UNIVERSITÉ DU LUXEMBOURG

Sex/gender considerations in research on cognitive ageing and dementia

Prof. Anja Leist, University of Luxembourg
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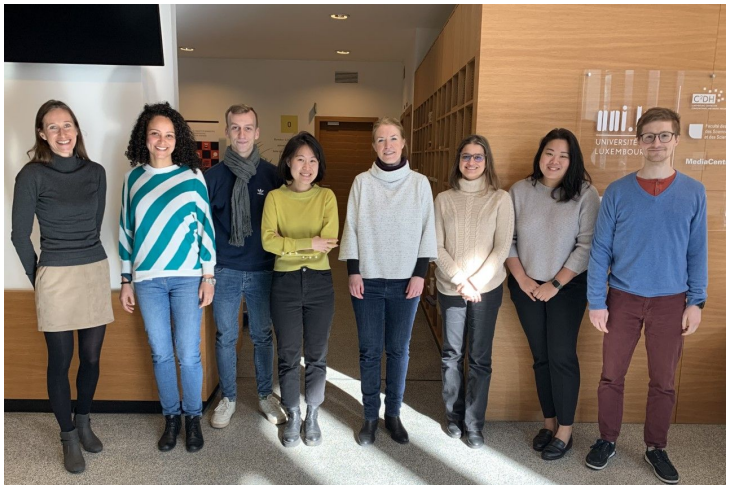
First things first: Thanks to team and collaborators



Team

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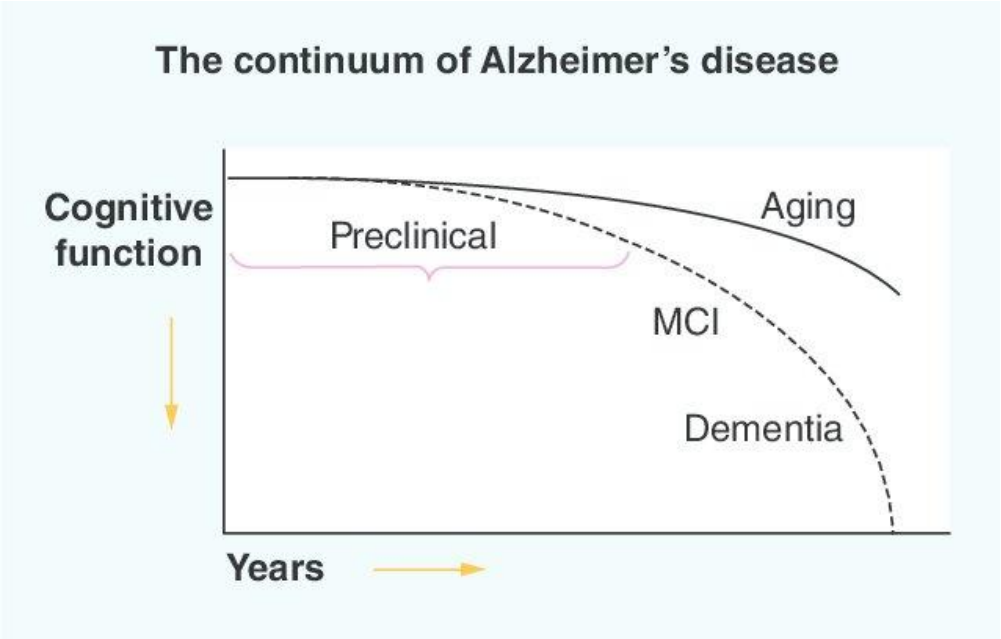
The course of cognitive decline - inevitable?



- Globally, more than 55 million people living with dementia, with an additional 10 million newly affected each year[1]
- 2023: First drugs to slow cognitive decline or improve ADLs received FDA approval[3]

Figure credit: DOI: 10.2217/bmm.14.42

[1] https://www.who.int/news-room/fact-sheets/detail/dementia

[2] 10.14283/jpad.2024.37

Neurodegenerative disease burden

- Age as strongest risk factor of neurodegenerative diseases.[1]
- Annual societal costs of dementia estimated at US $1313.4 billion for 55.2 million people with dementia in 2019 globally.[2]
- Modifiable factors in dementia estimated to contribute 40%, while genetic risk contributes ca. 7%.[3]
- Prevention, particularly primordial, safer and likely to be more cost-effective

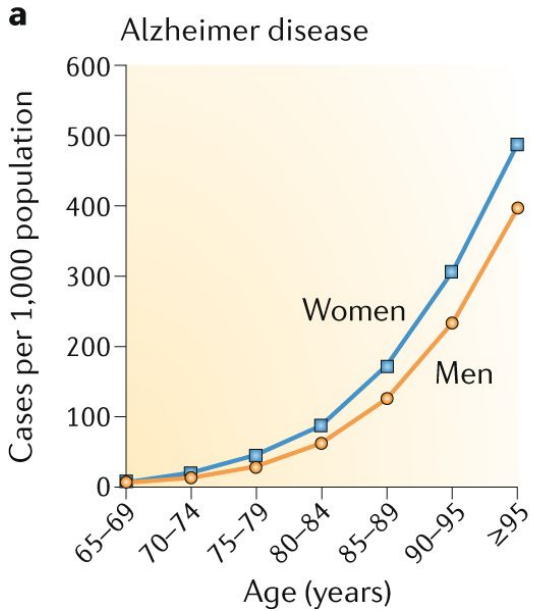


Figure: Hou et al. 2019. doi: 10.1038/s41582-019-0244-7

[1] Hou et al. 2019. doi: 10.1038/s41582-019-0244-7
[2] Wimo et al. 2023. doi: 10.1002/alz.12901
[3] Livingston et al. 2020. doi: 10.1016/S0140-6736(20)30367-6

