The role of prevention, environment and social norms in brain health:

What have we learned from small deeply-phenotyped samples and multi-country population-based cohorts?

Prof. Anja Leist, University of Luxembourg
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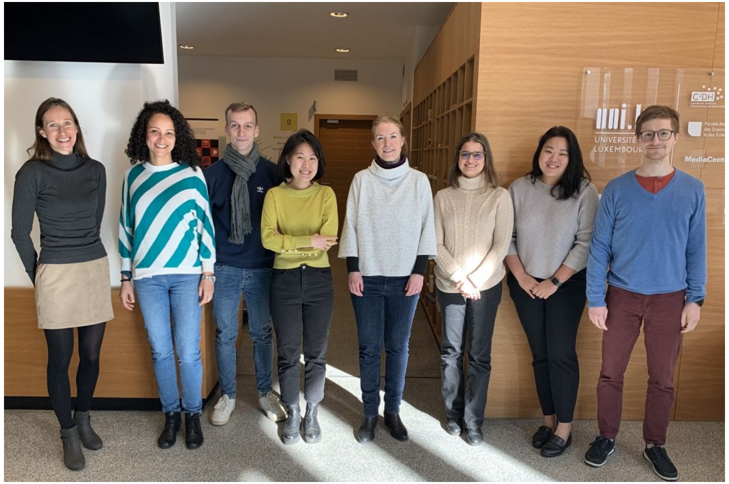
European Research Council
Established by the European Commission

An overview of 5+ years of research in the CRISP project
January 2019 to July 2024



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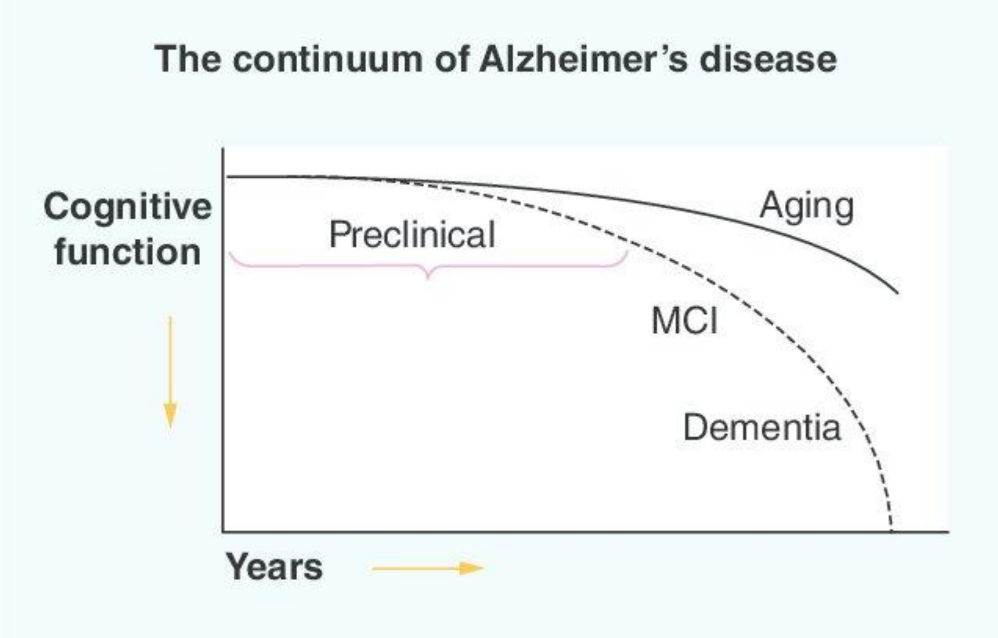
The course of cognitive decline - inevitable?



- Globally, more than 55 million people living with dementia, with an additional 10 million newly affected each year[1]
- 2020: Modifiable factors estimated to contribute 40%, while genetic risk contributes ca. 7%[2]
- 2023: First drugs to slow cognitive decline or improve ADLs received FDA approval[3]
- Prevention, particularly primordial, safer and likely to be more cost-effective

Figure credit: DOI: 10.2217/bmm.14.42
[1]https://www.who.int/news-room/fact-sheets/detail/dementia
[2]doi: 10.1016/S0140-6736(20)30367-6
[3]10.14283/jpad.2024.37

The role of context in cognitive ageing and dementia

The role of context and the social determinants of health

- Socioeconomic inequalities, i.e. deprivation
- Inequality of educational opportunity
- Gender inequalities

Social determinants of risk for dementia

UK Biobank: N=196,368 participants 60+, European ancestry

2006-10 initial assessment, follow-up until 2016-17

Dementia ascertained through hospital or death records

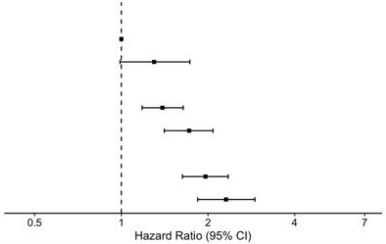
Polygenic risk score for developing dementia: Quintiles 1 (low), 2-4 (moderate), 5 (high genetic risk)

Townsend Deprivation Index

Figure 1. Risk of Incident Dementia for A Area-level and B Individual-level Socioeconomic Deprivation with Genetic Risk

