref.)
1	57/729	13·26	1·49 (0·92, 2·42)	1·44 (0·88, 2·34)
2	48/650	12·81	1·50 (0·91, 2·47)	1·45 (0·88, 2·39)
MetS (3-5)	136/1787	13·49	1·54 (0·99, 2·40)	1·47 (0·94, 2·30)

MetS: Metabolic syndrome
[a] Mean (SD) age at assessment=55·1 (2·9) years
[b] Mean (SD) age at assessment=65·0 (1·5) years
[c] Mean (SD) age at assessment=73·9 (1·9) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

eTable 1. Role of the number of metabolic components at <60, 60 to <70, and ≥70 years on the association between metabolic syndrome and incidence of dementia.

Number of MetS components	N Dementia cases/Total	Rate of dementia/ 1000 person-years	HR (95% CI)	
			Model 1[d]	Model 2[e]
At age <60 years[a], Median (IQR) follow-up 20.8 (15·5, 26·2) years				
0	97/2325	2·08	1 (Ref.)	1 (Ref.)
1	123/2145	2·85	1·29 (0·99, 1·68)	1·25 (0·96, 1·63)
2	92/1493	3·21	1·57 (1·17, 2·09)	1·48 (1·11, 1·98)
MetS (3-5)	81/1302	3·34	1·58 (1·17, 2·13)	1·50 (1·11, 2·02)
At age 60 years to <70 years[b], Median (IQR) follow-up 10·4 (6·4, 15·6) years				
0	75/1409	4·65	1 (Ref.)	1 (Ref.)
1	127/1753	6·20	1·30 (0·98, 1·73)	1·28 (0·96, 1·71)
2	100/1387	6·31	1·42 (1·05, 1·92)	1·38 (1·02, 1·86)
MetS (3-5)	115/2111	5·65	1·49 (1·11, 2·01)	1·40 (1·04, 1·89)
At age ≥70 years[c], Median (IQR) follow-up 4·2 (3·1, 7·1) years				
0	23/442	8·90	1 (Ref.)	1 (Ref.)
1	57/729	13·26	1·49 (0·92, 2·42)	1·44 (0·88, 2·34)
2	48/650	12·81	1·50 (0·91, 2·47)	1·45 (0·88, 2·39)
MetS (3-5)	136/1787	13·49	1·54 (0·99, 2·40)	1·47 (0·94, 2·30)

MetS: Metabolic syndrome
[a] Mean (SD) age at assessment=55·1 (2·9) years
[b] Mean (SD) age at assessment=65·0 (1·5) years
[c] Mean (SD) age at assessment=73·9 (1·9) years
[d] Model 1: analyses adjusted for sex, education, ethnicity, and birth cohort (5-year groups)
[e] Model 2: Model 1 plus adjustment for health-related behaviors (smoking, alcohol consumption, consumption of fruits and vegetables, and physical activity)

METABOLIC SYNDROME AND DEMENTIA

Typical approach:
Include participants with a wide age range at baseline

Older participants are more likely to develop dementia during the short follow-up but are also more likely to be in the preclinical pase of dementia

2 novel features:

1. Alternative thresholds to define “high metabolic risk”.
2. Assessment of MetS components in midlife and later life.

METABOLIC SYNDROME AND DEMENTIA

MetS definition

MetS: ≥3 cardiometabolic components

Non-MetS: 0-2 cardiometabolic components

Heterogeneity in metabolic risk in the reference category

A previous study on Korean adults, mean age 53.1 years at baseline, also found higher risk of dementia in those with one or more MetS components Cho Y. Endocrinol Metab 2021;36:424-35

Individual components of MetS are associated with dementia, notably when assessed at midflife

Walker KA. JAMA 2019;322:535-545.
Singh-Manoux A. Alzheimers Dement 2018;14:178-186.

→ We found elevated WC, low HDL-C and elevated blood pressure to be associated with dementia when prevalent before age 60.

METABOLIC SYNDROME AND DEMENTIA

- The conventional definition of MetS, requiring the prevalence of three or more components, is not optimal as risk for dementia accumulates over the entire scale of MetS components.

- MetS components when present before age 70 are associated with an increased risk of late-onset dementia.

- Our results show the importance of targeting all metabolic risk factors rather than the presence of metabolic risk clusters.

