Contextual and Individual Determinants of Cognitive Ageing and Dementia in a Global Perspective

Prof. Dr. Anja Leist, 14 February 2024

w/Dr. Fabiana Ribeiro, Dr. Anouk Geraets, Dr. Katherine Ford, Dr. Jason Settels, Jung Hyun Kim, MSc, Matthias Klee, MSc, Dr. Ariane Bertogg, and others

ECSR Network Workshop: Social Institutions and Cognitive Health in Older Age, U Hamburg

UNIVERSITÉ DU LUXEMBOURG

European Research Council
Established by the European Commission

Conflict of interest

Remunerated activities: consulting/speaking for Roche, December 2021, September 2022

CRISP
Cognitive Aging: From Educational Opportunities to Individual Risk Profiles

- Investigate the social and behavioral determinants of cognitive ageing and dementia
- Test contextual-level inequalities related to education, sex/gender, and socioeconomic conditions
- Use new methods for risk prediction and causal inference in observational data

Funded by the European Research Council (grant agreement no. 803239), 01/2019-07/2024

Structure of presentation

Moving from individual-level to contextual-level determinants of cognitive ageing and dementia

- Individual-level (modifiable) social and behavioural determinants
- Neighbourhood socioeconomic conditions
- Contextual determinants in a global perspective

Individual-level (Modifiable) Social and Behavioural Determinants

Why social and behavioral determinants of cognitive ageing and dementia?

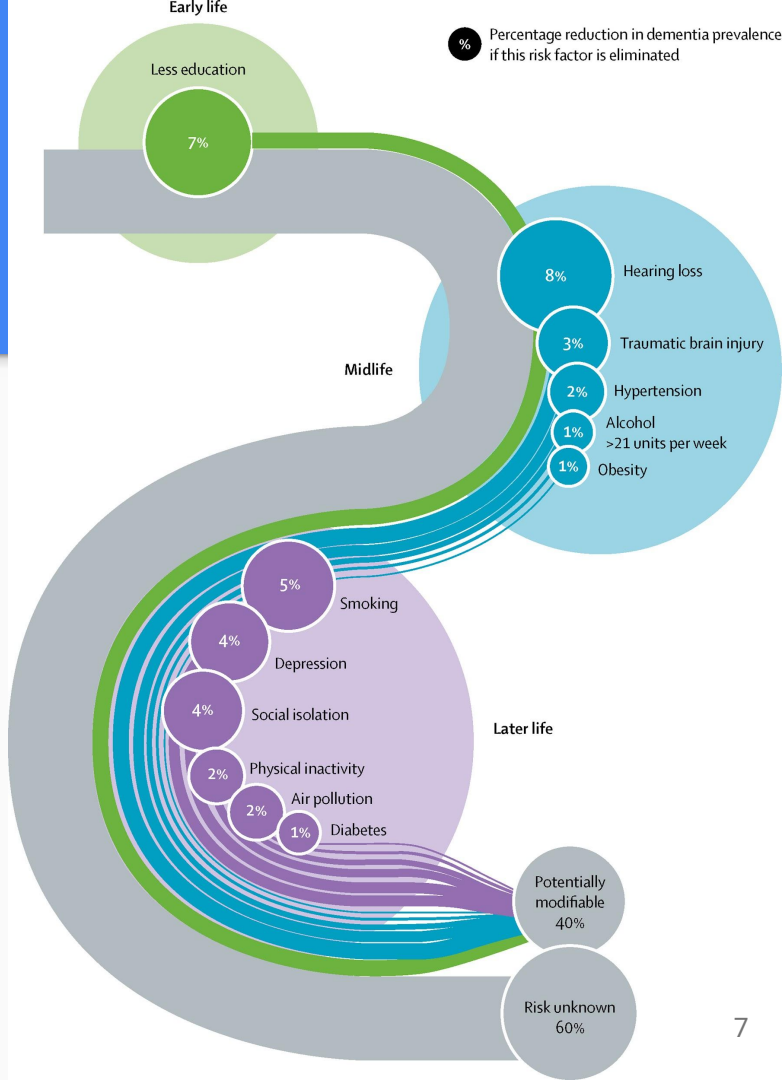
- Dementia: Range of conditions characterized by memory impairment.
- Cognitive impairment and dementia are among the great societal challenges of ageing societies
- Alzheimer medication has been shown to delay cognitive decline (van Dyck et al., 2022), but no cure (reversal) available once cognitive impairment is present.
- Modifiable social and behavioral risk factors explain up to 40% of all dementia cases (Livingston et al., 2020)
- Important to understand (1) dementia risk of vulnerable individuals and (2) potential for dementia prevention

van Dyck, C. H., Swanson, C. J., … & Iwatsubo, T. (2022). Lecanemab in Early Alzheimer's Disease. New England Journal of Medicine, NEJMoa2212948. https://doi.org/10.1056/NEJMoa2212948
Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., ... & Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, 396(10248), 413-446.

Modifiable dementia risk

Potentially modifiable risk factors account for up to 40% to all dementia diagnoses.