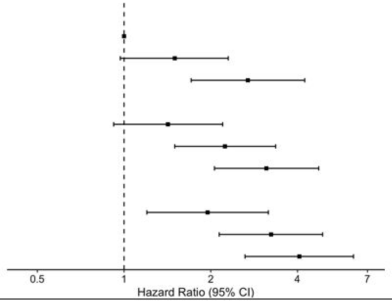
A Area-level Socioeconomic Deprivation

Subgroup	Total No.[a]	No. Dementia Cases / Person-Years[a]	HR (95% CI)	P Value
Low Genetic Risk				
Low-to-Moderate Deprivation	31,648	177 / 249,647	1 [Reference]	
High Deprivation	7,626	70 / 59,124	1.30 (0.99-1.73)	.06
Intermediate Genetic Risk				
Low-to-Moderate Deprivation	94,316	744 / 744,724	1.39 (1.18-1.64)	<.001
High Deprivation	23,505	294 / 182,389	1.72 (1.41-2.08)	<.001
High Genetic Risk				
Low-to-Moderate Deprivation	31,131	345 / 246,144	1.96 (1.63-2.35)	<.001
High Deprivation	8,142	139 / 63,285	2.31 (1.84-2.91)	<.001



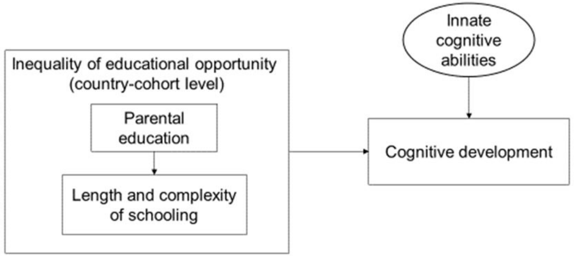
B Individual-level Socioeconomic Deprivation

Subgroup	Total No.[a]	No. Dementia Cases / Person-Years[a]	HR (95% CI)	P Value
Low Genetic Risk				
Low Deprivation	8,110	25 / 63,790	1 [Reference]	
Intermediate Deprivation	23,624	134 / 186,093	1.50 (0.97-2.30)	.07
High Deprivation	7,540	88 / 58,887	2.69 (1.71-4.24)	<.001
Intermediate Genetic Risk				
Low Deprivation	23,417	103 / 184,307	1.42 (0.92-2.20)	.12
Intermediate Deprivation	70,774	614 / 558,529	2.24 (1.50-3.36)	<.001
High Deprivation	23,630	321 / 184,276	3.12 (2.06-4.74)	<.001
High Genetic Risk				
Low Deprivation	7,747	46 / 61,124	1.95 (1.20-3.17)	.01
Intermediate Deprivation	23,423	294 / 184,928	3.24 (2.14-4.89)	<.001
High Deprivation	8,103	144 / 63,377	4.06 (2.63-6.26)	<.001



Klee, M., Leist, A. K., Veldsman, M., Ranson, J. M., & Llewellyn, D. J. (2023). Socioeconomic deprivation, genetic risk and incident dementia. *American Journal of Preventive Medicine.* doi: 10.1016/j.amepre.2023.01.012

The role of schooling



Participants to the Survey of Health, Ageing and Retirement in Europe: 25,544 women, 20,904 men with 2-6 assessments, three 10-year birth cohorts born after 1940

Cognition: Immediate and delayed recall, verbal fluency

Inequality of educational opportunity data from the World Bank Global Database on Intergenerational Mobility

Controlling for range of contextual- and individual-level confounders

Associations of level of IEO on level of and rate of change in three cognitive measures in stratified multilevel (mixed-effects) models.

	Women			Men		
	Immediate recall	Delayed recall	Verbal fluency	Immediate recall	Delayed recall	Verbal fluency
	Coeff. (CI)	Coeff. (CI)	Coeff. (CI)	Coeff. (CI)	Coeff. (CI)	Coeff. (CI)
(Intercept)	−0.27 *** (−0.34 to −0.19)	−0.20 *** (−0.28 to −0.12)	−0.29 *** (−0.39 to −0.19)	−0.30 *** (−0.37 to	−0.26 *** (−0.33 to −0.19)	−0.25 *** (−0.35 to −0.16)
IEO	−1.23 ** (−1.97 to −0.48)	−0.97 * (−1.78 to −0.16)	−1.77 ** (−2.84 to −0.70)	−0.94 ** (−1.50 to −0.38)	−0.60 (-1.20 to −0.00)	−1.79 *** (−2.74 to −0.84)
IEO*age	0.17 * (0.02–0.32)	−0.17 * (−0.32 to −0.02)	−0.39 *** (−0.53 to −0.24)	0.48 *** (0.32–0.65)	0.01 (-0.16 – 0.18)	−0.16 (-0.32 – 0.01)

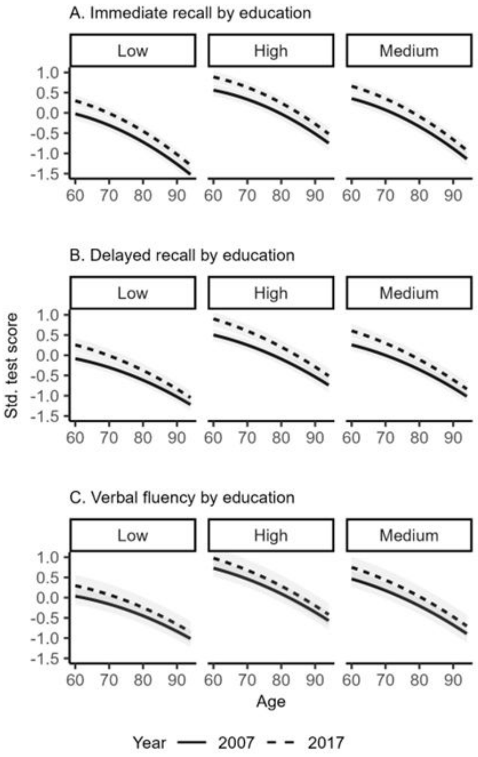
Leist, A. K., Bar-Haim, E., & Chauvel, L. (2021). Inequality of educational opportunity at time of schooling predicts cognitive functioning in later adulthood. *SSM - Population Health*, doi: 10.1016/j.ssmph.2021.100837