HEARING AND DEMENTIA

nature aging

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Association of midlife hearing impairment and hearing aid use with incident dementia: analysis of two UK-based longitudinal cohort studies

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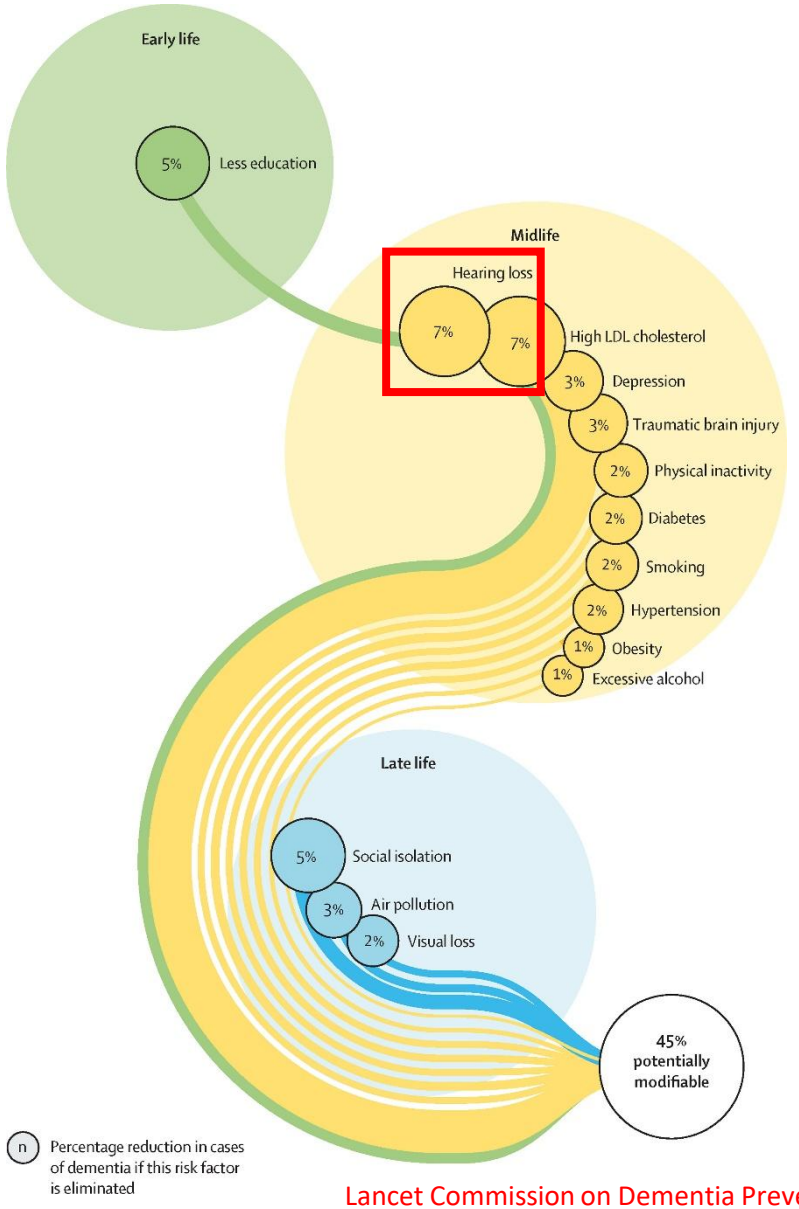
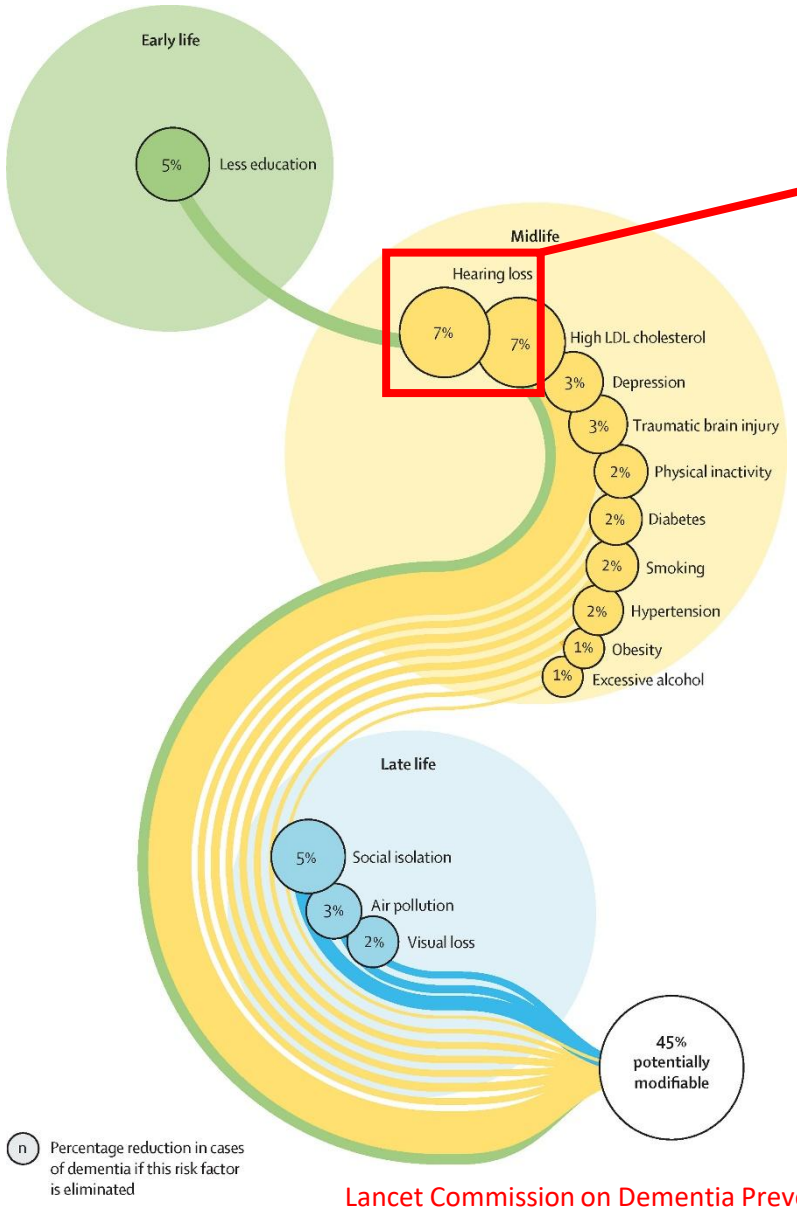
HEARING AND DEMENTIA