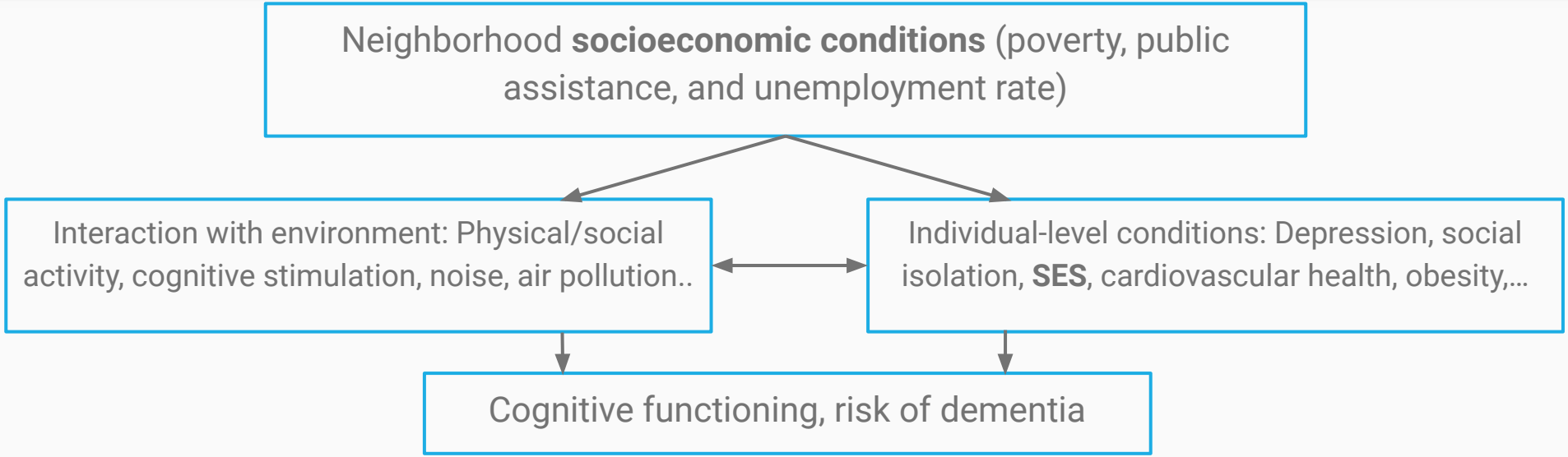
In comparison, genetic risk for dementia contributes to approximately 7% of all dementia diagnoses.



Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., ... & Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, 396(10248), 413-446.

Neighbourhood Socioeconomic Conditions

Why neighborhood socioeconomic disadvantage?



Clarke, P. J., Ailshire, J. A., House, J. S., Morenoff, J. D., King, K., Melendez, R., & Langa, K. M. (2012). Cognitive function in the community setting: the neighbourhood as a source of 'cognitive reserve'?. J Epidemiol Community Health, 66(8), 730-736.

Cadar, D., Lassale, C., Davies, H., Llewellyn, D. J., Batty, G. D., & Steptoe, A. (2018). Individual and area-based socioeconomic factors associated with dementia incidence in England: evidence from a 12-year follow-up in the English longitudinal study of ageing. JAMA psychiatry, 75(7), 723-732.

Do Changes in Neighborhood Conditions Go Along With Changes in Cognitive Functioning?

Jason Settels, PhD

Changes in neighborhood socioeconomic disadvantage?

- National Social Life, Health and Aging Project (NSAP) (*n* = 1837)
- Longitudinal design: wave 2 (2010-11), wave 3 (2015-16)

- Outcome: Montreal Cognitive Assessment adaptation (CCFM), executive function, visuo-construction skills, naming, memory, attention, language, abstract thinking, and orientation

Settels, J., & Leist, A. K. (2021). Changes in neighborhood-level socioeconomic disadvantage and older Americans' cognitive functioning. *Health & Place*, 68, 102510.

Changes in neighborhood socioeconomic disadvantage?

Neighborhood socioeconomic disadvantage:

- Poverty, public assistance, and unemployment rate
- Rates standardized and averaged; scores at wave 2 subtracted from scores at wave 3
- Census-tract level: 1,200-8,000 individuals, optimum size 4,000 individuals
- 598 census tracts, with 1 to 25 respondents per census tract

→ OLS regressions and mediation analyses

Settels, J., & Leist, A. K. (2021). Changes in neighborhood-level socioeconomic disadvantage and older Americans' cognitive functioning. *Health & Place*, 68, 102510.

Table 1. Mediating pathways.

Larger Variable	Component Variables
Community involvement	Volunteer work in the past year
	Attendance at meetings of organized groups in the past year
	Attendance at religious services
Size of close social network	–
Social support	Social support from family
	Social support from friends
Community social capital	–
Total household assets	–
Physical activity	–
Substance consumption	Alcoholic drinks per week
	Cigarettes per day
Depressive symptoms	–

Mediators between changes in neighborhood socioeconomic disadvantage and changes in cognitive functioning

Settels, J., & Leist, A. K. (2021). Changes in neighborhood-level socioeconomic disadvantage and older Americans' cognitive functioning. *Health & Place*, 68, 102510.

Table 2
Descriptive statistics for time-changing variables (N = 1837).