The Flynn effect 2007-2017

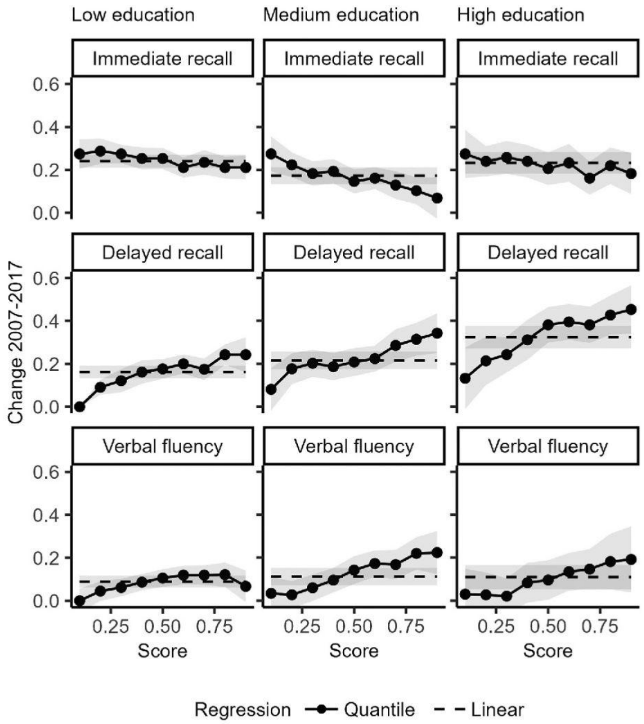
N=32,773 SHARE respondents from 12 countries, aged 60-94 years

Cognitive performance of individuals at similar ages compared 10 years apart

General cohort gains 2007-2017



Gains across performance levels 2007-2017



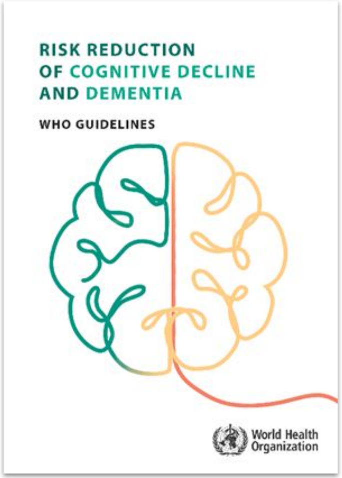
Rehnberg, J., Fors, S., Ford, K. J., Leist, A. K. (2024). Cognitive performance trends among European older adults: exploring variations across cohorts, gender, and educational levels (2007-2017). *BMC Public Health*. doi:10.1186/s12889-024-19123-3

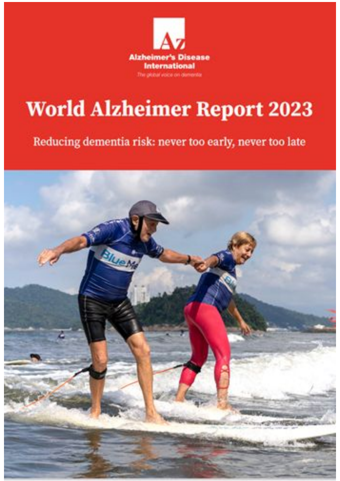
The role of gender-role norms and gender inequalities

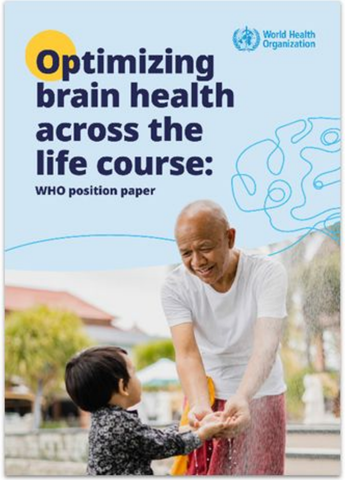
- The role of gender-role attitudes (“when jobs are scarce…”, “...cut down paid work for sake of family”) and employment biographies[1]
- The role of gender inequalities for dementia risk playing out through lower-quality nutrition, teenage pregnancy, limited education and career opportunities of women in Latin American countries[2]

[1] Bertogg., A., & Leist, A. K. (2023). Gendered life courses and cognitive functioning in later life: The role of gender norms and employment biographies. *European Journal of Ageing*. doi: 10.1007/s10433-023-00751-4
[2] Ribeiro, F., Crivelli, L., & Leist, A. K. (2023). Gender inequalities as contributors to dementia in Latin America and Caribbean Countries: what factors are missing from research? *The Lancet Healthy Longevity*. doi: 10.1016/S2666-7568(23)00052-1