Lancet Commission on Dementia Prevention, Intervention, and Care 2024

HEARING AND DEMENTIA



6 studies were used to estimate HR for PAF

- 4 were based on people >65 years.
- 1 included people >50 years but mean age at hearing assessment was ≈70 years.
- 1 measured hearing status at a median age of 59.9 years.

All studies have a follow-up between 6 and 12 years
All used objective measures

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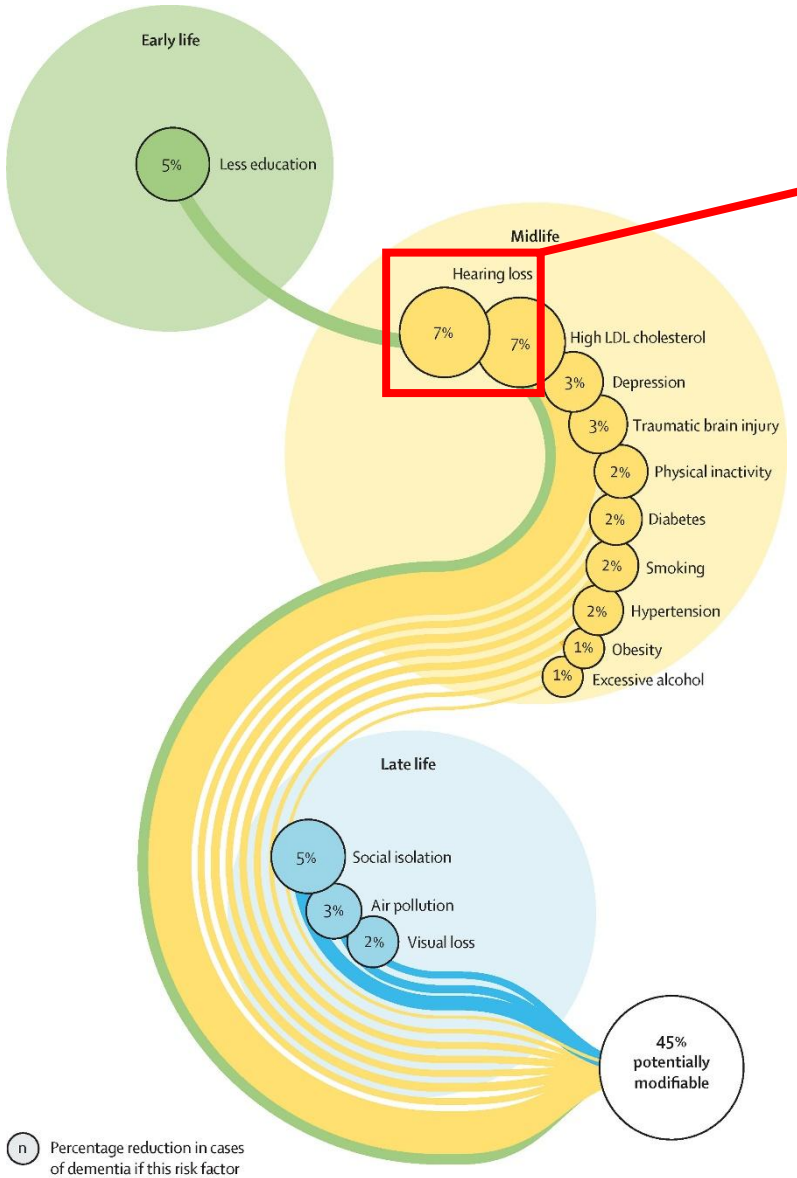
HEARING AND DEMENTIA