Variables	Wave 2		Wave 3		Change over Waves 2 and 3	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean/ %	Standard Deviation
Dependent Variable						
Cognitive Functioning (0–20)	15.26	3.15	14.58	3.54	−0.68	2.67
Independent Variable						
Neighborhood-Level Socioeconomic Disadvantage	−0.07	0.78	−0.09	0.77	−0.01	0.55
Mediating Variables						
Depressive Symptoms (1–4)	1.40	0.42	1.47	0.44	0.07	0.43
Close Social Ties (0–7)	4.60	1.50	4.19	1.31	−0.42	1.66
Physical Activity (0–5)	2.90	1.78	2.66	1.86	−0.24	1.94
Number of Alcoholic Drinks per Week	2.78	5.98	2.33	5.09	−0.45	4.23
Number of Cigarettes per Day	1.39	4.84	0.97	4.04	−0.41	3.02
Social Support from Family (0–3)	2.42	0.68	2.40	0.68	−0.01	0.76
Social Support from Friends (0–3)	2.03	0.83	1.98	0.78	−0.07	0.80
Logged Total Household Assets[1]	12.02	3.03	11.85	3.22	−0.13	2.81
Neighborhood Social Capital	0.04	0.56	0.05	0.56	0.01	0.51
Frequency of Volunteer Work in Past Year (0–6)	2.36	2.12	2.25	2.17	−0.12	1.78
Frequency of Attendance at Meetings of Organized Groups in Past Year (0–6)	2.89	2.12	2.77	2.20	−0.16	2.01
Frequency of Attendance at Religious Services (0–5)	2.67	1.77	2.57	1.77	−0.09	1.16
Control Variable						
Change in Census Tract						
Did not Change Census Tracts between Waves 2 and 3	–	–	–	–	82.47%	–
Changed Census Tracts between Waves 2 and 3	–	–	–	–	17.53%	–

[1] To adjust for inflation, amounts from wave 2 were multiplied by 1.086449 before being log transformed.

Settels, J., & Leist, A. K. (2021). Changes in neighborhood-level socioeconomic disadvantage and older Americans' cognitive functioning. *Health & Place*, 68, 102510.

Table 4
OLS regressions of change in cognitive functioning.

VARIABLES	Wave(s) of Assessment	Model 1	Model 2
Change in Census Tact-Level Socioeconomic Disadvantage	Change W2 to W3	−0.414* (0.172)	−0.337* (0.159)
Female (ref. male)	W2	−0.283 (0.150)	−0.191 (0.149)
Black (ref. White)	W2	0.236 (0.270)	0.336 (0.274)
Hispanic, Non-Black		0.953* (0.407)	0.812* (0.395)
Other		0.387 (0.341)	0.397 (0.336)
Census Tract Logged Population Density (Persons per Square Mile)	W2		−0.031 (0.050)
Census Tract Located in MSA (ref. Not Located in MSA)	W2		−0.021 (0.229)
Age	W2		−0.065*** (0.013)
Separated or Divorced (ref. Married or Living with a Partner)	W2		−0.329 (0.299)
Widowed			−0.123 (0.237)
Never Married			0.011 (0.476)
No Children (ref. Three or More Children)	W2		0.168 (0.297)
One or Two Children			−0.137 (0.166)
High School Diploma (ref. University Degree)	W2		−0.343* (0.172)
Less than High School Diploma			−0.120 (0.267)