The role of modifiable risk factors in cognitive ageing and dementia







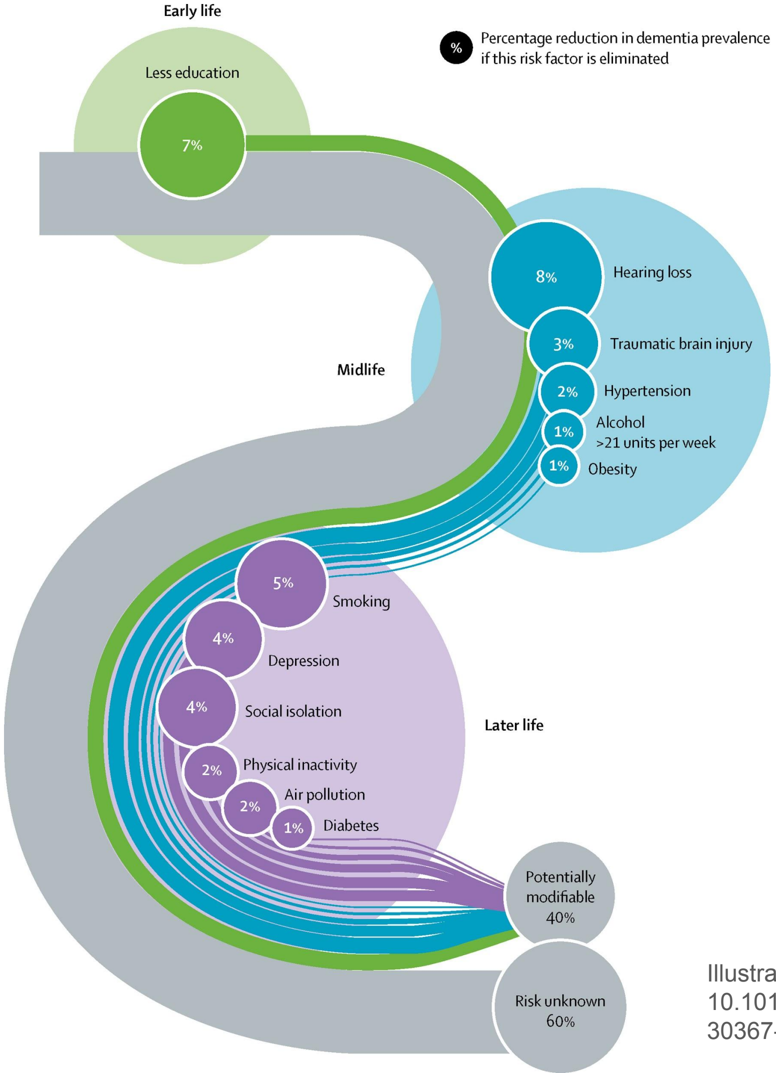
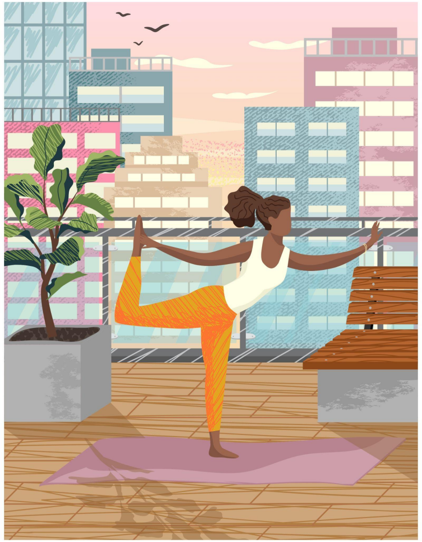


Illustration credit: doi: 10.1016/S0140-6736(20)30367-6

Modifiable risk factors in dementia - potential for prevention



Sex/gender differences in (modifiable) risk burden and dementia risk

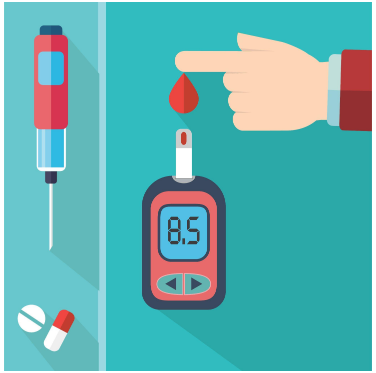
- Differences in risk burden, but no differences in risk factor-outcome relationships for risk of dementia in the English Longitudinal Study on Ageing[1]
- Meta-analysis: Increased dementia risk in women due to higher life expectancy and fewer educational and occupational opportunities in Latin America; further vulnerable groups low-educated and rural residents[2]

[1]Geraets, A. F. J., & Leist, A. K. (2023). Sex/gender and socioeconomic differences in modifiable risk factors for dementia. *Scientific Reports*, *13*(80). doi: 10.1038/s41598-022-27368-4
[2]Ribeiro, F., Teixeira-Santos, A. C., Caramelli, P., & Leist, A. K. (2022). Systematic review and meta-analyses on the prevalence of dementia in Latin America and Caribbean countries: Exploring sex, rurality, age, and education as possible determinants. *Aging Research Reviews*, *81*, 101703. doi: 10.1016/j.arr.2022.101703

The role of glycemia in menopausal factors

- Age at natural menopause, occurrence of bilateral oophorectomy, hysterectomy and age at surgery (n=147,119 women; mean±SD age 55.2 ±8.0 years at baseline)
- Glycemia assessed through fasting glucose levels and HbA1c
- Incident dementia assessed through hospital and death records

Mediation of early age at natural menopause and incident dementia only through HbA1c (4.7%).



Early and surgical menopause linked to less favourable glycemia markers.

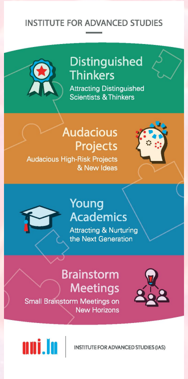
Geraets, A.F.J., Ford, K.J., May, P., Kidd, E.J., Leist, A.K. The associations of age at menopause, bilateral oophorectomy, and hysterectomy with glycemia and risk of dementia. Tentatively accepted at *Social Science & Medicine*.