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All used objective measures

Stephan BCM. *Lancet Healthy Longev.* 2024

PAF Hearing Impairment = 7.2%

15 included studies
Objective & Self-reported hearing impairment
Most studies had a mean age >65 years

Lancet Commission on Dementia Prevention, Intervention, and Care 2024

HEARING AND DEMENTIA

Our aim was to examine the association of hearing impairment and hearing aid use in midlife with incident late-onset dementia (after 65 years) using data from the Whitehall II (WII) and UK Biobank (UKB) studies.

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Exposure

Whitehall II	**UK Biobank**
Self-reported Hearing impairment and aid	Self-reported Hearing impairment and aid
	Objective hearing impairment
Assessed at ≈56 years	Assessed at ≈56 years

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	Objective hearing impairment
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Outcome

Whitehall II	**UK Biobank**
All-cause dementia EHR	All-cause dementia EHR
Follow-up until March 2023 Median follow-up: 25 years	Follow-up until October 2022 Median follow-up: 14 years

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Covariates

Sociodemographic: age (as timescale), sex, ethnicity, living alone (marital status in the WII cohort) and education.
BMI and health-related behaviors (smoking, alcohol consumption, fruit and vegetable consumption, and physical activity).
Number of chronic conditions including coronary heart disease, stroke, hypertension, heart failure, diabetes, cancer, chronic kidney disease, chronic obstructive pulmonary disease, liver disease, depression, mental disorders, and arthritis or rheumatoid arthritis.

HEARING AND DEMENTIA

Table 2 Associations of reported hearing impairment and hearing aid use with incident dementia in the WII and UKB cohort studies

	No. of dementia cases (total)	Rate per 1,000 person-years (95% CI)	HR (95% CI)		
			Model 1[a]	Model 2[b]	Model 3[c]
WII[d,e]					
Hearing impairment					
No	519 (5,608)	4.09 (3.75, 4.46)	Reference	Reference	Reference
Yes	173 (1,446)	5.41 (4.66, 6.28)	1.15 (0.97, 1.37)	1.15 (0.96, 1.36)	1.14 (0.96, 1.35)
Hearing aid use					
No	666 (6,888)	4.29 (3.97, 4.63)	Reference	Reference	Reference
Yes	26 (166)	7.22 (4.92, 10.61)	1.06 (0.72, 1.58)	1.07 (0.72, 1.58)	1.05 (0.71, 1.55)
UKB[f,g]					
Hearing impairment					
No	3,190 (219,599)	1.09 (1.05, 1.13)	Reference	Reference	Reference
Yes	3,734 (158,294)	1.79 (1.74, 1.85)	**1.17 (1.11, 1.22)**	**1.15 (1.10, 1.21)**	**1.12 (1.07, 1.17)**
Hearing aid use					
No	6,399 (366,898)	1.32 (1.28, 1.35)	Reference	Reference	Reference
Yes	525 (10,995)	3.74 (3.43, 4.07)	**1.31 (1.20, 1.44)**	**1.30 (1.19, 1.42)**	**1.23 (1.12, 1.34)**
Pooled data					
Hearing impairment[h]	159,740 (384,947)	NA	**1.16 (1.11, 1.22)**	**1.15 (1.10, 1.21)**	**1.12 (1.07, 1.17)**
Hearing aid use[i]	11,161 (384,947)	NA	**1.30 (1.19, 1.42)**	**1.29 (1.18, 1.40)**	**1.22 (1.12, 1.33)**

