Preventing Cognitive Decline and Dementia
A Way Forward

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for

Committee on Preventing Cognitive Decline
National Academies of Science, Engineering and Medicine

ADC Directors' Meeting
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Key Report Terminology

- ***Age-related cognitive decline*** **(ARCD): Deterioration in cognitive performance that can be a normal part of aging**
- ***Mild cognitive impairment*** **(MCI): A level of deterioration from normal cognitive function that is identifiable but without significant functional impairment in daily activities**
- ***Clinical Alzheimer's-type dementia*** **(CATD): Impairment severe enough that an individual cannot function independently**

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The Task

Examine the evidence on interventions for delaying or slowing ARCD and preventing, delaying, or slowing MCI and CATD, and recommend:

- **Interventions supported by sufficient evidence to be incorporated into public health strategies and messages**
- **Areas for future research**

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Committee on Preventing Dementia and Cognitive Impairment

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Study Background and Process

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Time for a Fresh Look at the Evidence

- 2010 AHRQ Review and state-of-the-science conference – no firm conclusions could be drawn regarding the efficacy of interventions
- 2015 IOM Cognitive Aging report – examined intervention and risk factor studies, but was not focused on MCI and dementia
- Pathophysiology increasingly better understood as new research emerges

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A Novel Study Model

Phase I: NASEM committee informs the design of an AHRQ systematic review

- Committee met with EPC December 2015
- AHRQ draft review released in September 2016 (final review, January 2017)

Phase II: NASEM Committee draws from the AHRQ systematic review and other evidence sources

- Testimony at Oct 2016 public workshop,
- Observational studies

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Why Supplemental Sources?

- AHRQ review focused only on RCT data
- RCTs challenging (eg, long follow-up requirement, comorbid conditions, secular dementia trends) and, in some cases, unethical
- Supplemental sources of evidence
  - Testimony from public workshop
  - Prospective cohort studies (intervention and risk factor studies)
  - Neurobiological studies (mechanistic and brain imaging biomarker studies)
  - Knowledge of benefits, harms, and costs

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Use of the Bradford Hill Criteria for Causal Inference

- When experimental evidence is lacking and epidemiological evidence suggests an association, Bradford Hill criteria can be used to determine if causal inferences can be drawn
- Criteria include: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence
- Where experimental evidence was inconsistent, committee used Bradford Hill criteria to assess whether relationship of interventions to cognitive outcomes consistent with causality

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Communicating With the Public About Interventions

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Strength of the Evidence for Interventions

- Insufficient evidence to justify a public health information campaign to encourage adoption of specific interventions
- Three interventions supported by encouraging, but inconclusive evidence
  - Cognitive training
  - Blood pressure management for people with hypertension
  - Increased physical activity
- All have minimal risk of harm, and two known to be beneficial for other conditions

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Cognitive Training
AHRQ Review Findings

- ACTIVE trial showed a complex cognitive training intervention can have long-term beneficial effects on cognitive performance and instrumental activities of daily living (IADL)
- Improvements in cognitive performance generally only in trained domain
- Methodological limitations of ACTIVE include booster selection process, use of a no-contact control, high attrition levels at 5- and 10-year time points, and no direct comparison of intervention arms
- Other cognitive training intervention studies too short to assess effects on ARCD, MCI and CATD

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Cognitive Training
Supplemental Evidence

- No observational studies identified for cognitive training
- Observational studies have suggested participating in cognitively stimulating activities (reading, games, craft activities) may lower risk of cognitive impairment
- Low educational attainment known modifiable risk factor for dementia

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Cognitive Training
Conclusions

- Despite limitations of ACTIVE trial, moderate strength RCT evidence suggests cognitive training can delay or slow ARCD
- No evidence that such beneficial long-term cognitive effects obtained with commercial, computer-based “brain training” applications
- No evidence that cognitive training prevents, delays, or slows MCI and CATD

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Blood Pressure Management
AHRQ Review Findings