Inequalities in research on neurodegenerative diseases

Less research funding on conditions affecting women more often or exclusively

Lower enrollment of women in drug trials on neurodegenerative diseases

Sex/gender inequalities in research on and treatment of medical conditions

Less knowledge on presentation of symptoms of disease in women

Less knowledge on response to treatment and quality of care outcomes in women

Similar symptom presentation (e.g. pain reports) shows sex/gender differences in treatment, referrals

Sex/gender differences in prevalence of and disability resulting from brain diseases

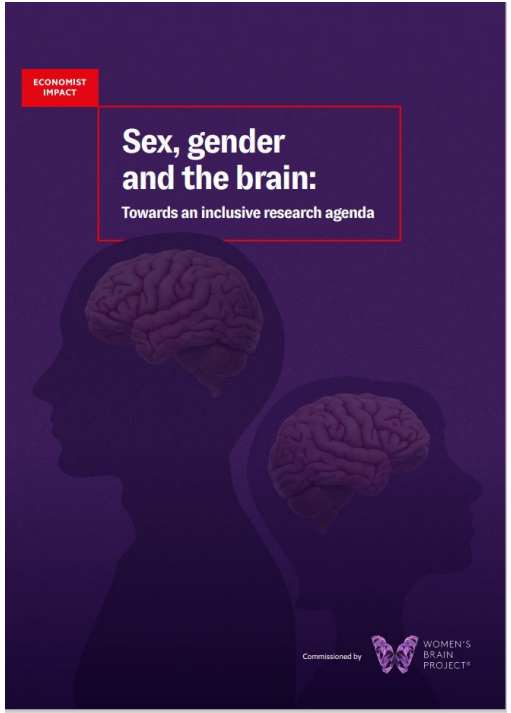
Stroke: Second leading cause of death, leading cause of disability. Women bear 55% of global burden (f/m prevalence: 1,463 vs. 1,160 per 100,000)

Dementia: 55m people today; 139m in 2050. Women bear two thirds of global burden. Women account for 60% of AD caregivers.

Parkinson's Disease: Over 8m people: 4.6m men and 3.8m women. More disabling for men than women (f/m DALYs: 68 vs. 94 per 100,000).

Multiple Sklerosis: 2.8m people; most common disabling neurological disease in young people. Women bear two thirds of global burden (f/m prevalence: 31 vs. 15 per 100,000)

Migraine: Second-most disabling condition (1st: back pain). 1.04bn people. Women have 2-3 times higher risk of migraine. More disabling for women (f/m DALYs 685 vs. 403 per 100,000).



Last accessed 24 June 2024 from: https://impact.economist.com/perspectives/sites/default/files/womensbrainproject_report_230306.pdf

Accountability of sex and gender in health research

Policy & practice

Differentiating sex and gender in health research to achieve gender equity

Michelle R Kaufman,[a] Evan L Eschliman[a] & Tahilin Sanchez Karver[a]

Abstract Effectively tracking progress on initiatives focused on gender equity requires clear differentiation between the terms sex
gender. Sex usually refers to a person's biological characteristics, whereas gender refers to socially constructed roles and norms. Altho
both terms are often treated as binaries, gender is a spectrum and sex may include intersex individuals. While the terms are interrelated,
are sometimes conflated or used interchangeably in health data. Their fundamental distinctions, however, have implications for the con
of research and the design of interventions targeting sex- and gender-based health disparities. We use the example of coronavirus dis
2019 to show how conflating these terms in data collection makes it difficult to ascertain whether disparities in infection rates, morb
and mortality are determined by sex or gender. Although the exact process of collecting data on sex and gender may need to be ada
for specific contexts, there are steps that can be taken so that health data better reflect the differences between these concepts. Possible
actions include using a two-step data collection process to determine both sex and gender of individuals, and encouraging recognition of
intersex, third gender, transgender and gender nonbinary people. There also needs to be acceptance and commitment by data collectors
and research editors; for example, by using tools such as the Sex and Gender Equity in Research checklist. With clearer distinctions between
these foundational terms and how they are used in health data, we can achieve more accurate research findings, better-tailored interventions
and better progress towards gender equity.

ELSEVIER

Nursing Outlook

Volume 72, Issue 4, July–August 2024, 102194

Ensuring accountability for consideration of sex as a biological variable in research

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Highlights

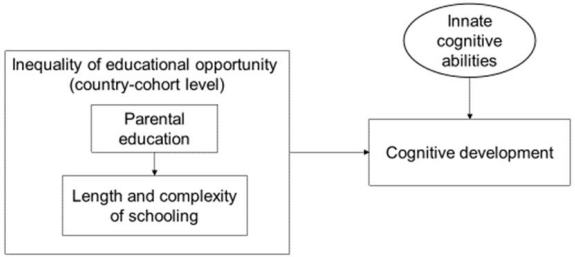
- Omics-based clinical discoveries explain the influences of sex and gender on health and disease.
- Despite consensus that sex and gender are distinct constructs, their use in research is unreliable.

