

# How to actively protect against dementia. Epidemiological data from Luxembourg

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Anja Leist, University of Luxembourg

*Mardis en Neurosciences, CHL, 5 February 2020*

## Dementia

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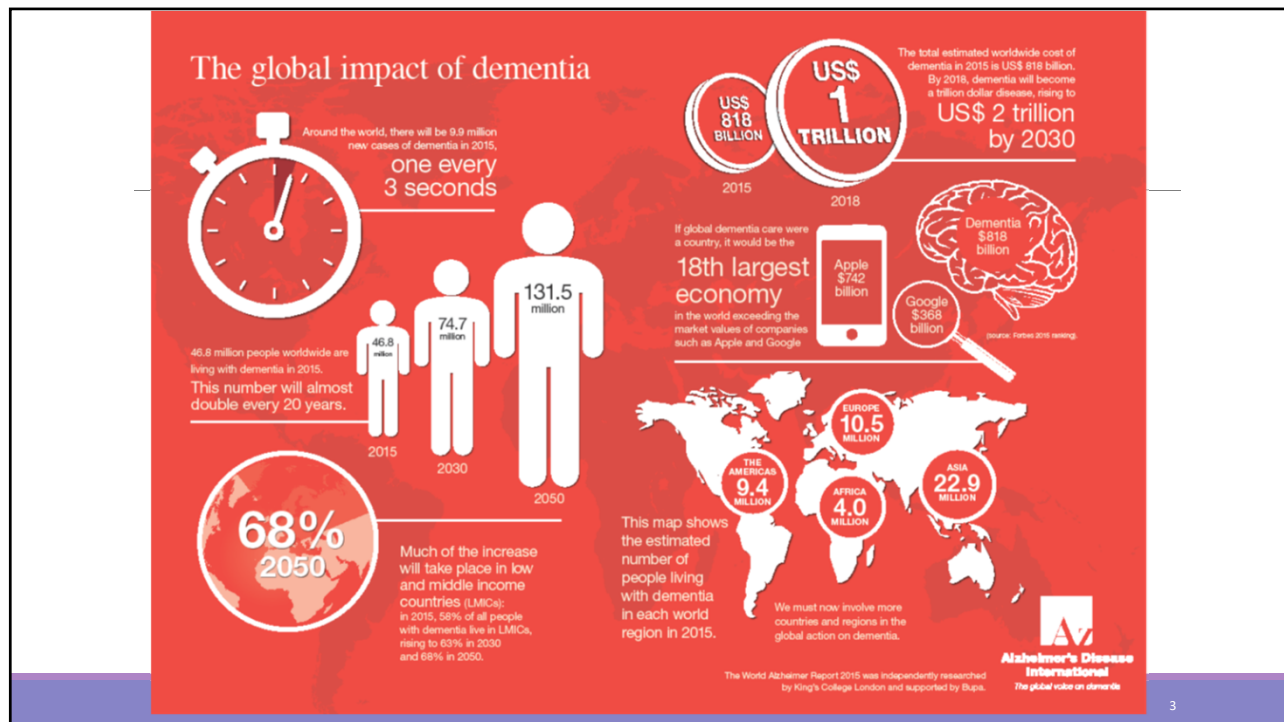
- Range of conditions characterized by memory impairment
- Alzheimer's Disease (40-60%), vascular dementia (up to 40 %), mixed, Lewy-Body, Parkinson's dementia etc.

### Medical Treatment

- There is no medical treatment able to cure dementia
- In October 2019, Biogen requested FDA approval of aducanumab after re-analysis of data of 2 trials that were ended in March 2019. On 28 January 2020, FDA approved a re-dosing study to begin approx. in March 2020.