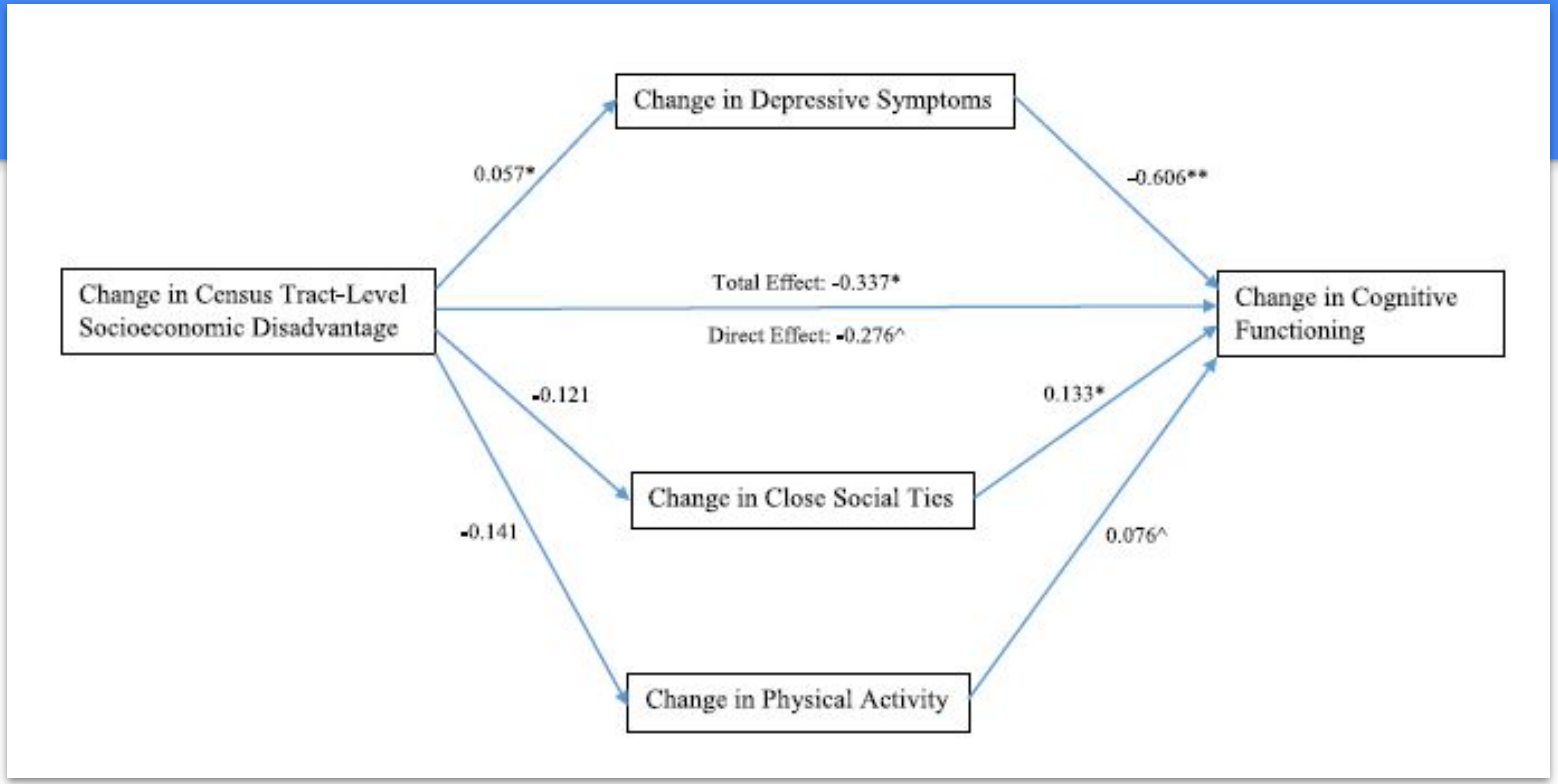
Main analyses

Increase in neighborhood socioeconomic disadvantage was associated with stronger declines in cognitive functioning

+ controlling for self-rated physical health, health problems, working for pay, length of residence in local area, changed census tract, participation in wave 1, census-tract level population density.

Settels, J., & Leist, A. K. (2021). Changes in neighborhood-level socioeconomic disadvantage and older Americans' cognitive functioning. *Health & Place*, 68, 102510.

Mediation analyses

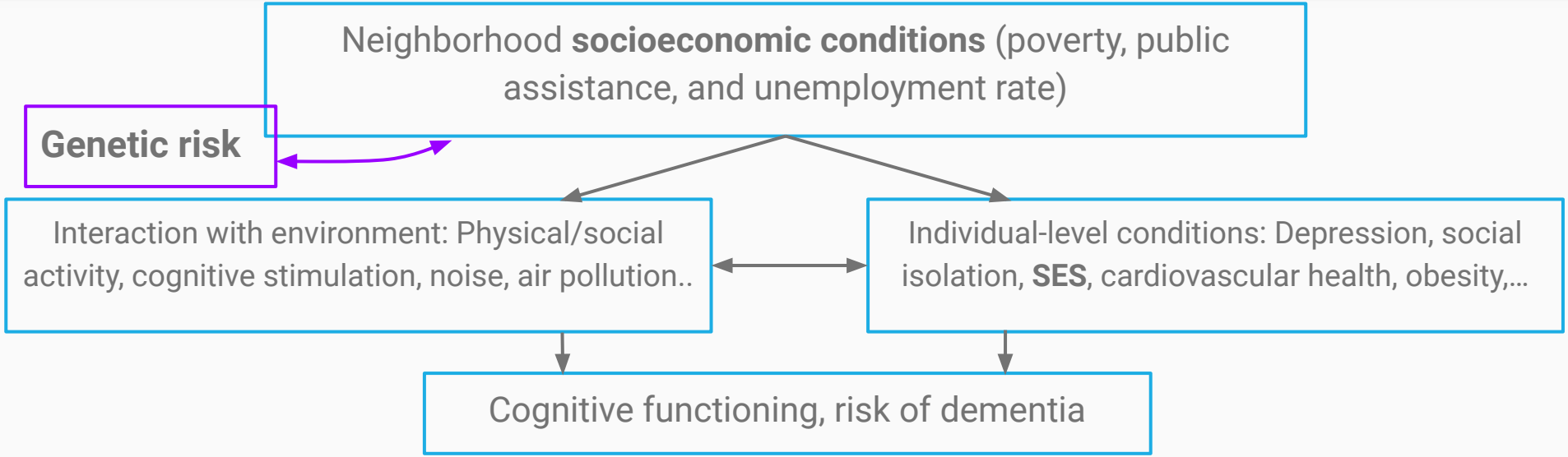


Settels, J., & Leist, A. K. (2021). Changes in neighborhood-level socioeconomic disadvantage and older Americans' cognitive functioning. *Health & Place*, 68, 102510.

Do Neighbourhood Socioeconomic Conditions Interact With Genetic Risk of Dementia?

Matthias Klee

Why neighborhood socioeconomic disadvantage?



Neighbourhood deprivation x genetic risk

- UK Biobank: 196,368 participants 60+, European ancestry
- Time-to-event design: 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)

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*. https://doi.org/10.1016/j.amepre.2023.01.012

Neighbourhood deprivation x genetic risk

Townsend Deprivation Index:

- Unemployment, home ownership, car ownership and household overcrowding rate
- From baseline assessment and national census output areas (40 to 125+ households)
- Quintiles 1-4 (low) compared against quintile 5 (high deprivation)

Individual-level socioeconomic deprivation: home, car ownership, housing type, annual household income