doi: 10.2471/BLT.22.289310; doi: 10.1016/j.outlook.2024.102194

The role of context and the social determinants of health

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

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

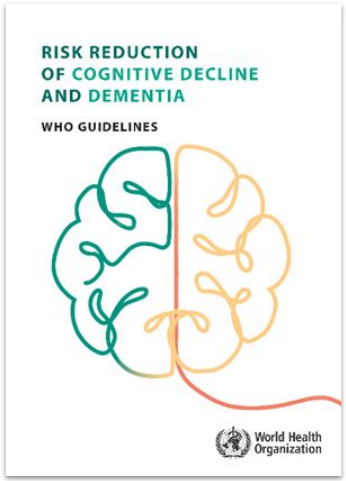
Controlling for range of contextual- and individual-level confounders

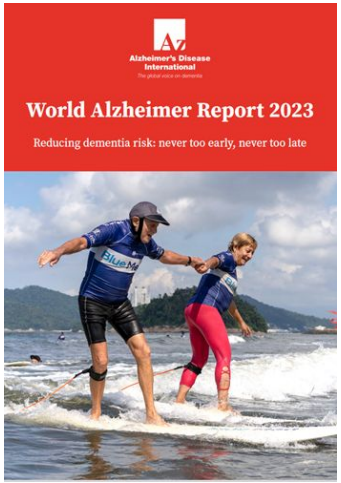
Associations of level of IEO on level of and rate of change in three cognitive measures in stratified multilevel (mixed-effects) models.

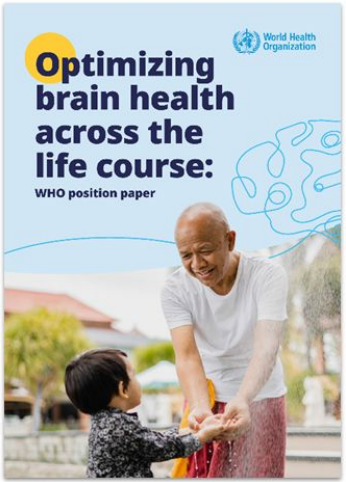
	Women			Men		
	Immediate recall	Delayed recall	Verbal fluency	Immediate recall	Delayed recall	Verbal fluency
	Coeff. (CI)	Coeff. (CI)	Coeff. (CI)	Coeff. (CI)	Coeff. (CI)	Coeff. (CI)
(Intercept)	−0.27 *** (−0.34 to −0.19)	−0.20 *** (−0.28 to −0.12)	−0.29 *** (−0.39 to −0.19)	−0.30 *** (−0.37 to	−0.26 *** (−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 role of modifiable risk factors in cognitive ageing and dementia







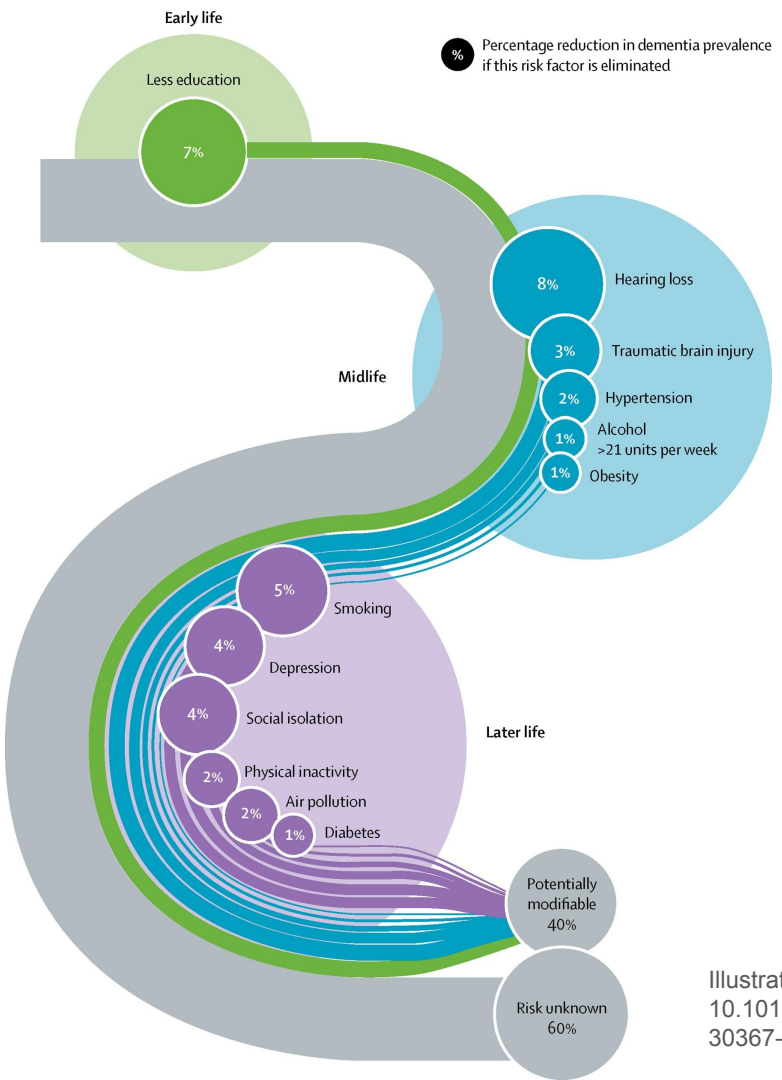


Illustration credit: doi: 10.1016/S0140-6736(20)30367-6

Sex/gender and socioeconomic differences in modifiable risk factors for dementia

Dr. Anouk Geraets

Sex/gender and socioeconomic differences in modifiable risk factors for dementia

Sex/gender and socioeconomic differences in dementia and modifiable risk factors for dementia

Different risk factor prevalence or different exposure-outcome relationships?