### Risk Reduction and Prevention

- Onset and progression of dementia are highly variable
- Lifestyle changes can help delay onset and progression of the disease



## Facts on dementia funding and progress

- Goal of finding a disease-modifying therapy by 2025 (G8 Summit 2013)
  - US Government increased funding for Alzheimer's and related research: \$562 million in 2013; \$2.6 billion in 2019
  - Dementia research still seriously underfunded and underresearched compared to other diseases<sup>1</sup>
- WHO Global Action Plan on Dementia, May 2017
  - To improve conditions for people living with dementia across countries, 15 national dementia plans per year need to be initiated
  - Update Oct. 2018: 3 national plans being prepared



Pickett et al., 2018; World Alzheimer Report, 2015

<sup>1</sup>Rate of publications on neurodegenerative diseases versus cancer is 1:12, World Dementia Council Report, 2018

# Cognitive reserve and brain health

## Cognitive reserve (CR)

Stern et al. (2018), p. 2: “The term CR refers to the adaptability (i.e., efficiency, capacity, flexibility ... of cognitive processes that helps to explain **differential susceptibility** of cognitive abilities or day-to-day function to brain aging, pathology, or insult.”

Further recent reviews by Cabeza et al., 2018; Nilsson & Lövdén, 2018

Nilsson and Lövdén / *Alzheimer's Research & Therapy* (2018) 10:24  
https://doi.org/10.1186/s13195-018-0262-8

### REVIEW

## Naming is not explaining: future directions for the “cognitive reserve” and “brain maintenance” theories

Jonna Nilsson<sup>1</sup> and Martin Lövdén<sup>2</sup>

### Abstract

Contemporary imaging measures of the human brain explain less than half of the difference and change among older adults. Researchers have advanced several theories and concepts to better explain these individual differences in cognitive aging. Taking the fundamental empirical sciences as a starting point, we here evaluate how such complementary theories (cognitive reserve, in an attempt to clarify these theories gauge their usefulness, and can be further developed. We demonstrate that although both theories are highly useful for empirical work, they can be further developed by detailing the theoretical and operational that they propose. We propose a few ways forward in these directions.

**Keywords:** Cognitive aging, Dementia, Cognitive reserve, Brain maintenance

### Background

Science has a long way to go in mapping cognition to the brain. People differing in cognitive ability may have identical brains, or conversely measurable individuals with different brains may display identical cognitive functioning. In fact, contemporary imaging measures of the human brain cannot explain much more than 40% of the differences in cognitive functioning and change among older adults [1–10]. Several theories and concepts have been proposed for guiding research that aims to in-

crease a concept can be defined (e.g., fish or brain) or as a system (e.g., center of mass in the mind of humans, or concepts are abstract and concrete existence, they can't sample, the concept of a specimen of fish, and still in abstract, it is modeled

Alzheimer's  
Research & Therapy

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## Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing

Roberto Cabeza, Marjolijn Albert, Sylvie Belleville, Fergus J. M. Craik, Audrey Duarte, Cheryl L. Grady, Ulman Lindenberger, Lars Nyberg, Denise C. Park, Patricia A. Reuter-Lorenz, Michael D. Rugg, Jason Stafford

**Abstract** Cognitive ageing research examines the cognitive abilities that are preserved and/or those that decline with advanced age. There is great individual variability in cognitive ageing trajectories. Some older adults show little decline in cognitive ability compared with young adults and are thus termed “cognitively ageing”. By contrast, others exhibit substantial cognitive decline and may develop dementia. Human ageing research has led to a number of important advances in our understanding of the neural mechanisms underlying these two outcomes. However, interpreting the age-related changes and differences in brain structure, activation and functional connectivity that this research reveals is an ongoing challenge. Ambiguous terminology is a major source of difficulty in this venture. Three terms in particular — compensation, maintenance and reserve — have been applied to a number of different ideas and issues that continue to flourish

ARTICLE IN PRESS



Alzheimer's & Dementia (2018) 1–7

Alzheimer's  
&  
Dementia

### Review Article

## Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance

Yaakov Stern<sup>a,\*</sup>, Eider M. Arenaza-Urquijo<sup>b</sup>, David Barris-Fag<sup>a,b,c</sup>, Sylvie Belleville<sup>c</sup>, Marc Cantillon<sup>d</sup>, Gael Chetelat<sup>e</sup>, Michael Ewers<sup>f</sup>, Nicolas Franzmeier<sup>g</sup>, Gerd Kempermann<sup>h</sup>, William S. Kremen<sup>i</sup>, Oksana Okonkova<sup>j</sup>, Nikolaos Scarmeas<sup>k</sup>, Anja Selkoe<sup>l</sup>, Chinedu Udech-Momoh<sup>m</sup>, Michael Valera<sup>n</sup>, Prashanth Venuri<sup>o</sup>, Eero Vuoksimaa<sup>p</sup>, and the Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup

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## PERSPECTIVES

when there is no direct association between activity levels and performance in older adults<sup>1,2,3</sup>. By contrast, other studies have used the term compensation more restrictively to describe situations in which age-related increases in brain activity are directly correlated with better performance in older adults<sup>4,5</sup>. Moreover, it has also been unclear in the literature how the concepts of reserve, compensation and maintenance relate to one another.