- No evidence that BP management results in improved performance on cognitive tests
- Inconsistent RCT data for clinical outcomes – 1 of 4 RCTs evaluating MCI and CATD found beneficial effect of BP management on CATD incidence
- Excluding stroke-related dementia may underestimate the effect of antihypertension treatment

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Blood Pressure Management
Supplemental Evidence

- Cerebrovascular disease linked to dementia, vascular component of mixed dementia increasingly recognized
- Antihypertensives known to reduce stroke risk and subclinical cerebrovascular disease
- Prospective cohort studies have more consistently found associations between BP lowering and improved cognitive outcomes (dementia and cognitive performance)

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Blood Pressure Management
Conclusions

- RCT data do not offer strong support for BP management in patients with hypertension for delaying or slowing ARCD or preventing, delaying, or slowing MCI and CATD, although Syst-Eur trial provides some evidence of impact on risk of CATD
- Add-on trials with cardiovascular primary endpoints may not have been optimally designed to detect impact on cognitive outcomes
- Using Hill criteria, data from non-RCT studies suggest effects of BP management on incident CATD in hypertensives are consistent with a causal relationship

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Increased Physical Activity
AHRQ Review Findings

- Results from clinical trials of physical activity interventions were mixed in people with normal cognition and those with MCI
- Trial follow up periods generally too short to assess long term effects and MCI/CATD incidence rarely measured as an outcome
- Insufficient evidence to draw conclusions regarding the comparative effectiveness of aerobic activity and resistance training. Multicomponent intervention showed no benefit in largest RCT (LIFE trial)

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Increased Physical Activity
Supplemental Evidence

- Meta-analyses of observational studies have found consistently positive effects of physical activity on cognitive performance and dementia incidence
- In biomarker studies, physical activity has been shown to protect against declines in brain volume
- Physical activity may also reduce the risk of chronic conditions that are themselves risk factors for dementia (eg, hypertension, depression, diabetes)

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Increased Physical Activity
Conclusions

- Pattern of RCT results across different physical activity interventions provides an indication of effectiveness of increased physical activity for delaying or slowing ARCD
- Insufficient evidence to conclude whether increased physical activity will prevent, delay, or slow MCI or CATD
- Using Hill criteria, data from non-RCT studies suggest effects of physical activity on ARCD are consistent with a causal relationship

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Recommendation
Communicating with the Public

When communicating with the public, NIH, CDC and other interested organizations should make clear that positive effects of the following classes of interventions are supported by encouraging although inconclusive evidence:

- ***Cognitive training*** **to delay or slow ARCD;**
- ***Blood pressure management for people with hypertension*** **to prevent, delay, or slow CATD; and**
- ***Increased physical activity*** **to delay or slow ARCD**

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Future Research

A Way Forward

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Common Methodological Limitations

- Initiation of interventions at later life stages that may be outside optimal window for prevention
- Inadequate follow up to assess effects of interventions on long-term clinical outcomes
- Use of heterogeneous outcome measures and assessment tools precluded pooling results across studies
- Failure to collect baseline data on cognition
- Small sample sizes, underpowered studies, attrition
- Homogeneous study populations
- Suboptimal control groups

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Final Thoughts

- This report represents a snapshot of the state of the science in 2017 but new data constantly emerging and recs will need to be reassessed
- NIA and others need to consider criteria used to set the bar for public health messaging as RCTs may not always be possible or able to yield needed evidence
- RCTs and other studies have yielded encouraging data for some interventions and public should have access to this information to inform choices
- Committee is optimistic much more will be known on preventing ARCD and dementia in the near future

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Lancet Commission Report
July 20, 2017