English Longitudinal Study of Ageing (2008/2009 to 2018/2019)
N = 8,941 individuals, mean age, 66.1 ± 9.8 years; n = 4,935 (55.2%) women
Modifiable risk factors according to the LIBRA score.

Geraets, A. F. J., & Leist, A. K. (2023). Sex/gender and socioeconomic differences in modifiable risk factors for dementia. *Scientific Reports*. doi: 10.1038/s41598-022-27368-4

Sex/gender and socioeconomic differences in modifiable risk factors for dementia

- No overall sex/gender difference in dementia risk
- Dementia risk was higher among those with
  - Childhood deprivation [hazard ratio (HR) = 1.51 (1.17; 1.96)];
  - Lower occupational attainment [HR low versus high = 1.60 (1.23; 2.09) and HR medium versus high = 1.53 (1.15; 2.06)];
  - Low wealth [HR low versus high = 1.63 (1.26; 2.12)].

Geraets, A. F. J., & Leist, A. K. (2023). Sex/gender and socioeconomic differences in modifiable risk factors for dementia. *Scientific Reports*. doi: 10.1038/s41598-022-27368-4

Sex/gender and socioeconomic differences in modifiable risk factors for dementia

- Sex/gender differences in modifiable risk factors
  - Low cognitive activity was associated with a higher dementia risk for women [HR = 2.61 (1.89; 3.60)] compared to men [HR = 1.73 (1.20; 2.49)].
- No consistent socioeconomic differences in modifiable dementia risk factors.

⇨ Preference for population-based approach that tackles inequalities and modifiable risk factor burden directly, compared to individual approaches in dementia prevention.

Geraets, A. F. J., & Leist, A. K. (2023). Sex/gender and socioeconomic differences in modifiable risk factors for dementia. *Scientific Reports*. doi: 10.1038/s41598-022-27368-4

Sex/gender differences in (modifiable) risk burden and dementia risk
Dr. Fabiana Ribeiro

- 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 [1]
- Framework for identifying how gender inequalities translate into elevated dementia risk in women in Latin American countries[2]

[1]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

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

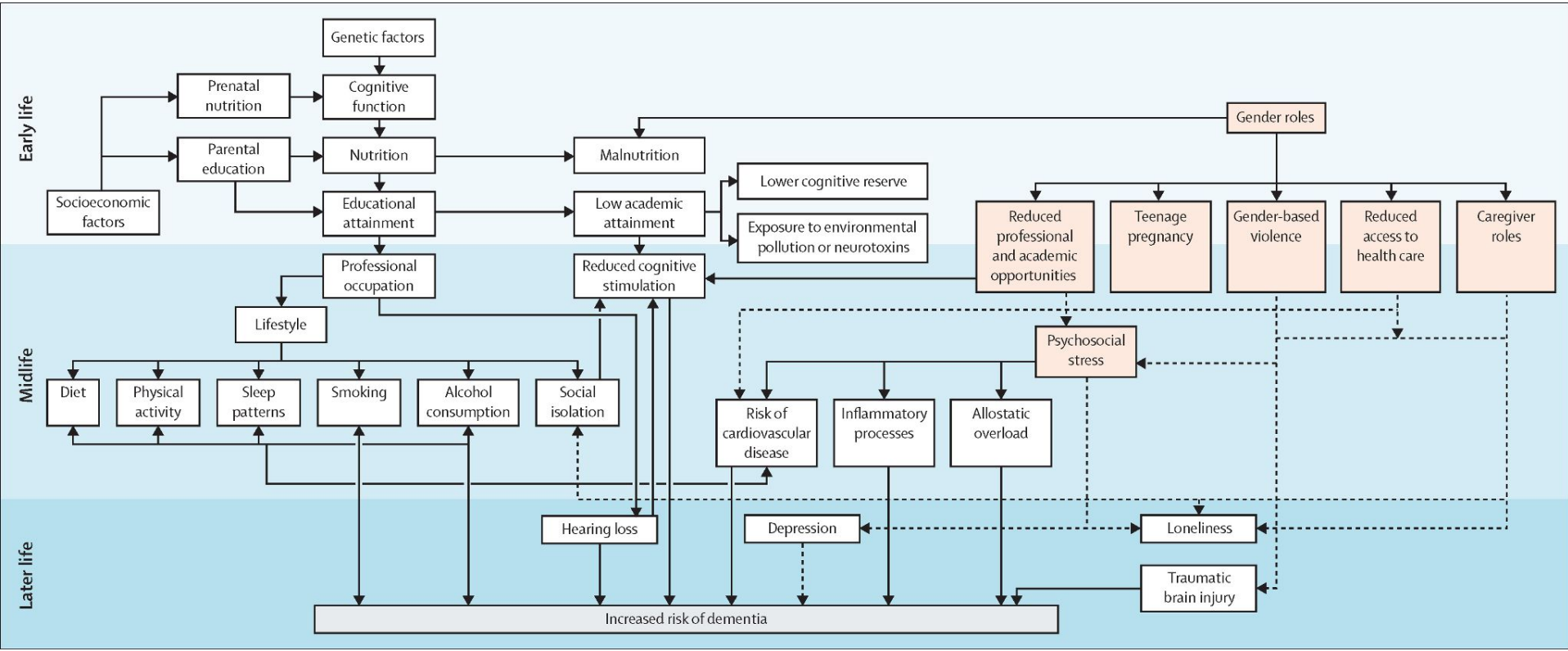
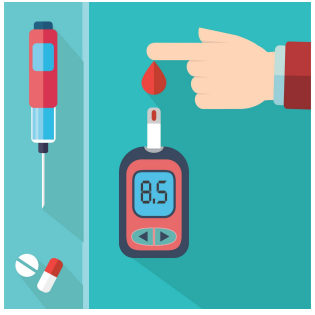