The role of the gut microbiome

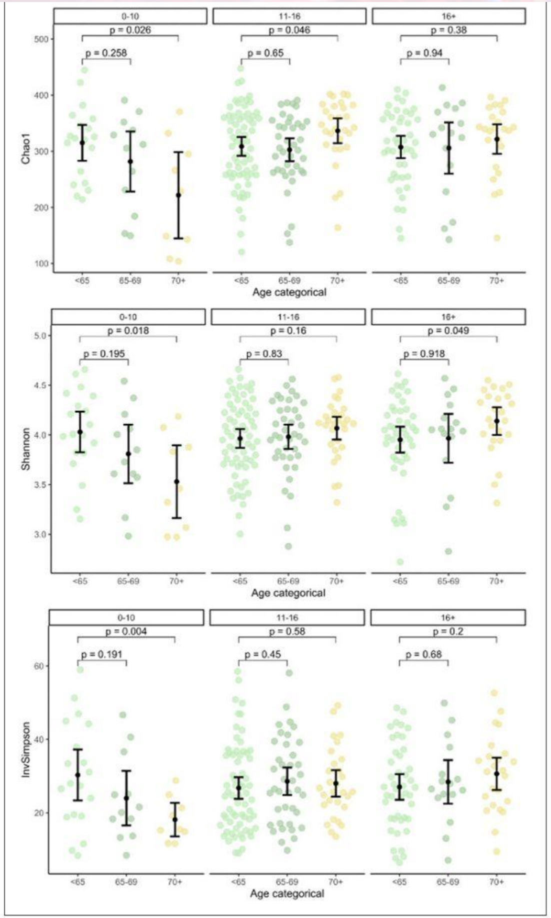
N=258 participants of the LUXPARK study without PD with and without Mild Cognitive Impairment

Test of gut microbiome diversity and differential abundance.

No mediation of the link between education and MCI, but education-specific microbiome signatures.



Klee, M., Aho, V. T. E., May, P., Heintz-Buschart, A., Landoulsi, Z., Jónsdóttir, S. R., Pauly, C., Pavelka, L., Delacour, L., Kaysen, A., Krüger, R., Wilmes, P., Leist, A. K., on behalf of the NCER-PD Consortium (2024). Education as risk factor of mild cognitive impairment: the link to the gut microbiome. *Journal of Prevention of Alzheimer's Disease*. doi: 10.14283/jpad.2024.19; Joint output for CRISP and IAS-AUDACITY MCI-BIOME



Note. Panels show alpha diversity stratified by age and education groups with 0-10, 11-16 and 16+ years of education. Reported P values refer to Student's t-Tests. InvSimpson = Inverse Simpson. Author MK.

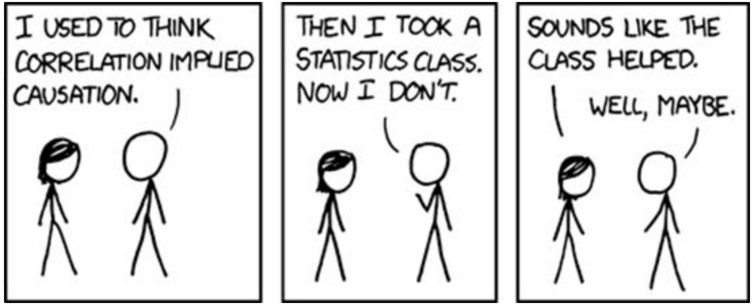
Some words on methods in cohort/panel studies

Using new methods to improve accuracy of detecting ‘probable’ dementia

- Validation of a dementia algorithm in the European SHARE (n=140,000 respondents), detection of ‘probable dementia’ without clinical assessment, reduced underreporting from 61.0 (95% CI, 53.3–68.7%) to 30.4% (95% CI, 19.3–41.4%)[1]
- Use of transfer learning to improve accuracy of dementia estimation for Blacks (Brier 0.049 vs. 0.061; AUC 0.84 vs. 0.81; AUPRC 0.52 vs. 0.39) and Hispanics (improved model calibration) in the U.S. HRS[2]

[1]Klee, M., Langa, K. M., & Leist, A. K. (2024). Performance of probable dementia classification in a European multi-country survey. *Scientific Reports.* doi: 10.1038/s41598-024-56734-7
[2]Kim, J. H., Langa, K. M., Glymour, M. M., Leist, A. K. Improving accuracy in the estimation of probable dementia in racially and ethnically diverse groups with penalized regression and transfer learning. *Under review*.

Description - Prediction - Causal inference



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RESEARCH METHODS

Mapping of machine learning approaches for description, prediction, and causal inference in the social and health sciences

Anja K. Leist[1]*, Matthias Klee[1], Jung Hyun Kim[1], David H. Rehkopf[2], Stéphane P. A. Bordas[3], Graciela Muniz-Terrera[4,5], Sara Wade[6]

Machine learning (ML) methodology used in the social and health sciences needs to fit the intended research purposes of description, prediction, or causal inference. This paper provides a comprehensive, systematic meta-mapping of research questions in the social and health sciences to appropriate ML approaches by incorporating the necessary requirements to statistical analysis in these disciplines. We map the established classification into description, prediction, counterfactual prediction, and causal structural learning to common research goals, such as estimating prevalence of adverse social or health outcomes, predicting the risk of an event, and identifying risk factors or causes of adverse outcomes, and explain common ML performance metrics. Such mapping may help to fully exploit the benefits of ML while considering domain-specific aspects relevant to the social and health sciences and hopefully contribute to the acceleration of the uptake of ML applications to advance both basic and applied social and health sciences research.