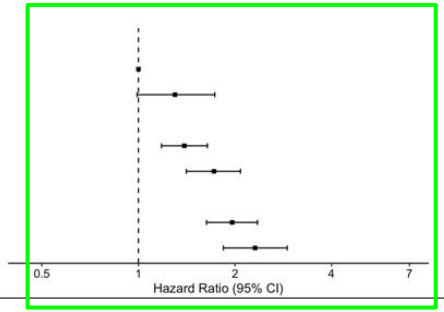
Klee, M., Leist, A. K., Veldsman, M., Ranson, J. M., & Llewellyn, D. J. (2023). Socioeconomic deprivation, genetic risk and incident dementia. *American Journal of Preventive Medicine*. https://doi.org/10.1016/j.amepre.2023.01.012
ONS. https://www.ons.gov.uk/methodology/geography/ukgeographies/censusgeography

Neighbourhood deprivation x genetic risk

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

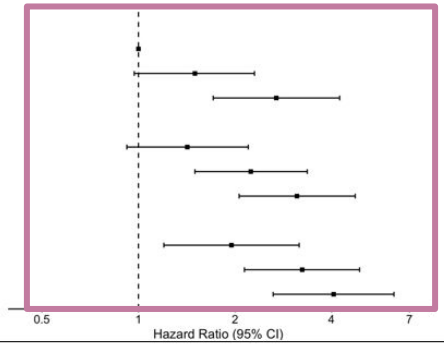
A Area-level Socioeconomic Deprivation

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



All Cox proportional-hazards regressions were adjusted for covariates relevant in polygenic risk analyses, age, sex, education, marital status, healthy lifestyle and depressive symptoms in last two weeks. Additionally, adjustments for individual-level (A) and area-level socioeconomic deprivation (B) were included.

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*. https://doi.org/10.1016/j.amepre.2023.01.012

Contextual Determinants in a Global Perspective

Why contextual-level inequalities in cognitive ageing and dementia?

Global variations in prevalence and determinants of cognitive ageing and dementia:

- Substantial **country-level variation** in population-based studies, difficult to exploit due to (necessary) variation in cognitive assessments
- **Sex/gender differences** in prevalence of dementia → impact of gender inequalities, e.g. gender-role attitudes (Bertogg & Leist, 2023)
- Cognitive development highly influenced by **schooling** → impact of schooling systems, educational opportunities (Leist, Bar-Haim, Chauvel, 2021)

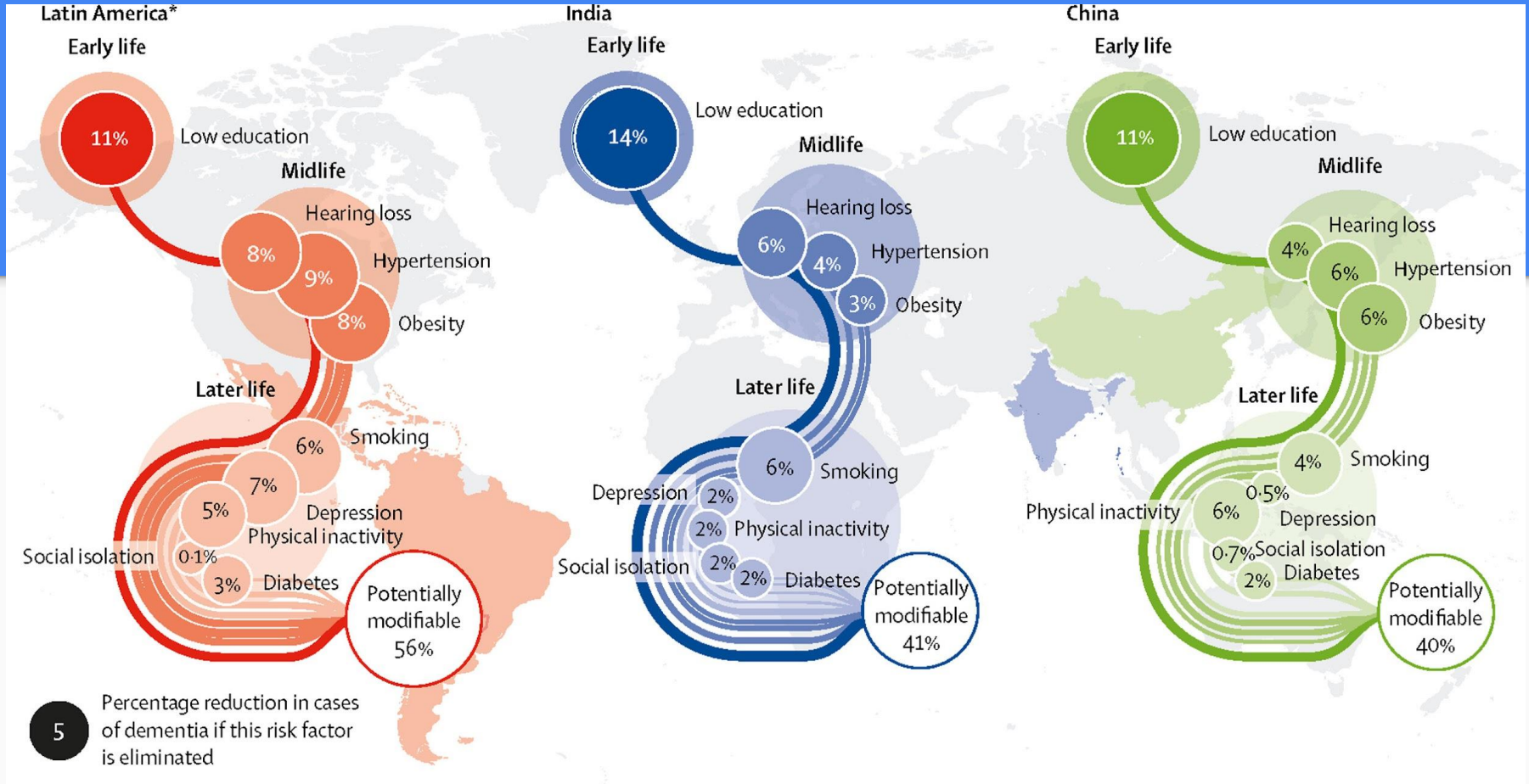
Bertogg., A., & Leist, A. K. (2023). Gendered life courses and cognitive functioning in later life: The role of gender norms and employment biographies. *European Journal of Ageing*. https://doi.org/10.1007/s10433-023-00751-4
Leist, A. K., Bar-Haim, E., & Chauvel, L. (2021). Inequality of educational opportunity at time of schooling predicts cognitive functioning in later adulthood. *SSM - Population Health*, doi: 10.1016/j.ssmph.2021.100837.