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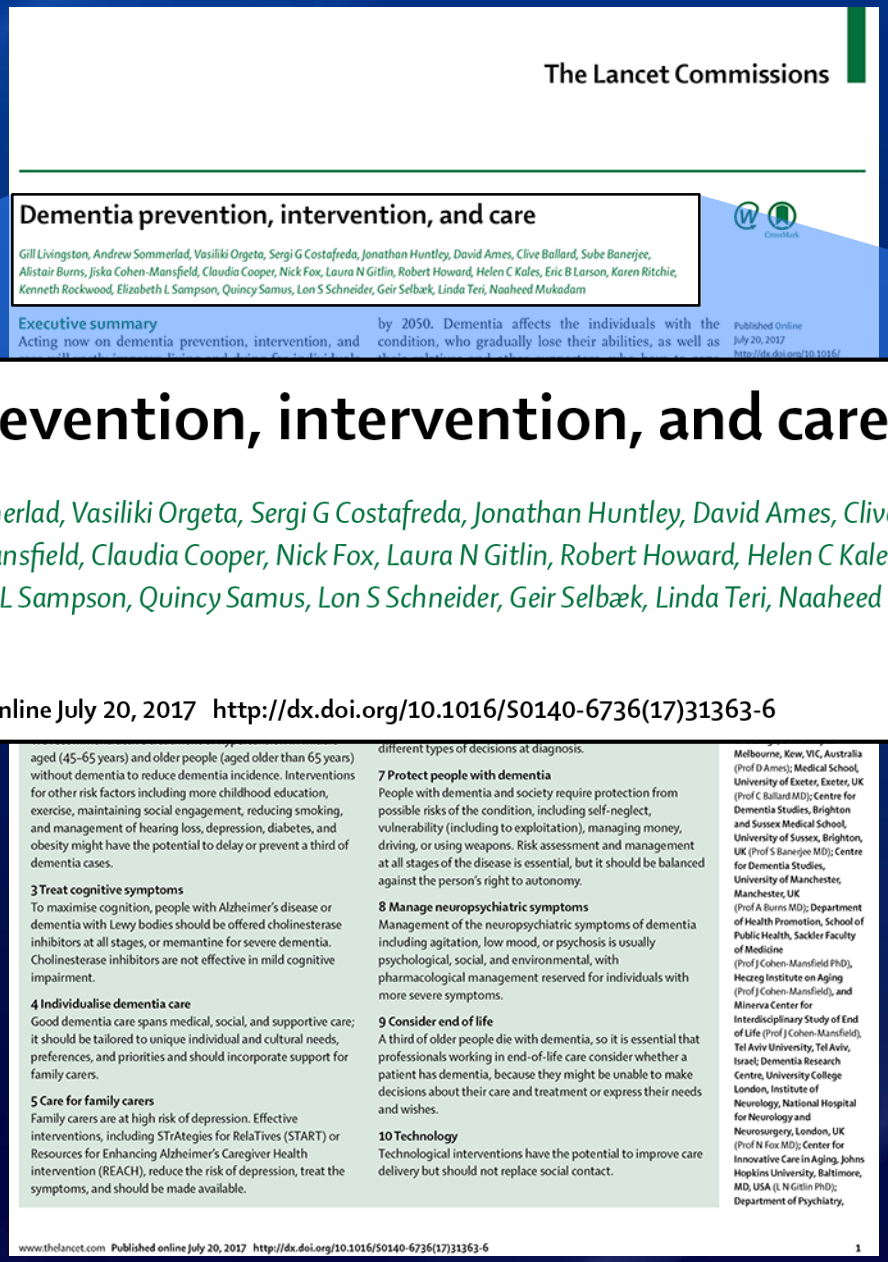

The Lancet Commissions

Dementia prevention, intervention, and care

Gill Livingston, Andrew Sommerlad, Vasiliki Orgeta, Sergi G Costafreda, Jonathan Huntley, David Ames, Clive Ballard, Sube Banerjee, Alistair Burns, Jiska Cohen-Mansfield, Claudia Cooper, Nick Fox, Laura N Gitlin, Robert Howard, Helen C Kales, Eric B Larson, Karen Ritchie, Kenneth Rockwood, Elizabeth L Sampson, Quincy Samus, Lon S Schneider, Geir Selbæk, Linda Teri, Naaheed Mukadam

Executive summary

Acting now on dementia prevention, intervention, and

by 2050. Dementia affects the individuals with the condition, who gradually lose their abilities, as well as

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aged (45–65 years) and older people (aged older than 65 years) without dementia to reduce dementia incidence. Interventions for other risk factors including more childhood education, exercise, maintaining social engagement, reducing smoking, and management of hearing loss, depression, diabetes, and obesity might have the potential to delay or prevent a third of dementia cases.