To address this terminological confusion, the authors of this Opinion article met in 2017 and worked to sharpen the definitions of these popular terms, while addressing the confusion about the definitions period. However, in this article, we emphasize the points of agreement. The terms maintenance, reserve and compensation can all be applied to aspects of ageing beyond the brain and cognition (such as bone density). However, here we focus on their use in structural and functional neuroimaging studies in healthy ageing humans (defined here as ageing in individuals who are apparently free of brain disease), although other related terms and methods are also discussed. Given the focus, the use of the terms maintenance,

Y. Stern (Columbia University, New York, NY, USA)  
E. M. Arenaza-Urquijo (Barcelona, Spain)  
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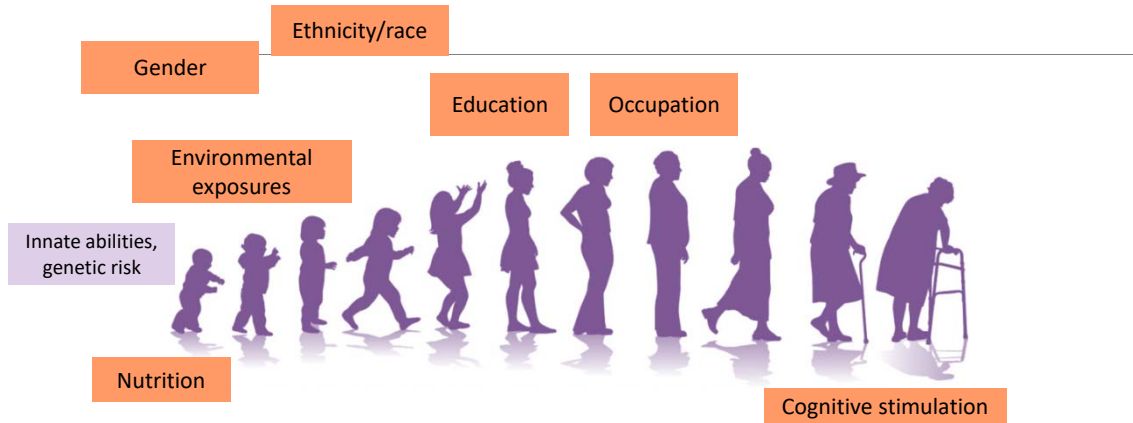
E. Vuoksimaa (Columbia University, New York, NY, USA)

and the Reserve, Resilience and Protective Factors PIA Empirical Definitions and Conceptual Frameworks Workgroup

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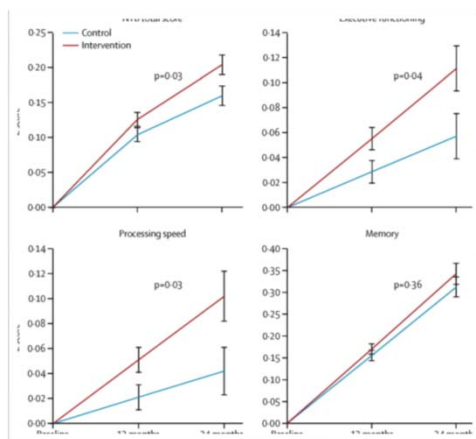
## Life course influences on cognitive functioning



Leist, Novella, Olivera, 2018; Leist & Mackenbach, 2014; Leist et al., 2013

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## First evidence on reducing risk of dementia



Behavioral multidomain intervention over two years:

- Exercise
- Nutritional advice
- Management of vascular risk factors
- Cognitive training
- (Social support)