Figure © Ribeiro et al. (2023), doi.org/10.1016/S2666-7568(23)00052-1

The role of glycemia in menopausal factors
Dr. Anouk Geraets



- 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

Geraets, A.F.J., Schram, M.T., Jansen, J.F.A., Köhler, S., van Boxtel, M.P.J., Eussen, S.J.P.M., Koster, A., Stehouwer, C.D.A., Bosma, H., & Leist, A.K. (2024). The associations of socioeconomic position with structural brain damage and connectivity and cognitive functioning: The Maastricht Study. *Social Science & Medicine*. https://doi.org/10.1016/j.socscimed.2024.117111

Introduction

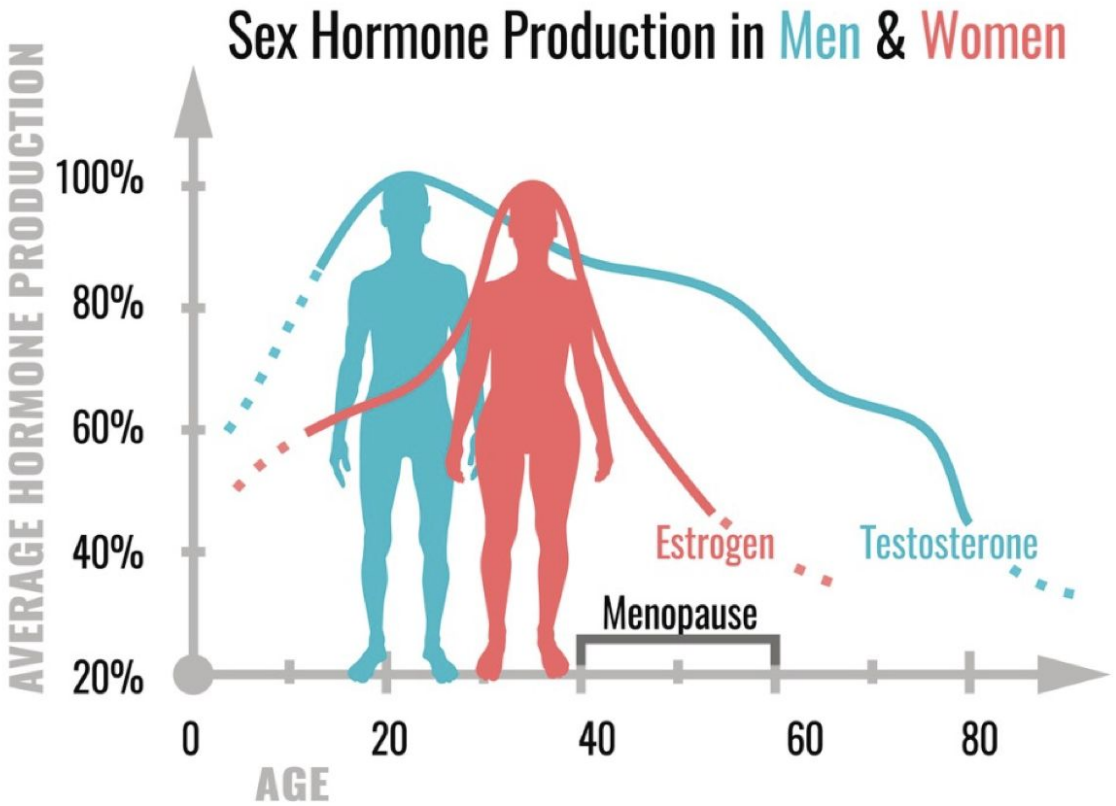
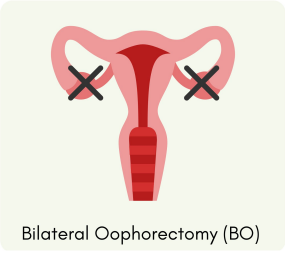


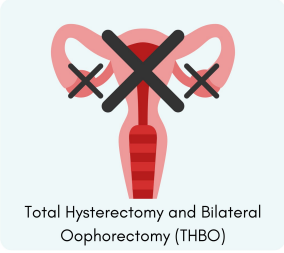
Image taken from Shutterstock

Introduction

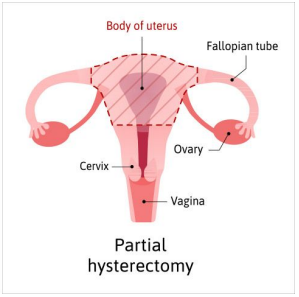
Early menopause (<45 years)



Bilateral Oophorectomy (BO)