3 Treat cognitive symptoms

To maximise cognition, people with Alzheimer's disease or dementia with Lewy bodies should be offered cholinesterase inhibitors at all stages, or memantine for severe dementia. Cholinesterase inhibitors are not effective in mild cognitive impairment.

4 Individualise dementia care

Good dementia care spans medical, social, and supportive care; it should be tailored to unique individual and cultural needs, preferences, and priorities and should incorporate support for family carers.

5 Care for family carers

Family carers are at high risk of depression. Effective interventions, including STrAtegies for RelaTives (START) or Resources for Enhancing Alzheimer's Caregiver Health intervention (REACH), reduce the risk of depression, treat the symptoms, and should be made available.

different types of decisions at diagnosis.

7 Protect people with dementia

People with dementia and society require protection from possible risks of the condition, including self-neglect, vulnerability (including to exploitation), managing money, driving, or using weapons. Risk assessment and management at all stages of the disease is essential, but it should be balanced against the person's right to autonomy.

8 Manage neuropsychiatric symptoms

Management of the neuropsychiatric symptoms of dementia including agitation, low mood, or psychosis is usually psychological, social, and environmental, with pharmacological management reserved for individuals with more severe symptoms.

9 Consider end of life

A third of older people die with dementia, so it is essential that professionals working in end-of-life care consider whether a patient has dementia, because they might be unable to make decisions about their care and treatment or express their needs and wishes.

10 Technology

Technological interventions have the potential to improve care delivery but should not replace social contact.

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NASEM Report vs. Lancet Commission Report

- Different methodologies
  - Evidence-based medicine review
  - Evidence plus expert opinion

- Different questions
  - Interventions
  - Interventions plus risk factors

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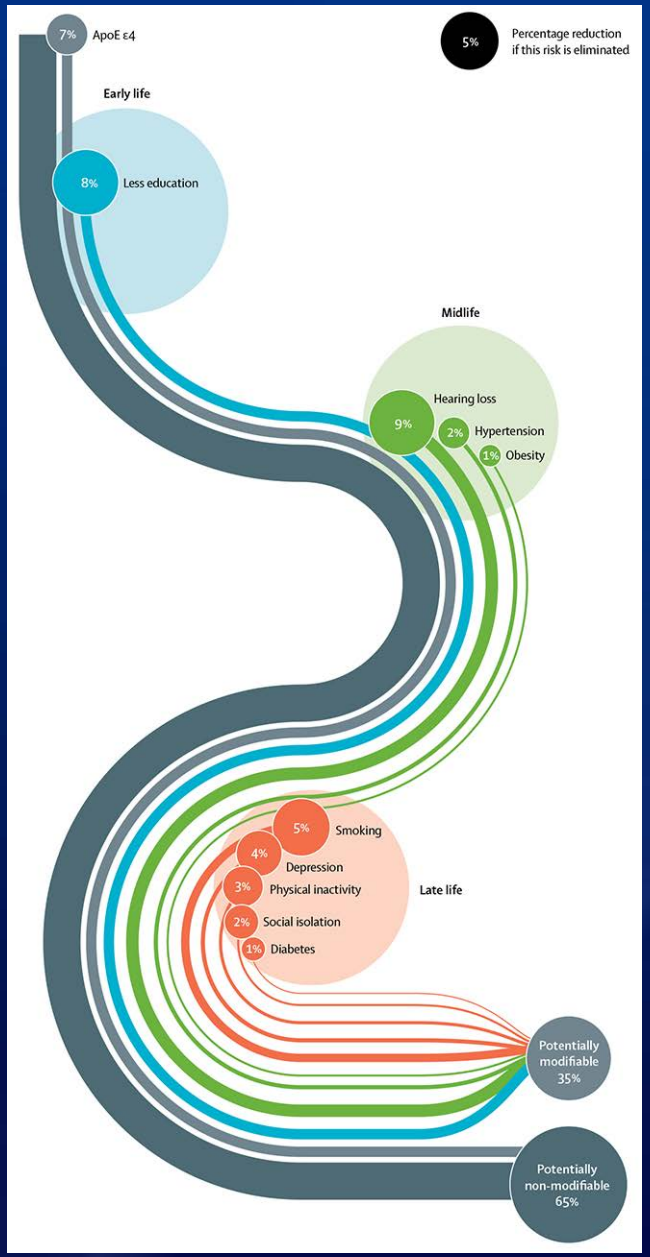
Life-Course Model of Contribution of Modifiable Risk Factors to Dementia