Ngandu, Kivipelto et al. (2015), Lancet

FINGER



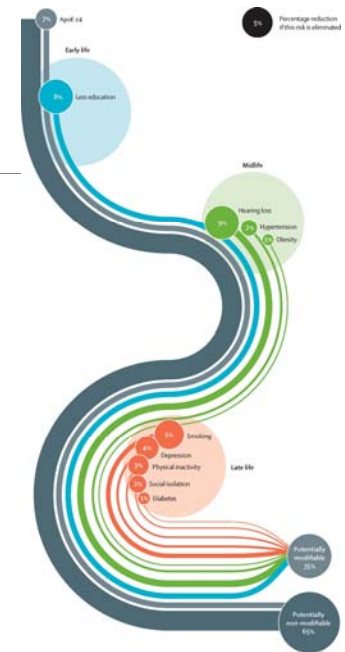
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## Prevention of /risk reduction in dementia

Nine modifiable risk factors could explain 35 % of the risk of dementia

- Education to a maximum of age 11-12 years (8%)
- Midlife hypertension
- Midlife obesity
- Hearing loss
- Late-life depression
- Diabetes
- Physical inactivity
- Smoking
- Social isolation

... in comparison: eliminating ApoE ε4 allele would reduce 7 % of dementia incidence



Livingston et al., 2017; Norton et al., 2014

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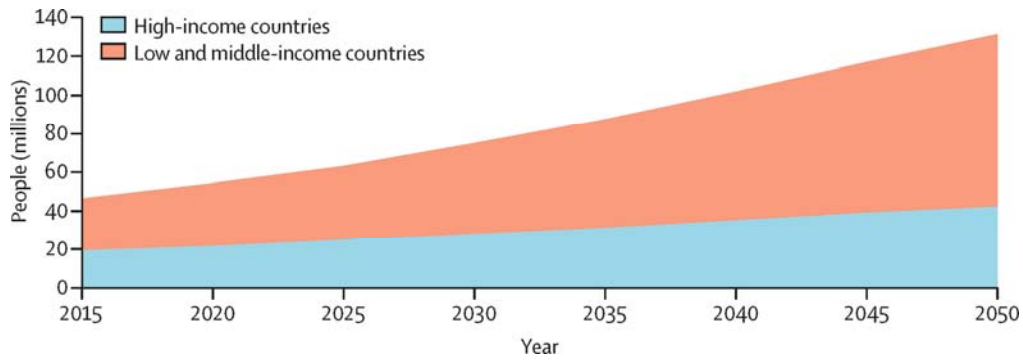
## Newer approaches: Lifestyle for Brain Health (LIBRA)

- Low/moderate alcohol consumption
- *Coronary heart disease*
- Physical inactivity
- *Renal dysfunction*
- Diabetes
- High cholesterol
- Smoking
- Obesity
- Hypertension
- Healthy diet (Mediterranean diet, low unsaturated fat intake)
- Depression
- High cognitive activity

Schiepers et al. (2018); Deckers, ..., & Köhler (2019)

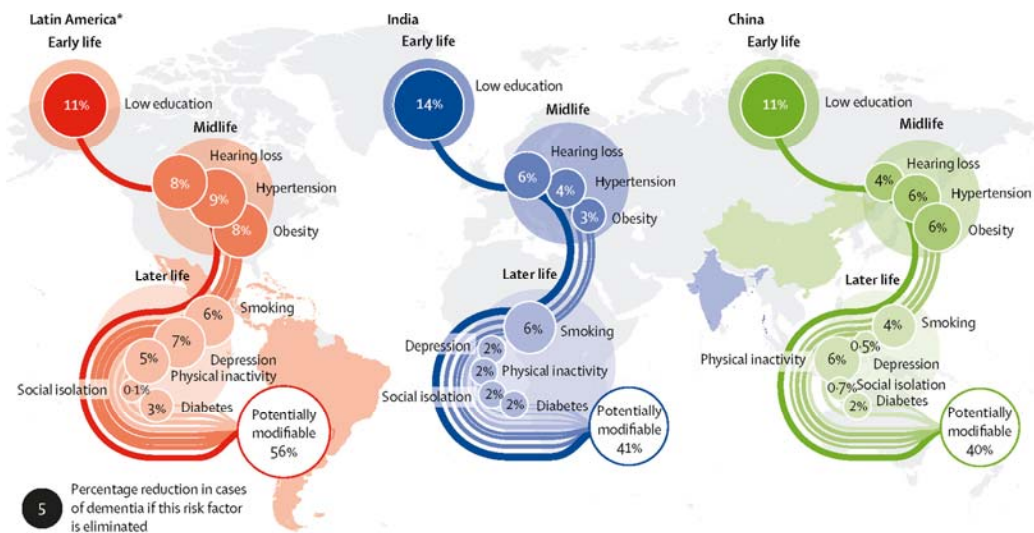
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## Increases in dementia cases