Cognitive impairment and dementia in different parts of the world

Country variation in prevalence and determinants of cognitive impairment and dementia

- Economic conditions and health systems
- Access to education
- Population health and life expectancy
- Access to nutrients vs. exposure to neurotoxins
- Gender inequalities

In a global perspective, data scarcity due to lacking clinical and research infrastructure create barriers to knowledge



Mukadam, N., Sommerlad, A., Huntley, J., & Livingston, G. (2019). Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. The Lancet Global Health, 7(5), e596-e603.

Background

- Compare dementia prevalence in lower-resource settings against prevalence in higher-resource settings[1-2]
- Secular trends in cognitive impairment prevalence in lower-resource settings against declining incidence of dementia in many high-income countries over the last two decades[3]
- Investigate the interplay between rising life expectancy, rising educational attainment, increases in cardiovascular risk and dementia prevalence in lower-resource settings[4]

[1]Ribeiro, F., Teixeira-Santos, A. C., & Leist, A. K. (2021). The prevalence of mild cognitive impairment in Latin America and the Caribbean: a systematic review and meta-analysis. *Aging & Mental Health*, https://doi.org/10.1080/13607863.2021.2003297
[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
[3]Wu, Y. T., ... & Brayne, C. (2017). The changing prevalence and incidence of dementia over time—current evidence. Nature Reviews Neurology, 13(6), 327-339.
[4]Ribeiro, F. S., Duarte, Y. A. d. O., Santos, J. L., F., & Leist, A. K. (2021). Changes in the prevalence of cognitive impairment and associated risk factors 2000-2015 in São Paulo, Brazil. BMC Geriatrics. https://doi.org/10.1186/s12877-021-02542-x

Secular Trends in Cognitive Impairment in Latin America and the Caribbean

Fabiana Ribeiro, PhD

Prevalence of mild cognitive impairment and dementia in LAC

- Prevalence of mild cognitive impairment in Latin America and the Caribbean higher than in high-income settings - relevant due to this being the group benefiting most from risk reduction efforts [1]
- Prevalence of dementia and mild cognitive impairment in Latin America and the Caribbean higher than in high-income settings; large geographical variation and few representative datasets [2]

[1]Ribeiro, F., Teixeira-Santos, A. C., & Leist, A. K. (2021). The prevalence of mild cognitive impairment in Latin America and the Caribbean: a systematic review and meta-analysis. *Aging & Mental Health*, https://doi.org/10.1080/13607863.2021.2003297
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Cognitive impairment in Sao Paulo, Brazil, 2000-2015

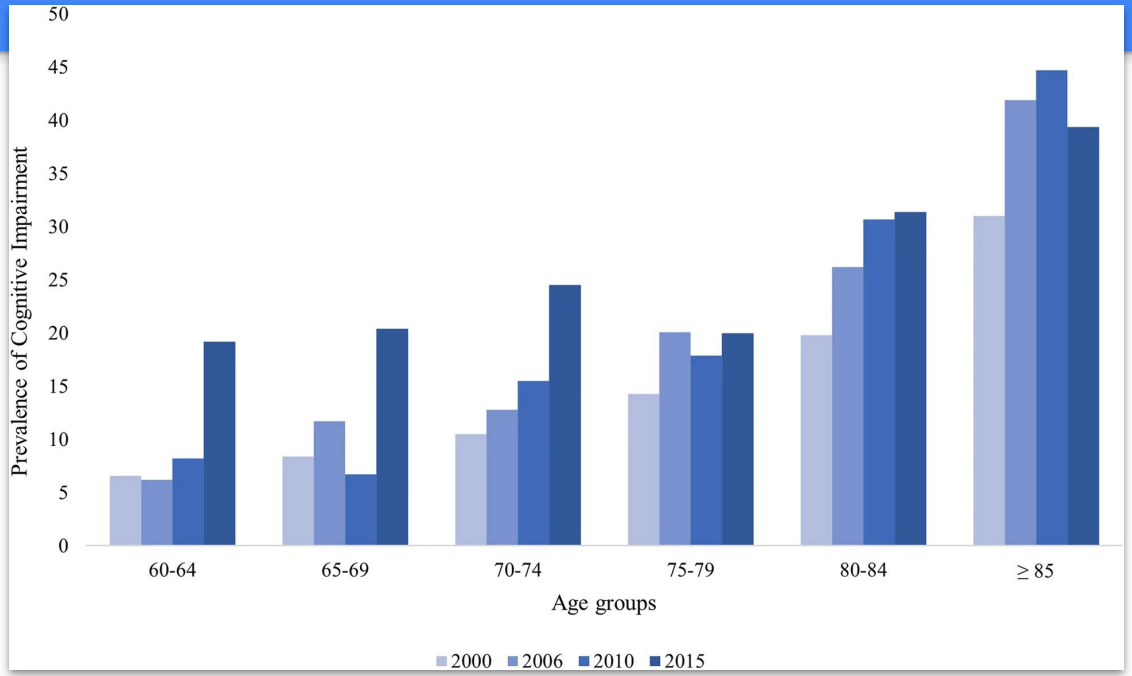
Health, Welfare and Aging survey, repeated cross-section with panel respondents, 2000, 2006, 2010, 2015