INTRODUCTION

Compared to many traditional statistical methods and with increasing availability of large datasets of relevance to the social and health sciences, machine learning (ML) methods have the potential to considerably improve aspects of empirical analysis. This includes advances in prediction, by fast processing of large amounts of data; in detecting nonlinear and higher-order relationships between exposures and confounders; and in improving accuracy of prediction. However, uptake of ML approaches in social and health research, spanning from sociology, psychology, and economics to social and clinical epidemiology and public health, has been rather slow and remains fragmented to this date. We argue that this is, in part, due to a lack of communication between the disciplines, the limited incorporating of domain knowledge into analytical approaches in the social and health sciences, and a lack of accessible overviews of ML approaches fitting the research goals in the social and health sciences.

The aims of this paper are to provide a high-level, nontechnical toolbox of ML approaches through the systematic mapping of research goals in the social and health sciences to appropriate ML methods; explain common metrics in ML; and point researchers to solutions to common problems in ML modeling. Our review focuses on research questions that involve datasets with human participants as research units and the analysis of clinically assessed or self-reported variables. In most studies in the social and health sciences using ML, we present here models that are trained on static datasets, that is, models are not continuously processing new data but rely on finite datasets from cohort studies or surveys after the end of data collection and cleaning.

[1]Department of Social Sciences, Institute for Research on Socio-Economic Inequality (IRSEI), University of Luxembourg, Esch-sur-Alzette, Luxembourg. [2]Department of Epidemiology and Population Health, Stanford University, Palo Alto, CA, USA. [3]Department of Engineering, University of Luxembourg, Esch-sur-Alzette, Luxembourg. [4]Centre for Dementia Prevention, University of Edinburgh, Edinburgh, UK. [5]Ohio University, Athens, OH, USA. [6]School of Mathematics, University of Edinburgh, Edinburgh, UK.
*Corresponding author. Email: anja.leist@uni.lu

Our review should be seen as complementary to introduction papers to ML in the fields of epidemiology and health research (*1*), psychology (*2*), and economics (*3*). For general introductions to statistical learning, interested readers are referred to excellent textbooks on these approaches (*4*, *5*).

The remainder of the review is organized as follows: The "Mapping research purposes in the social and health sciences to ML tasks" section outlines the main task of mapping research purposes in the social and health sciences to appropriate ML approaches. The "Basics of ML" section covers the basics of ML, specifically traditional ML categorizations, data preparation, model building, and "real-world" applications of ML. The next sections describe the mapping of ML approaches to research purposes of description, prediction, and causal inference, mapping appropriate ML methods and giving empirical examples. The "ML performance metrics" section gives an overview of ML performance metrics. The "Looking forward" section closes with an outlook.

MAPPING RESEARCH PURPOSES IN THE SOCIAL AND HEALTH SCIENCES TO ML TASKS

Common research purposes in the social and health sciences can be categorized, in a nutshell, as researchers' intentions to (i) describe phenomena, (ii) predict social or health outcomes, and (iii) find causes of and possibilities to intervene to improve these outcomes. We will, over the course of this review, present in more detail specific research questions related to description, prediction, and causal inference (*6*), even if not all research questions allow these strict distinctions. We will map these research questions to appropriate ML methods, using empirical studies as illustration where possible.

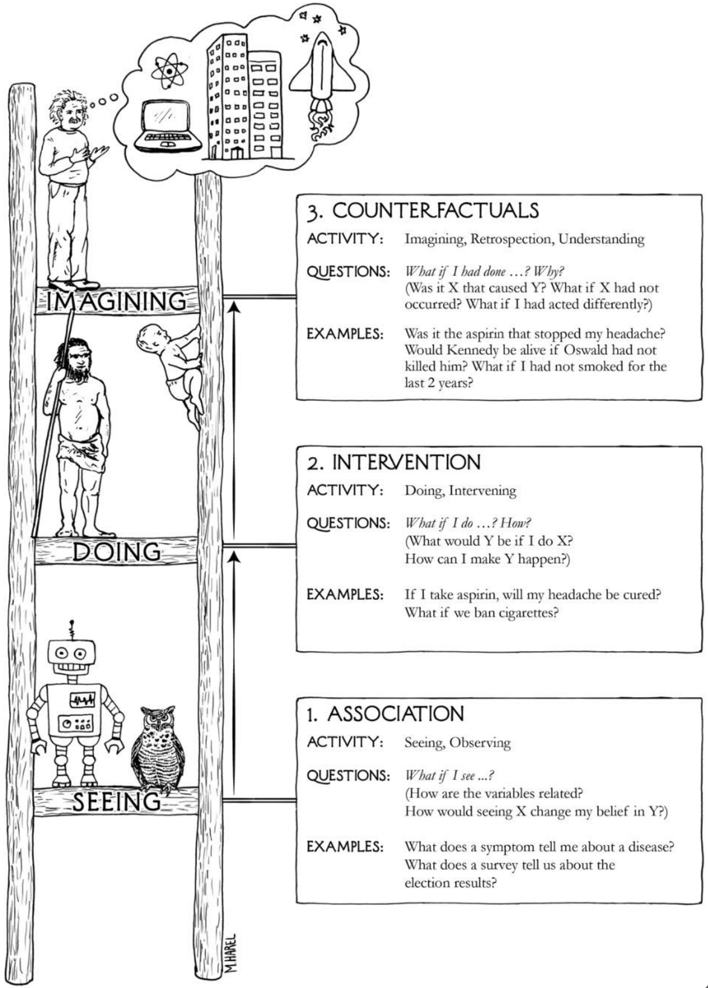
Methods summarized as ML in this review represent different traditions of data analysis, e.g., inferential statistics, statistical learning, and computational sciences. Their common denominator is the ability to process large amounts of data, while model building and model selection decisions are more driven by the data structure (data-driven) than in traditional inferential statistics.