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HEARING AND DEMENTIA

Table 3 PAFs for midlife hearing impairment

	Mean age (s.d.)	No. of men (%)	HR	Prevalence of exposure cases; total (%)	PAF (95% CI)[a]
Reported hearing impairment					
WII	55.9 (6.0)	4,973 (70.5)	1.14 (0.96, 1.35)	1,446; 7,054 (20.5)	2.79% (−0.82, 6.69)
UKB	56.2 (8.1)	179,650 (47.5)	**1.12 (1.07, 1.17)**	158,294; 377,893 (41.9)	4.79% (2.85, 6.65)
Pooled data[b]		184,623 (48.0)	**1.12 (1.07, 1.17)**	159,740; 384,947 (41.5)	4.74% (2.82, 6.59)
Concordant measures of hearing impairment (both reported and objective, UKB)					
Hearing impairment[c]	55.8 (8.3)	29,781 (44.1)	**1.27 (1.10, 1.47)**	7,560; 67,586 (11.2)	2.94% (1.11, 5.00)
Objective measure of hearing (UKB)					
SiN hearing impairment	56.5 (8.2)	54,852 (47.2)	**1.31 (1.17, 1.46)**	13,160; 116,256 (11.3)	3.38% (1.88, 5.10)

Bold formatting indicates statistical significance. HR values are calculated using cause-specific Cox regression.

[a] $\mathrm{PAF} = \frac{p(\mathrm{RR}-1)}{[1+p(\mathrm{RR}-1)]}$ where p is the prevalence of the exposure and RR is the relative risk of dementia due to that exposure. Because the prevalence of dementia is <10%, HR was used as a proxy of RR.

[b] HR is calculated using fixed-effects meta-analysis as no heterogeneity was found ($I^2 = 0.00\%$; $Q = 0.04$; and P for Q statistic = 0.85).

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HEARING AND DEMENTIA

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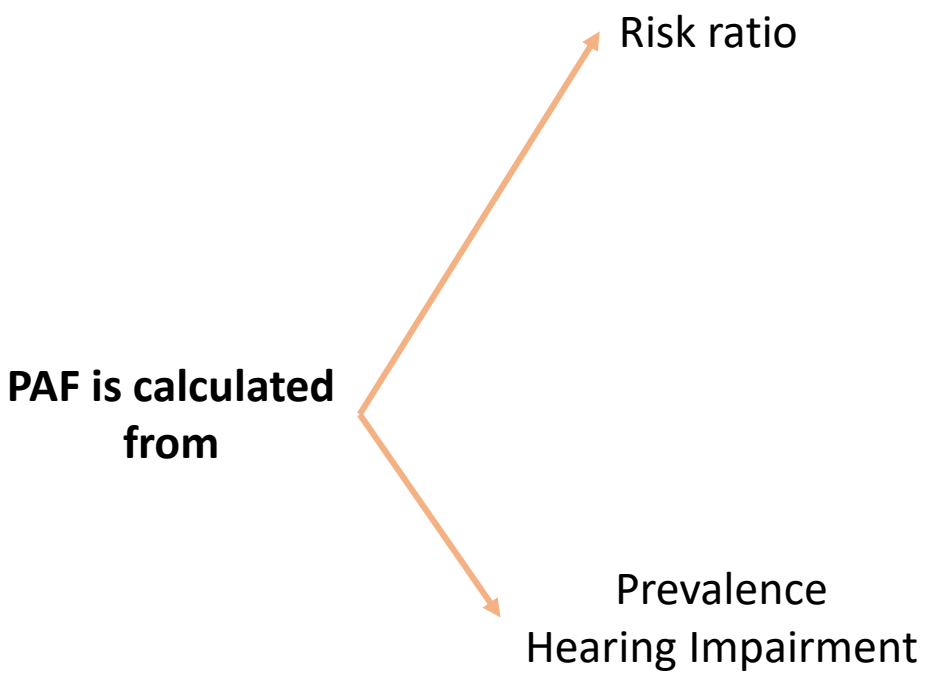
HEARING AND DEMENTIA