Livingston et al. (2017)

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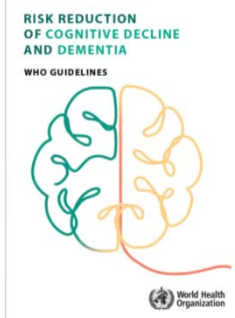


Mukadam et al. (2019)

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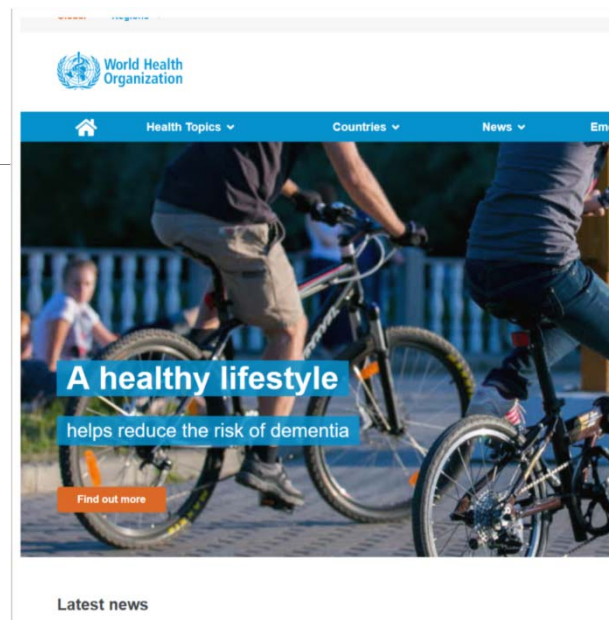
# How much do we really know about the value of behavior changes to reduce risk of cognitive aging and dementia?

ERC StG CRISP (2019-2023,  
grant agreement no. 803239)

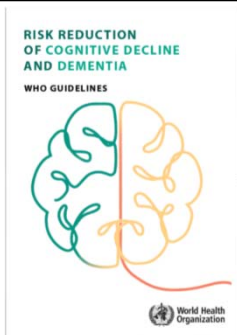


New World Health Organization  
Guidelines

*Published 14 May 2019  
In the Framework of the WHO Global  
Action Plan on the Public Health  
Response to Dementia (2017-2025)*







Interventions for **tobacco cessation** should be offered to adults who use tobacco since they may reduce the risk of cognitive decline and dementia in addition to other health benefits. *Quality of evidence: low; strength of the recommendation: strong*

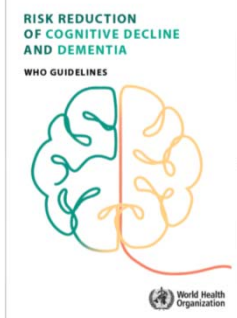
The **Mediterranean-like diet** may be recommended to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia. *Quality of evidence: moderate; strength of the recommendation: conditional*

Interventions aimed at **reducing or ceasing hazardous and harmful drinking** should be offered to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia in addition to other health benefits. *Quality of evidence: moderate (for observational evidence); strength of the recommendation: conditional*

There is insufficient evidence to recommend either **social activity**, **use of antidepressant medicines**, or **use of hearing aids** to reduce risk of cognitive decline/dementia.

There is low quality of evidence to recommend **cognitive interventions**, **weight management**, **(hypertension)**, **management of diabetes mellitus**, **management of dyslipidaemia** to reduce risk of dementia.