Leist, A. K., Klee, M., Kim, J. H., Rehkopf, D. H., Bordas, S. P. A., Muniz-Terrera, G., & Wade, S. (2022). Mapping of machine learning approaches for description, prediction, and causal inference in the social and health sciences. *Science Advances*. *8*(42). doi: 10.1126/sciadv.abk1942

Using new methods to get closer to causal inference

Rungs of Judea Pearl's causal ladder:

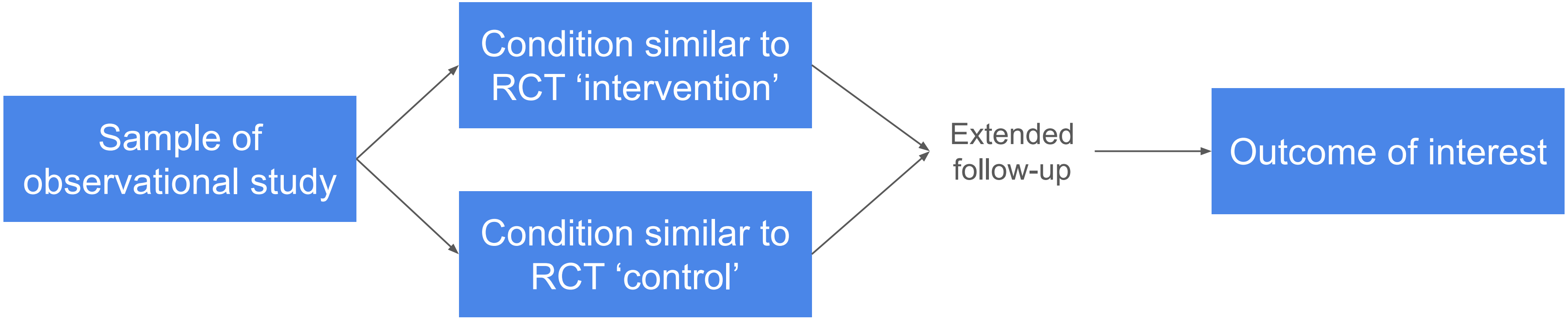
- Estimate associations (descriptive)
- Do an intervention
- Imagine counterfactuals



Pearl, J., & Mackenzie, D. (2018). The Book of Why: the new science of cause and effect. Basic books.

And how we applied this thinking

…by ‘emulating’ trials inspired by Miguel Hernán



And how we applied this thinking

…to test the role of working after age 65+ for cognitive functioning and other health outcomes

Sample of observational study

Eligibility criteria, working histories

Condition similar to RCT ‘intervention’

Condition similar to RCT ‘control’

Extended follow-up

Outcome of interest

Kim, J.-H., Muniz-Terrera, G., & Leist, A. K. (2023). Does (re-)entering the labor market at advanced ages protect against cognitive decline? A panel-matching difference-in-differences approach. *Journal of Epidemiology and Community Health*, 77(10), 663-669. doi: 10.1136/jech-2022-220197

Korea: KLoSA, N=1,872

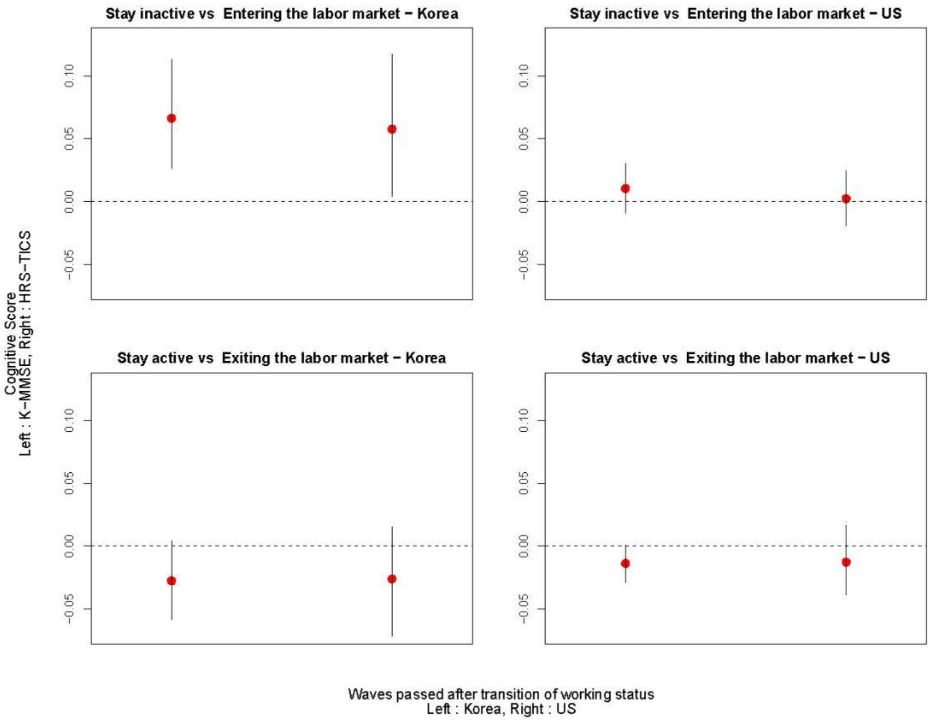
Cognitive functioning: K-MMSE

U.S.: HRS, N=4,070

Entering/exiting work after age 65

Cognitive functioning: Telephone Interview for Cognitive Status (TICS)