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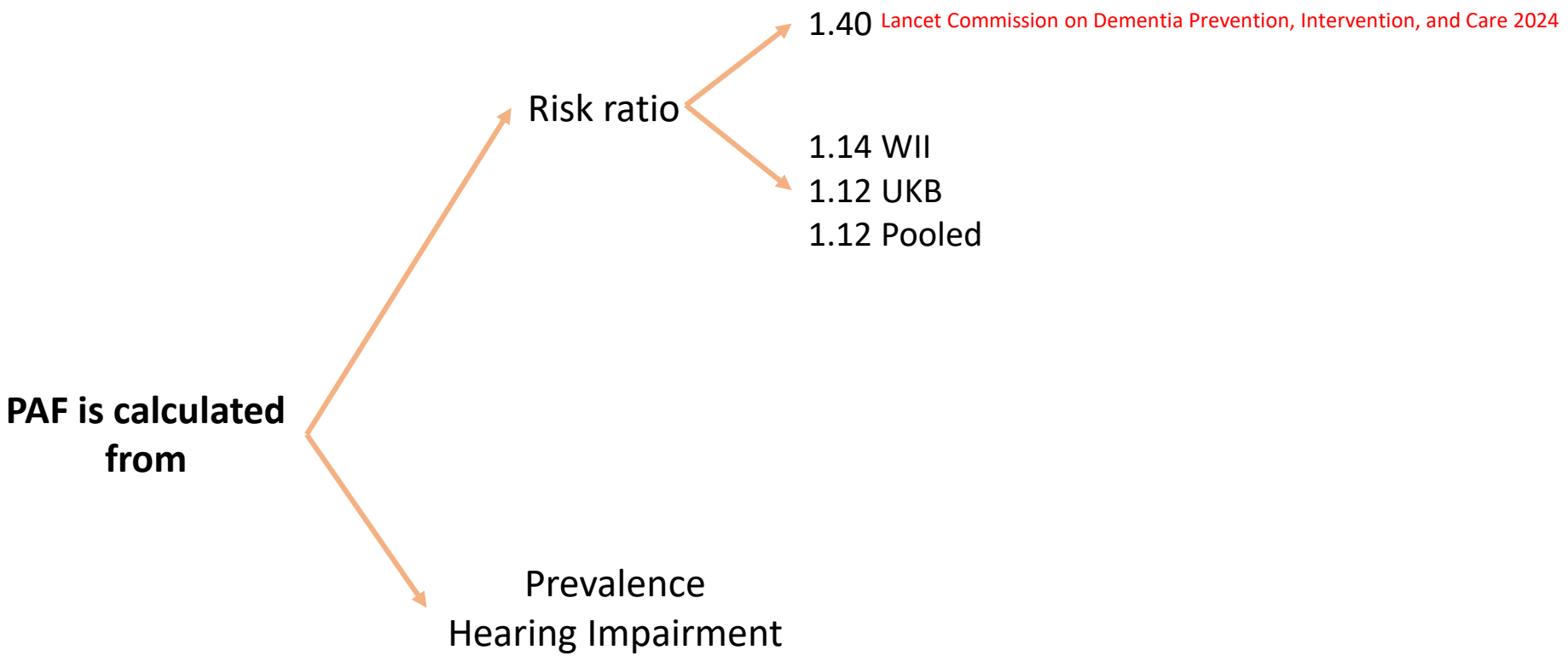

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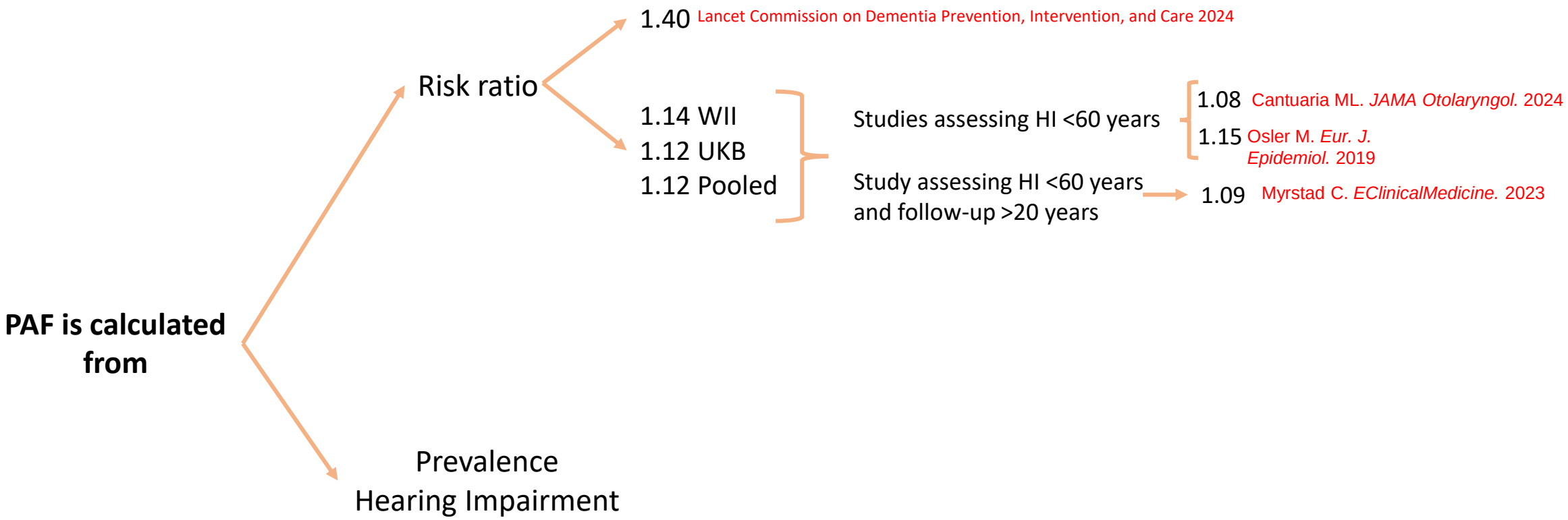