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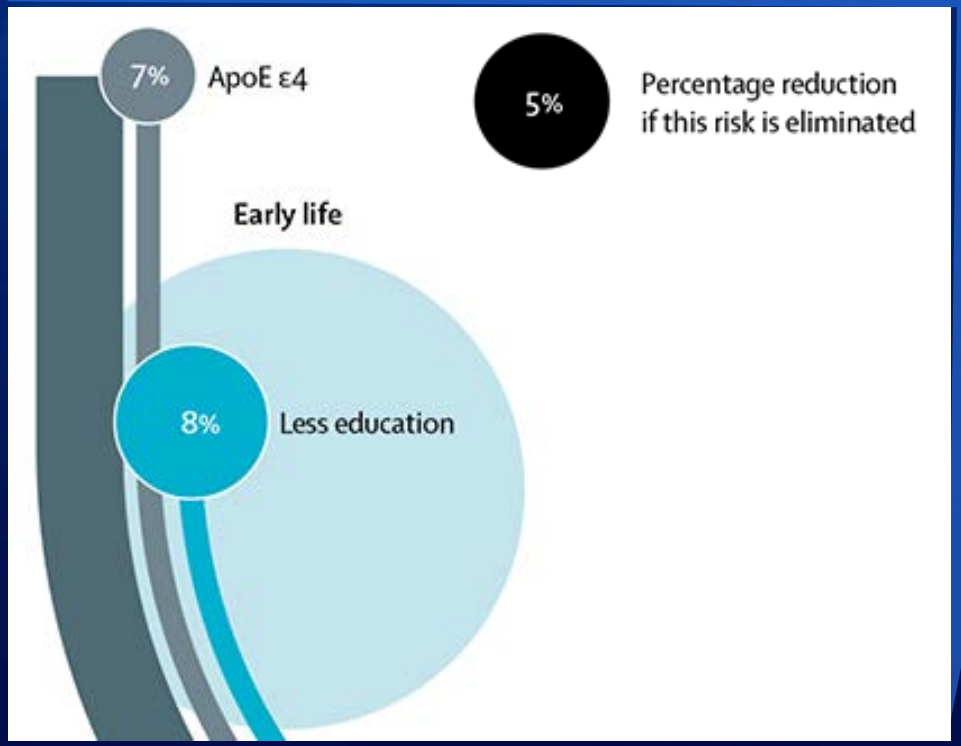