Total Hysterectomy and Bilateral Oophorectomy (THBO)



Partial hysterectomy

Increased dementia risk

https://doi.org/10.1016/j.socscimed.2024.117111

Introduction

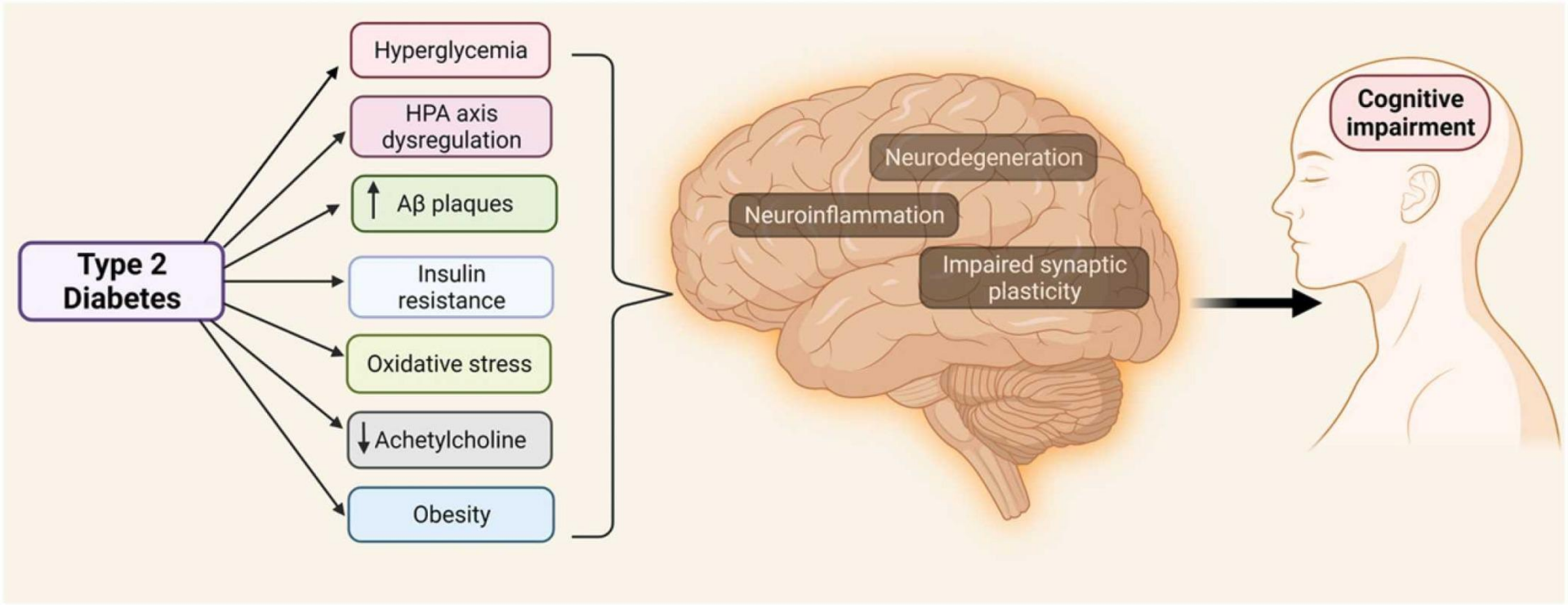
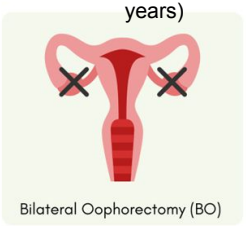


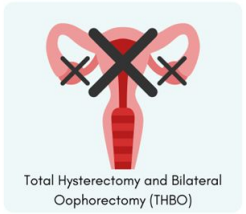
Image taken from Dutta et al., Pharmacological Research, 202

Introduction

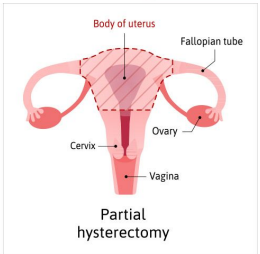
Early menopause (<45 years)



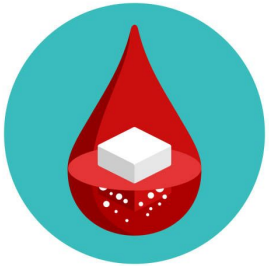
Bilateral Oophorectomy (BO)



Total Hysterectomy and Bilateral Oophorectomy (THBO)



Partial hysterectomy



Glycaemia

Increased dementia risk

https://doi.org/10.1016/j.socscimed.2024.117111

Methods – Study sample and design

We used data from the population-based UK Biobank cohort (n=147,119 women; mean±SD age 55.2±8.0 years at baseline; 1,385 incident dementia cases).

This study included follow-up data for dementia risk until November 6, 2021 (mean follow-up duration 12.4±1.6 years).

Enabling scientific discoveries that improve human health

https://doi.org/10.1016/j.socscimed.2024.117111

Methods - Measurements

Menopausal factors: menopausal status, bilateral oophorectomy, hysterectomy, and age at menopause or surgery were self-reported.

Age was treated as both a continuous and categorical variable (<45 years of age).

Markers of glycemia: baseline fasting plasma glucose (mmol/L) and hemoglobin A1c (HbA1c; mmol/mol) levels standardized into z-scores.