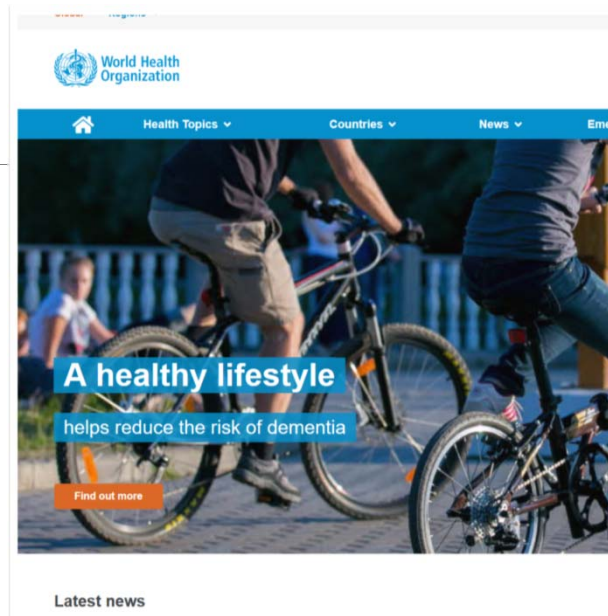
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**Physical activity should be recommended to adults with normal cognition to reduce the risk of cognitive decline**

*Quality of the evidence: moderate*

*Strength of the recommendation: strong*



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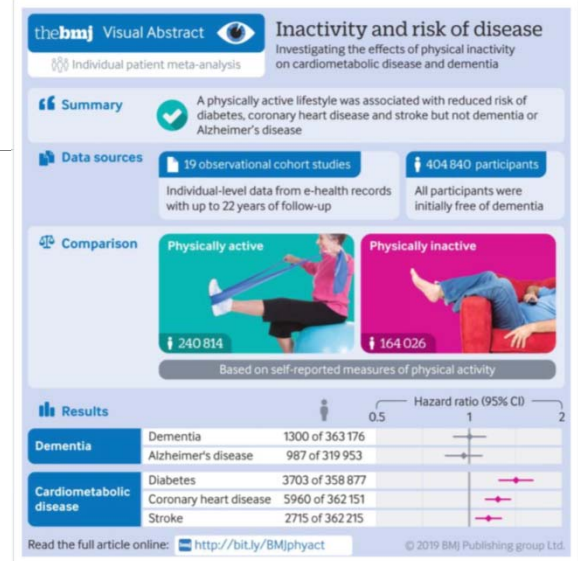
**RESEARCH**

**Physical inactivity, cardiometabolic disease, and risk of dementia: an individual-participant meta-analysis**

Mika Kivimäki,<sup>1,2,3</sup> Archana Singh-Manoux,<sup>1,4</sup> Jaana Pentti,<sup>2,5</sup> Séverine Sabia,<sup>1,4</sup> Solja T Nyberg,<sup>7</sup> Lars Alfredsson,<sup>6</sup> Marcel Goldberg,<sup>7</sup> Anders Knutsson,<sup>8</sup> Markku Koskenvuo,<sup>9</sup> Aki Koskinen,<sup>9</sup> Anne Kouvonen,<sup>10,11,12</sup> Maria Nordin,<sup>13,14</sup> Tuula Oksanen,<sup>2</sup> Timo Strandberg,<sup>2,15,16</sup> Sakari B Suominen,<sup>5,17</sup> Tores Theorell,<sup>13</sup> Jussi Vahtera,<sup>5,18</sup> Ari Väänänen,<sup>7</sup> Marianna Virtanen,<sup>19</sup> Peter Westerholm,<sup>20</sup> Hugo Westerlund,<sup>11</sup> Marie Zins,<sup>6</sup> Sudha Seshadri,<sup>21,22</sup> G David Batty,<sup>1</sup> Pety N Sipilä,<sup>23</sup> Martin J Shipley,<sup>1</sup> Joni V Lindholm,<sup>2</sup> Jane E Ferrie,<sup>1,23</sup> Markus Jokela,<sup>2,4</sup> on behalf of the IPD-Work consortium