Outcome: abbreviated Mini-Mental State Exam, education-adjusted

Associated protective and risk factors: education, cardiovascular risk factors

Ribeiro, F. S., de Oliveira Duarte, Y. A., Santos, J. L. F., & Leist, A. K. (2021). Changes in prevalence of cognitive impairment and associated risk factors 2000–2015 in São Paulo, Brazil. BMC geriatrics, 21(1), 1-10. https://doi.org/10.1186/s12877-021-02542-x

Prevalence of cognitive impairment by age group 2000-2015



Increases in prevalence of cognitive impairment, specifically 60-79 years, 2000-2015

Increases in formal education and income, 2000-2015

Increases in prevalence of diabetes, hypertension, overweight/obesity, 2000-2015

Ribeiro, F. S., de Oliveira Duarte, Y. A., Santos, J. L. F., & Leist, A. K. (2021). Changes in prevalence of cognitive impairment and associated risk factors 2000–2015 in São Paulo, Brazil. BMC geriatrics, 21(1), 1-10. https://doi.org/10.1186/s12877-021-02542-x

Hidden Factors Related to Gender Inequalities in LAC Countries

Fabiana Ribeiro, PhD

Expanding the Framework on Modifiable Determinants of Dementia

Building on the Livingston modifiable risk factors for dementia by adding a sex/gender and socio-environmental, life course dimension to risk factors for dementia

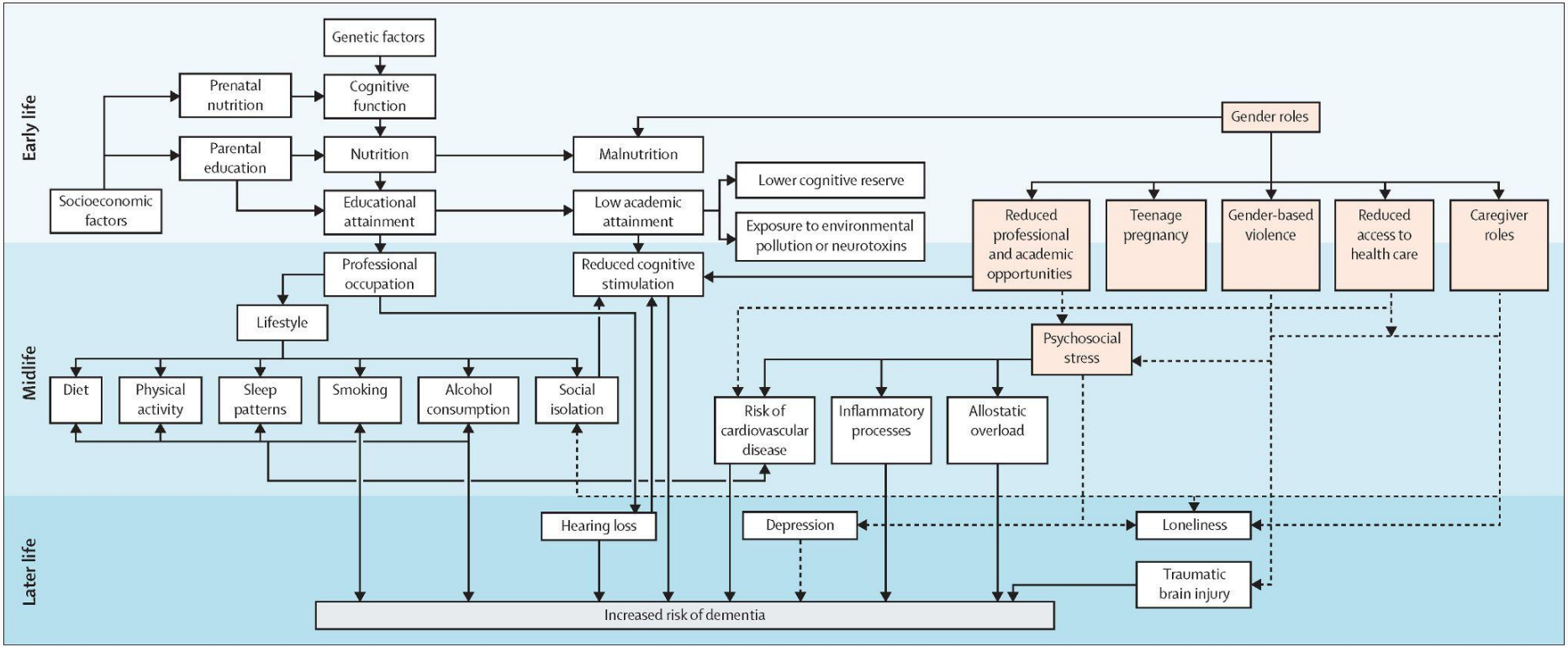
Higher prevalence of dementia in LAC countries, affecting women disproportionately often.