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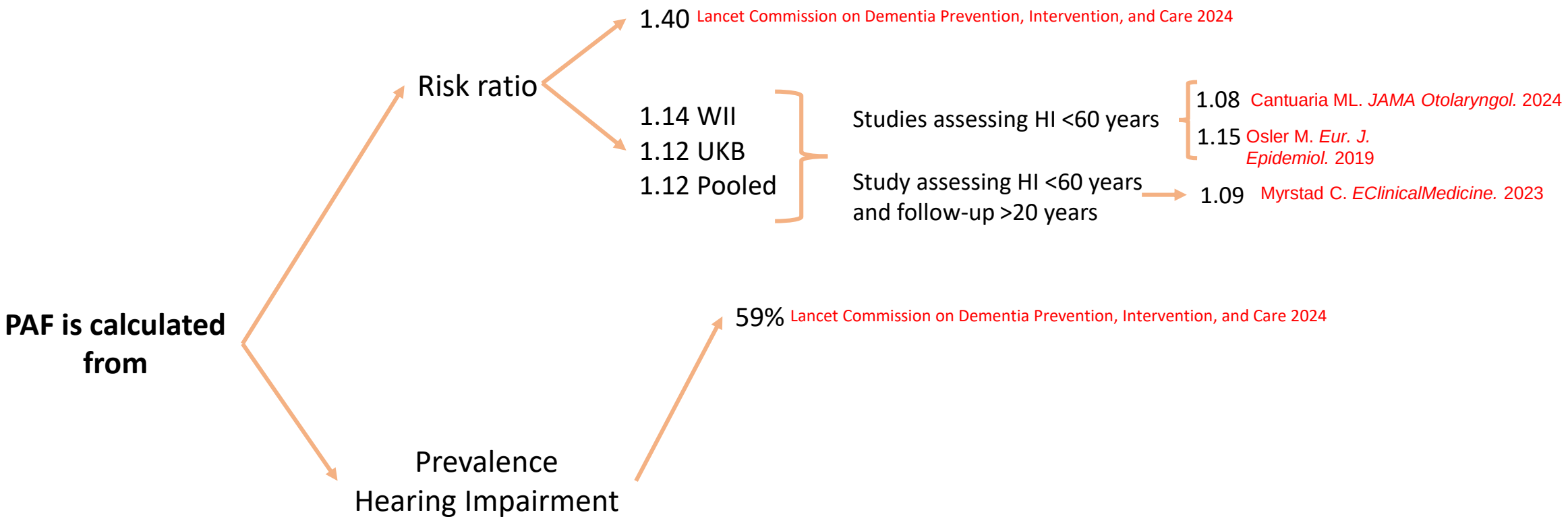