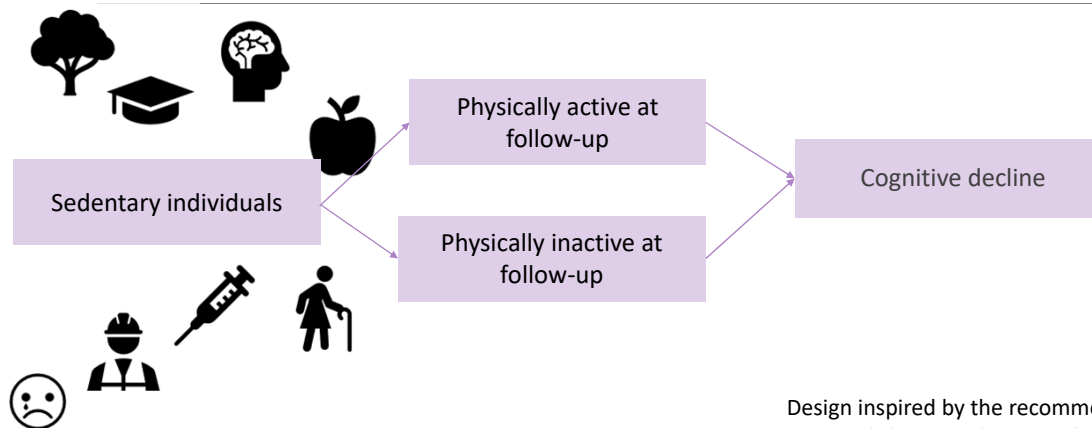
published 17 April 2019 in *BMJ*:

**In analyses that addressed bias due to reverse causation, physical inactivity was not associated with all-cause dementia or Alzheimer's disease**



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Should doctors prescribe physical activity?



Design inspired by the recommendations on target trials by Miguel Hernan & Jamie Robins

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## Have a look!

### THE BOOK OF WHY

The New Science of Cause and Effect

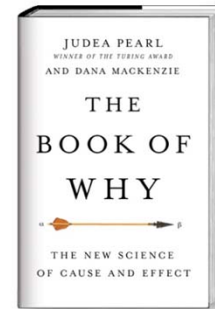
Coming May 15, 2018 from Basic Books

Friends,

We are thrilled to introduce our forthcoming book, *The Book of Why: The New Science of Cause and Effect*.

"Correlation is not causation." This mantra, chanted by scientists for more than a century, has led to a virtual prohibition on causal talk. Today, that taboo is dead.

The causal revolution has cut through a century of confusion and established causality—the study of cause and effect—on a firm scientific basis.



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## Cognitive functioning and dementia in the Survey of Health, Ageing and Retirement in Europe (SHARE)

### Self-reported diagnosis of dementia

- "Doctor told you had" Alzheimer's disease, dementia, organic brain syndrome, senility or any other serious memory impairment
- Not population-representative: underdiagnosis, bias due to self-report, selective attrition/non-participation

### Cognitive functioning

- Orientation (4 items): assessed at entry wave
- Numeracy (4 arithmetic tasks): assessed at entry wave
- Verbal fluency (number of animals named in 1 min)
- Immediate and delayed recall (remembering ten-word list immediately and after standardized delay)

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## Prevalence of dementia in Luxembourg

### *Cognitive impairment no dementia (CIND)*

- 11% of participants of the MemoVie study aged 65+ (Perquin, ..., & Diederich (2013))
- Would translate to **9,716 cases of CIND** in Luxembourg\* (Perquin et al. 2013)
- 65-74 years: 1.5%; 75-84 years: 5.4% in SHARE (0-1 points on a 4-point orientation scale)

### *Dementia*

- 3.8% of people aged 65+ in a population-representative sample (Perquin, Diederich et al. 2015)
- Would translate to **3,356 cases of dementia in Luxembourg\*** (prevalence from Perquin et al. 2015)
- 2.4% in 65+ year-olds in SHARE (65-74 years: 1.5%; 75-84 years: 4.3%; self-reported diagnosis of doctor)

\*A total of 88,328 persons aged 65+ living Luxembourg on 1 January 2019 (Statec 2020)

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## Prevention potential in Luxembourg?