Dementia: dementia diagnosis was ascertained from hospital records until 06-11-2021.

https://doi.org/10.1016/j.socscimed.2024.117111

Methods – Statistical analyses

- Stata 18.
- Cox proportional hazard regression analyses tested the associations between menopausal factors and dementia risk.
- Linear regression analyses tested the associations of menopausal factors with glycemia.
- Causal mediation was tested using the mediate command. Age at natural or surgical menopause was standardized and a standard deviation of +1 was compared to a standard deviation of -1.
- All analyses were adjusted for age at baseline, educational attainment, and history of hormone replacement therapy.
- A two-sided p-value <0.05 was considered statistically significant.

https://doi.org/10.1016/j.socscimed.2024.117111

Results – Characteristics of study population

Characteristic	Incident dementia	
	No (n=145,734)	Yes (n=1,385)
Demographics		
Age (years)	**55.1 ± 8.0**	**63.7 ± 5.3**
High educational attainment, n (%)	**60,588 (41.6)**	**467 (33.7)**
Menopausal factors		
Pre-menopausal, n (%)	**46,260 (31.7)**	**51 (3.7)**
Natural menopause, n (%)	**82,699 (58.0)**	**1,072 (82.0)**
Bilateral oophorectomy, n (%)	9,730 (6.7)	109 (7.9)
Hysterectomy, n (%)	**3,816 (2.6)**	**75 (5.4)**
Age natural menopause (years)	50.3 ± 4.5	50.0 ± 5.0
Early natural menopause (< 45 years), n (%)	7,579 (9.2)	111 (10.7)
Age bilateral oophorectomy (years)	45.7 ± 6.7	46.2 ± 7.2
Early bilateral oophorectomy (< 45 years), n (%)	3,510 (36.6)	35 (34.7)
Age hysterectomy (years)	41.4 ± 6.4	41.5 ± 7.6
Early hysterectomy (< 45 years), n (%)	2,578 (68.5)	55 (74.3)
Ever used hormone replacement therapy, n (%)	49,065 (33.7)	779 (56.3)
Glycemia		
Fasting plasma glucose (mmol/L)	**5.0 ± 1.0**	**5.3 ± 1.5**
HbA1c (mmol/mol)	**35.4 ± 5.6**	**38.0 ± 8.5**

Data are presented as means ± standard deviation or number (%). HbA1c indicates hemoglobin A1c; HDL, high-density lipoprotein. Statistically significant associations using a two-sided *p*-value < 0.05 are presented in bold.

https://doi.org/10.1016/j.socscimed.2024.117111

Results 1 – Menopausal factors and glycaemia with dementia risk

	Incident dementia HR (95% CI)	p-value
Menopausal factors		
Bilateral oophorectomy aged ≥ 50 years [a] (n=95,710)	0.87 (0.71;1.06)	0.169
Hysterectomy aged ≥ 50 years [a] (n=90,719)	1.10 (0.86;1.39)	0.449
Age natural menopause (years) (n=82,406)	**0.97 (0.96;0.98)**	**<0.001**
Early natural menopause (n=82,406)	**1.32 (1.08;1.60)**	**0.006**
Age bilateral oophorectomy (years) (n=9,687)	0.97 (0.95;1.00)	0.063
Early bilateral oophorectomy (n=9,687)	1.43 (0.95;2.17)	0.089
Age hysterectomy (age) (n=3,837)	0.98 (0.95;1.02)	0.301
Early hysterectomy (n=3,837)	1.60 (0.95;2.71)	0.079
Markers of glycemia		
Fasting plasma glucose (per 1 SD) (n=147,119)	**1.15 (1.10;1.20)**	**<0.001**
HbA1c (per 1 SD) (n=147,119)	**1.21 (1.16;1.26)**	**<0.001**

n=1,254 dementia cases for bilateral oophorectomy aged ≥ 50 years; n=1,223 dementia cases for hysterectomy aged ≥ 50 years; n=1,035 dementia cases for age at natural menopause; n=101 dementia cases for age at bilateral oophorectomy; n=74 dementia cases for age at hysterectomy; n=1,385 dementia cases for glucose and HbA1c. HR indicates hazard ratio; CI, confidence interval; SD, standard deviation; HbA1c, hemoglobin A1c. Analyses are adjusted for age, educational level, and history of hormone replacement therapy. Statistically significant associations using a two-sided *p*-value < 0.05 are presented in bold. [a] Compared to post-menopausal women without surgical interference prior to menopause. Statistically significant associations using a two-sided *p*-value < 0.05 are presented in bold.

https://doi.org/10.1016/j.socscimed.2024.117111

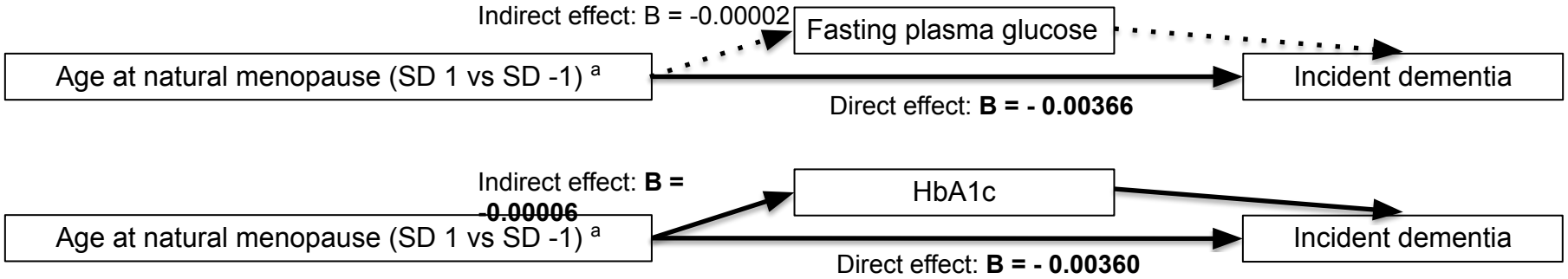
Results 2 – Menopausal factors with glycaemia