Matching difference-in-difference



Kim, J.-H., Muniz-Terrera, G., & Leist, A. K. (2023). Does (re-)entering the labor market at advanced ages protect against cognitive decline? A panel-matching difference-in-differences approach. *Journal of Epidemiology and Community Health*, 77(10), 663-669. doi: 10.1136/jech-2022-220197

And how we applied this thinking

…to test the role of hearing aids in hearing impairment for dementia risk

Sample of observational study

Eligibility criteria: hearing impairment

Condition similar to RCT ‘intervention’

Condition similar to RCT ‘control’

Extended follow-up

Outcome of interest

Mur, J., Klee, M., Solomon, A., Johnson, C., Littlejohns, T. J., Muniz-Terrera, G., Leist, A.K. A hypothetical intervention on the use of hearing aids for the risk of dementia in people with hearing loss in UK Biobank. Revise & resubmit at *American Journal of Epidemiology*.

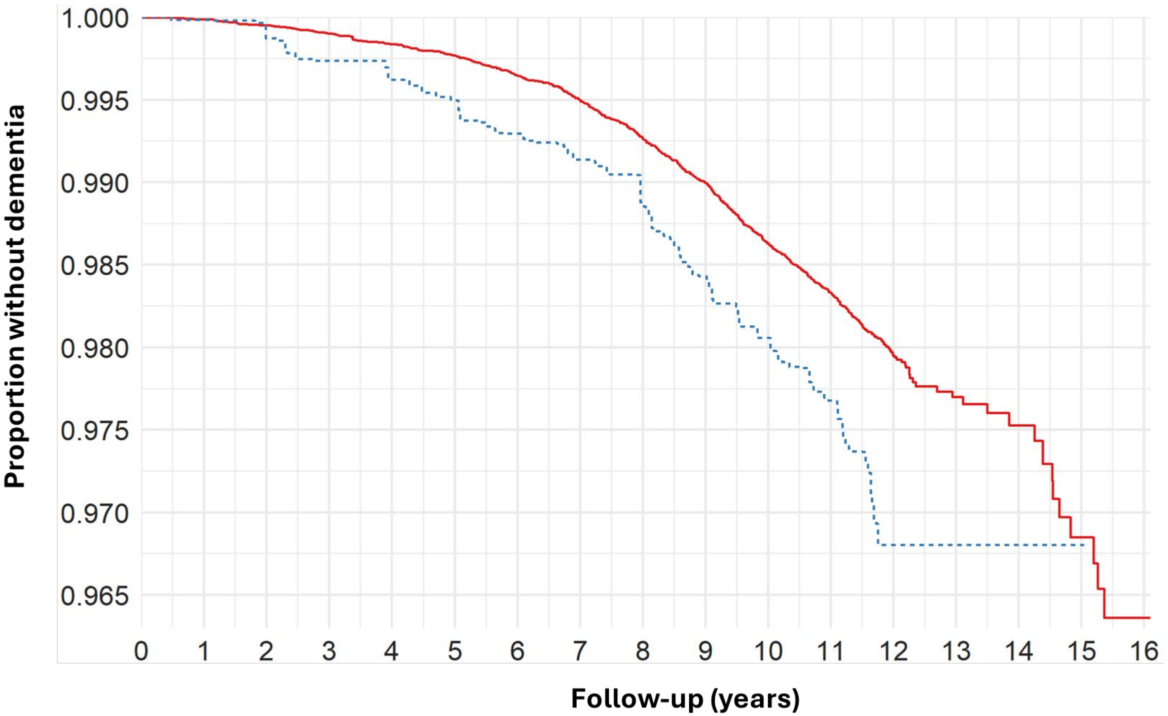
N=60,633 UKB participants with HL

N=4,063 (6.7%) HA users

Mean follow-up of 11.4 years

Dementia ascertained through hospital, death, primary care records

N=857 incident dementia; N=106 HA users (blue); N=751 non-users (red)



Mur, J., Klee, M., Solomon, A., Johnson, C., Littlejohns, T. J., Muniz-Terrera, G., Leist, A.K. A hypothetical intervention on the use of hearing aids for the risk of dementia in people with hearing loss in UK Biobank. Revise & resubmit at *American Journal of Epidemiology*.

Studies

Korean Longitudinal Study of Aging (KLoSA)

ELSA
English Longitudinal Study of Ageing

DE MAASTRICHT STUDIE

HRS HEALTH AND RETIREMENT STUDY

1946 National Survey of Health and Development

UKRI Medical Research Council

SHARE ERIC
SURVEY OF HEALTH, AGEING AND RETIREMENT IN EUROPE

uk biobank
Enabling scientific discoveries that improve human health

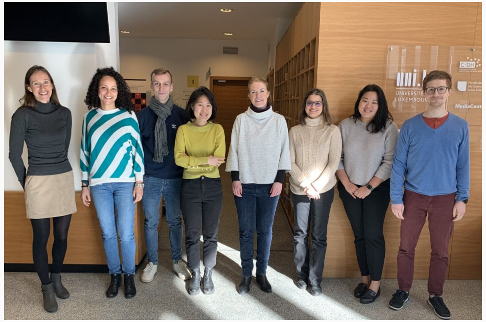
Your brain health matters

getbrainhealthy.org

The practical application of the CRISP project:

Get Brain Healthy: A platform to promote brain health at the workplace


Thank you



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Affiliated projects

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