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*. https://doi.org/10.1016/S2666-7568(23)00052-1

Additional risk factors related to gender roles affecting women in LAC countries :

- Teenage pregnancy
- Levels of education and occupational segregation
- Access to the health-care system and the caregiver role
- Social isolation and loneliness
- Nutrition: Food insecurity; overweight and obesity
- Gender-based violence
- Differential exposures to alcohol consumption and smoking

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*. https://doi.org/10.1016/S2666-7568(23)00052-1



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*. https://doi.org/10.1016/S2666-7568(23)00052-1

Structure of presentation

Moving from individual-level to contextual-level determinants of cognitive ageing and dementia

- Individual-level (modifiable) social and behavioural determinants
- Neighbourhood socioeconomic conditions
- Contextual determinants in a global perspective

CRISP output (selection)

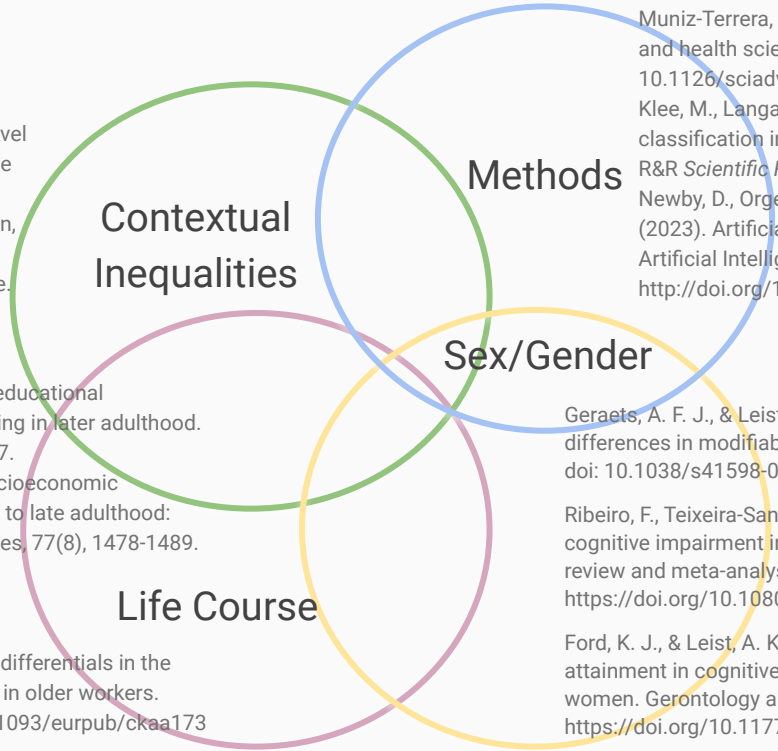
Neighborhood socioeconomic disadvantage
Settels, J., & Leist, A. K. (2021). Changes in neighborhood-level socioeconomic disadvantage and older Americans' cognitive functioning. *Health & Place*, 68, 102510.
Klee, M., Leist, A. K., Veldsman, M., Ranson, J. M., & Llewellyn, D. J. (2023). Socioeconomic deprivation, genetic risk and incident dementia. American Journal of Preventive Medicine. https://doi.org/10.1016/j.amepre.2023.01.012

Schooling and childhood socioeconomic conditions
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.
Ford, K. J., Kobayashi, L., & Leist, A. K. (2022). Childhood socioeconomic disadvantage and pathways to memory performance in mid to late adulthood: What matters most? Journals of Gerontology: Social Sciences, 77(8), 1478-1489. doi:10.1093/geronb/gbac075

Psychosocial work characteristics
Ford, K., Batty, G. D., & Leist, A. K. (2021). Examining gender differentials in the association of low control work with cognitive performance in older workers. European Journal of Public Health, 31(1), 174–180, doi: 10.1093/eurpub/ckaa173

Employment transitions
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. http://dx.doi.org/10.1136/jech-2022-220197

Partnership
Bertogg, A., & Leist, A. K. (2021). Partnership and cognitive aging in Europe: Mediating factors and social stratification. Journals of Gerontology: Social Sciences, https://doi.org/10.1093/geronb/gbab020.



Leist, A. K., Klee, M., Kim, J. H., Rehkopf, D. H., Bordas, S. P. A., Muniz-Terrera, G., & Wade, S. (2022). Machine learning in the social and health sciences. *Science Advances.* 8(42). doi: 10.1126/sciadv.abk1942
Klee, M., Langa, K.M., Leist, A.K. Algorithms for probable dementia classification in the Survey of Health, Ageing and Retirement in Europe. R&R *Scientific Reports*.
Newby, D., Orgeta, V., …Leist, A. K., Llewellyn, D. J., & Ranson, J. M. (2023). Artificial intelligence for dementia prevention. Special Issue on Artificial Intelligence in Dementia at Alzheimer's & Dementia. http://doi.org/10.1002/alz.13463

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

Ribeiro, F., Teixeira-Santos, A. C., & Leist, A. K. (2021). The prevalence of mild cognitive impairment in Latin America and the Caribbean: a systematic review and meta-analysis. *Aging & Mental Health*, https://doi.org/10.1080/13607863.2021.2003297

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Thank you!

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