Menopausal factors	Fasting plasma glucose (per 1 SD) B (95% CI)	HbA1c (per 1 SD) B (95% CI)
Bilateral oophorectomy aged < 50 years [a] (n=47,518)	**0.052 (0.002;0.101)**	**0.216 (0.166;0.267)**
Bilateral oophorectomy aged ≥ 50 years [b] (n=95,710)	0.064 (0.045;0.083)	**0.062 (0.043;0.081)**
Hysterectomy aged < 50 years [a] (n=46,561)	**-0.002 (-0.091;0.087)**	**0.140 (0.048;0.231)**
Hysterectomy aged ≥ 50 years [b] (n=90,719)	**0.065 (0.037;0.093)**	**0.087 (0.060;0.115)**
Age natural menopause (years) (n=82,406)	**-0.001 (-0.003;-0.000)**	**-0.003 (-0.005;-0.002)**
Early natural menopause (n=82,406)	**0.027 (0.008;0.047)**	**0.064 (0.044;0.083)**
Age bilateral oophorectomy (years) (n=9,687)	**-0.008 (-0.011;-0.005)**	**-0.006 (-0.009;-0.003)**
Early bilateral oophorectomy (n=9,687)	**0.087 (0.047;0.127)**	**0.084 (0.043;0.124)**
Age hysterectomy (age) (n=3,837)	**-0.009 (-0.014;-0.003)**	**-0.009 (-0.014;-0.004)**
Early hysterectomy (n=3,837)	**0.076 (0.007;0.146)**	**0.079 (0009;0.150)**

B indicates unstandardized regression coefficient; CI, confidence interval; SD, standard deviation; HbA1c, hemoglobin A1c. Analyses are adjusted for age, educational level, and history of hormone replacement therapy. Statistically significant associations using a two-sided *p*-value < 0.05 are presented in bold. [a] Compared to pre-menopausal women without surgical interference. [b] Compared to post-menopausal women without surgical interference prior to menopause. Statistically significant associations using a two-sided *p*-value < 0.05 are presented in bold.

https://doi.org/10.1016/j.socscimed.2024.117111

Results 3 – Mediation analyses

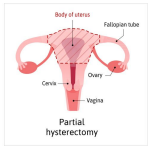


n=82,406. Analyses are adjusted for age, educational level, and history of hormone replacement therapy. Statistically significant associations using a two-sided *p*-value < 0.05 are presented in bold. [a] Age is standardized and a standard deviation of 1 is compared to a standard deviation of -1.

https://doi.org/10.1016/j.socscimed.2024.117111

Key points

Glycaemia



HbA1c

Increased dementia risk

https://doi.org/10.1016/j.socscimed.2024.117111

Implications

- More studies are needed to investigate alternative mechanisms like genetics, environment, inflammation, lifestyle, socioeconomic position, and comorbidities.
- Women who undergo natural menopause at a young age should be monitored for both hyperglycemia and cognitive decline.
- Addressing modifiable risk factors could have a significant protective effect against both hyperglycemia and cognitive decline and dementia.
- Interventional studies that test the effect of hormone replacement therapy should consider genetic risk for dementia.

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The role of gender-role norms and gender inequalities

- The role of gender-role attitudes: “Men should have more right to job than women when jobs are scarce”, “Women should be prepared to cut down on paid work for sake of family”, and employment biographies for later-life cognitive functioning[1]
- Mechanisms: work-related cognitive stimulation and multiple-role benefits
- Longer spells of both full-time and part-time employment beneficial for cognitive functioning
- For women, we find that part-time employment—as a means of reconciling family tasks and professional careers—comes with higher cognitive benefits
- Longer spells of homemaking in women are less beneficial for cognitive functioning, as are longer spells of unemployment.

[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*. https://doi.org/10.1007/s10433-023-00751-4
Received the Excellence prize of the EHMS and the Vontobel prize for Ageing Research, 2024.

Your brain health matters

getbrainhealthy.org

CRISP follow-up: Societal impact generation through website, workshops, public talks in collaboration with

GetBrainHealthy.org: Scaling Science Promotion and Brain Health Education to the Public

Melissa Chan, Global Brain Health Institute fellow
Dr. Laure Pauly, neuroscience specialist and science communicator

Luxembourg National Research Fund

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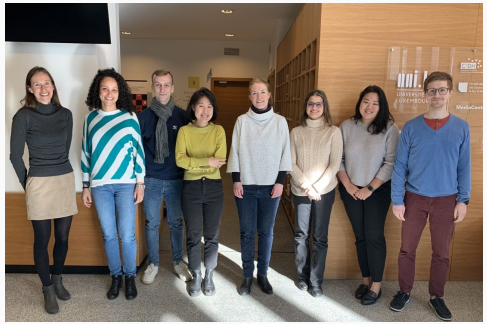

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