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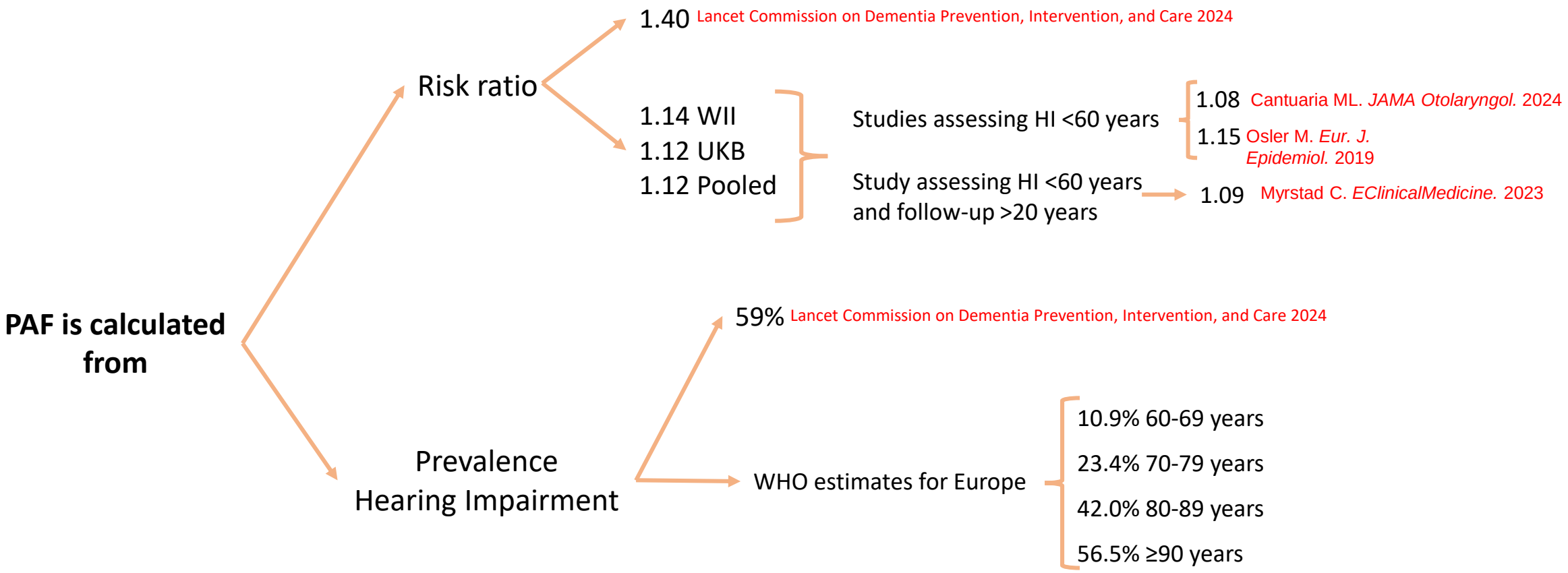

HEARING AND DEMENTIA

PAF is calculated from

- Risk ratio
  - 1.40 Lancet Commission on Dementia Prevention, Intervention, and Care 2024
  - 1.14 WII
    1.12 UKB
    1.12 Pooled
    - Studies assessing HI <60 years
      - 1.08 Cantuaria ML. *JAMA Otolaryngol.* 2024
      - 1.15 Osler M. *Eur. J. Epidemiol.* 2019
    - Study assessing HI <60 years and follow-up >20 years → 1.09 Myrstad C. *EClinicalMedicine.* 2023
- Prevalence Hearing Impairment
  - 59% Lancet Commission on Dementia Prevention, Intervention, and Care 2024
  - WHO estimates for Europe
    - 10.9% 60-69 years
    - 23.4% 70-79 years
    - 42.0% 80-89 years
    - 56.5% ≥90 years
  - 18.9% in WII
    37.2% in UKB
    - In participants <60 years → 14.8% Myrstad C. *EClinicalMedicine.* 2023
  - 20.5% in WII
    41.9% in UKB
    - In the total sample
  - 11.3% in UKB → Objective Hearing Impairment

HEARING AND DEMENTIA

	Unweighted PAF	Weighted PAF
Lancet Commission on Dementia Prevention, Intervention, and Care 2024	19.1%	7.2%
Stephan BCM. *Lancet Healthy Longev.* 2024	15.6%	7%
Reported Hearing Impairment (Pooled)	4.7%	
Concordant Hearing Impairment (UKB)	2.9%	
Objective Hearing Impairment (UKB)	3.4%	

HEARING AND DEMENTIA

- Age at measurement of hearing impairment (for prevalence), and the length of follow-up (to exclude reverse causation) play a role in estimates of PAF for late-onset dementia.

- Our findings suggest a modest association between midlife hearing impairment and incident dementia, and do not support the unweighted PAF estimates of 15.6% and 19.1% in recent meta-analyses, in which the results on both the risk ratio and prevalence of hearing impairment are based primarily on data on older adults.

- Although our findings suggest weaker associations than those in recent meta-analyses, they do not refute a potential link between hearing impairment and dementia.

CONCLUSIONS

Age is not just a covariate; it is central to dementia research

- **Follow-up matters:** short follow-up can capture preclinical dementia rather than causal risk.
- **Repeated measures matter:** trajectories can reveal patterns missed by single assessments.
- **Methods matter:** observational studies must explicitly address age, reverse causation and competing risk
- **Timing matters:** risk factors may have different meanings in midlife and late life.

Take-home message:
In dementia epidemiology, when we measure risk factors may be as important as what we measure.

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