- 7 risk factors: Diabetes, midlife hypertension, midlife obesity, physical inactivity, smoking, depression and educational attainment (Norton et al. 2014)
- + hearing loss (9%) and social isolation (2%) (Livingston et al. 2017)
- + Alcohol consumption + high cholesterol (Deckers et al. 2019; Lourida, ... & Llewellyn, 2019)
- *Total of 11 risk factors*

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## Prevalence of risk factors in Luxembourg

Later mid-life (50-64 years); early old age (65-74 years); old age (75-84 years)

- **Up to primary education:** 34.3% total, up to 48.5% of 75-84 year-olds; *gender differences:* 60.4% females vs. 34.5% of males in old age
- **High blood pressure:** 33.5% in total, up to 41.1% of 75-84 year-olds; *gender differences:* 40.2% of males vs 34.1% of females in early old age
- **Obesity:** 24.9% in total, up to 29.2% of 65-74 year-olds; *gender differences:* 32.7% in males vs 25.2% in females in early old age
- **High cholesterol:** 33.9% in total, up to 39.2% of 65-74 year-olds; *gender differences:* early old: 42.0% in males vs 36.1% in females
- **Depression:** 28.3% in total, up to 31.4% of 65-74 year-olds; *gender differences:* 33.7% in females vs 21.9% in males

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## Prevalence of risk factors in Luxembourg

- **Diabetes:** 11.6% in total, up to 19.8% in 75-84 year-olds; *gender differences:* 19.9% in males vs 12.8% in females in early old age; 24.4% male vs. 15.8% female in old age
- **Hearing impairment:** 2.1% in total, up to 3.5% in 75-84 year-olds; *no gender differences*
- **Physical inactivity** (absence of vigorous physical activity): 37.8% in total, up to 57.4% in 75-84 year-olds; *gender differences:* 43.8% in females vs 36.7% in males in early old age
- **Smoking:** 16.4%, up to 20.8% of 50-64 year-olds; *gender differences:* later midlife highest prevalence: 22.4% in males vs. 19.4% in females
- **Alcohol consumption** daily: 16.0% in total, up to 21.2% of 65-74 year-olds; *gender differences:* 28.8% in males vs 12.8% in females in early old age: 30.3% in males and 12.2% in females in old age
- **Social isolation:** 3.6% in total, up to 3.9% of 65-74 year-olds; *no gender differences*

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## Contribution of modifiable risk factors

Outcome: cognitive impairment/dementia (low orientation **and/or** diagnosis of dementia; age 65-84 years: 4.01%)

Risk score: sum of 11 risk factors

25% of the SHARE respondents have three or more risk factors ( $M = 2.40$ ,  $SD = 1.62$ )

After adjusting for sex and age, each 1-point increase in the risk score was associated with a 39% increase in likelihood of having cognitive impairment (OR 1.39, CI 1.17-1.65; 1,971 respondents aged 50-84).

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programme  
démence  
prévention

Le programme démence prévention

Gardez votre cerveau en forme



En prévenant les troubles cognitifs légers de façon personnalisée

Dans une certaine mesure, vieillir et oublier davantage peut être normal. Pour autant, beaucoup d'inquiétudes émergent lorsque les oublis s'accroissent et que les facultés mentales diminuent au-delà des seuils normaux : Est-ce que je deviens dément ? Le suis-je déjà ? Que puis-je faire contre l'oubli ?

Si vous aussi vous cherchez des réponses à ces questions, parlez à votre médecin. Il peut vous rediriger vers le programme démence prévention - pdp - au Luxembourg. Ce programme s'adresse aux individus dont la capacité mentale diminue et indique une déficience cognitive légère (en anglais : Mild Cognitive Impairment, MCI).



Le pdp a pour but de prévenir une démence naissante ou du moins de la retarder et souhaite montrer de nouvelles façons de rester en forme mentalement.





LE GOUVERNEMENT  
DU GRAND-DUCHÉ DE LUXEMBOURG  
Ministère de la Santé

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## Inequalities in Dementia



Risk of Dementia

Dementia Care



Dementia  
Research

Dementia  
Treatment



Leist, JAGS letter to editor, 2017

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## Thank you!



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Based on research funded by the European Research Council  
Grant agreement no. 803239, PI Anja Leist



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