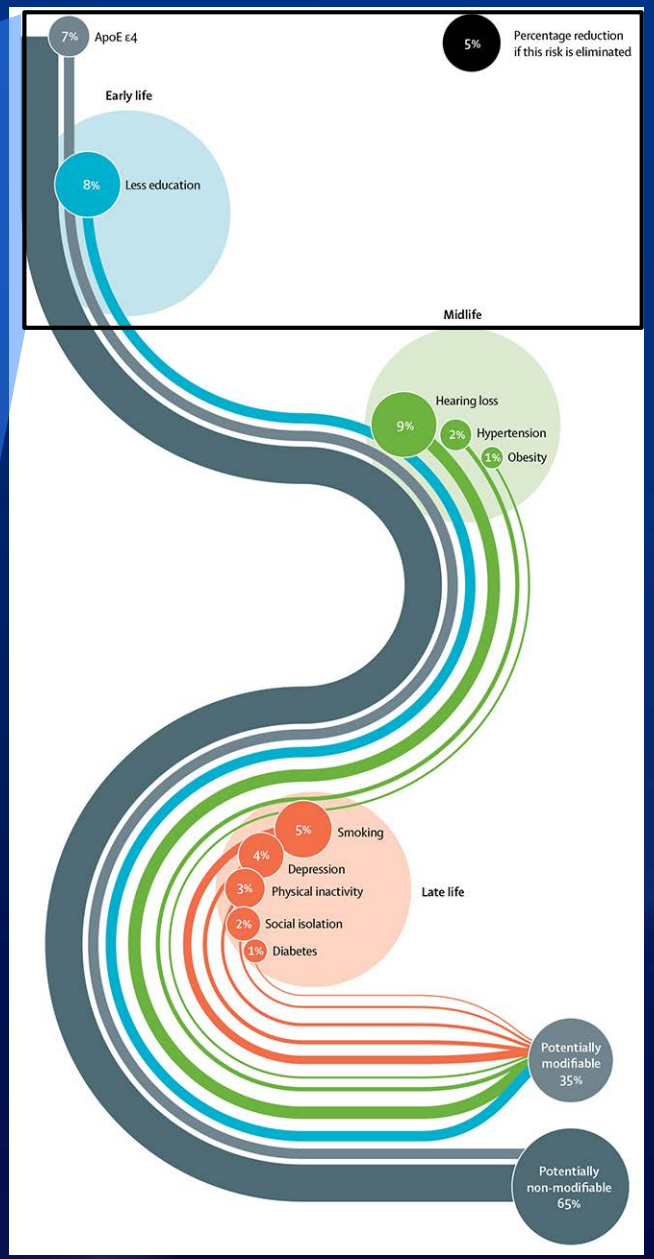

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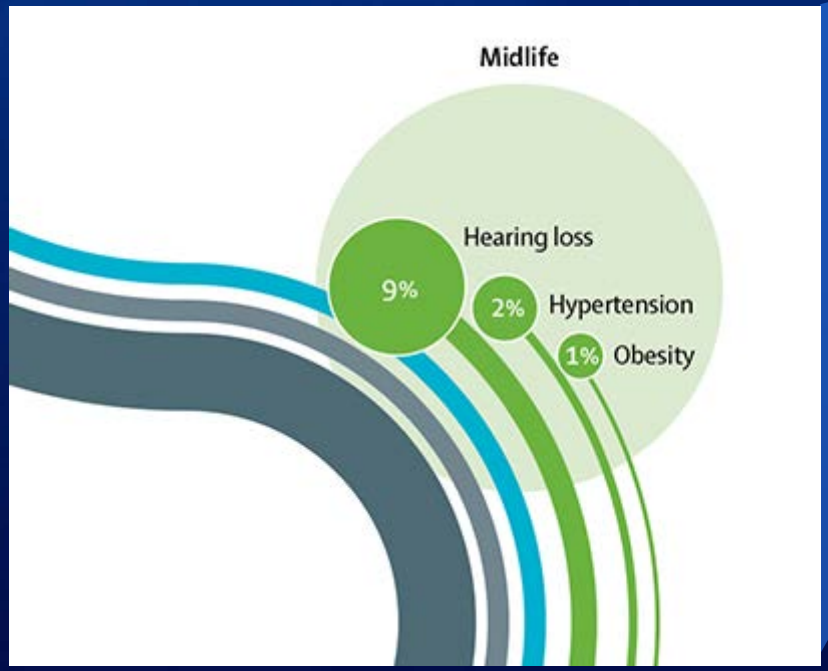

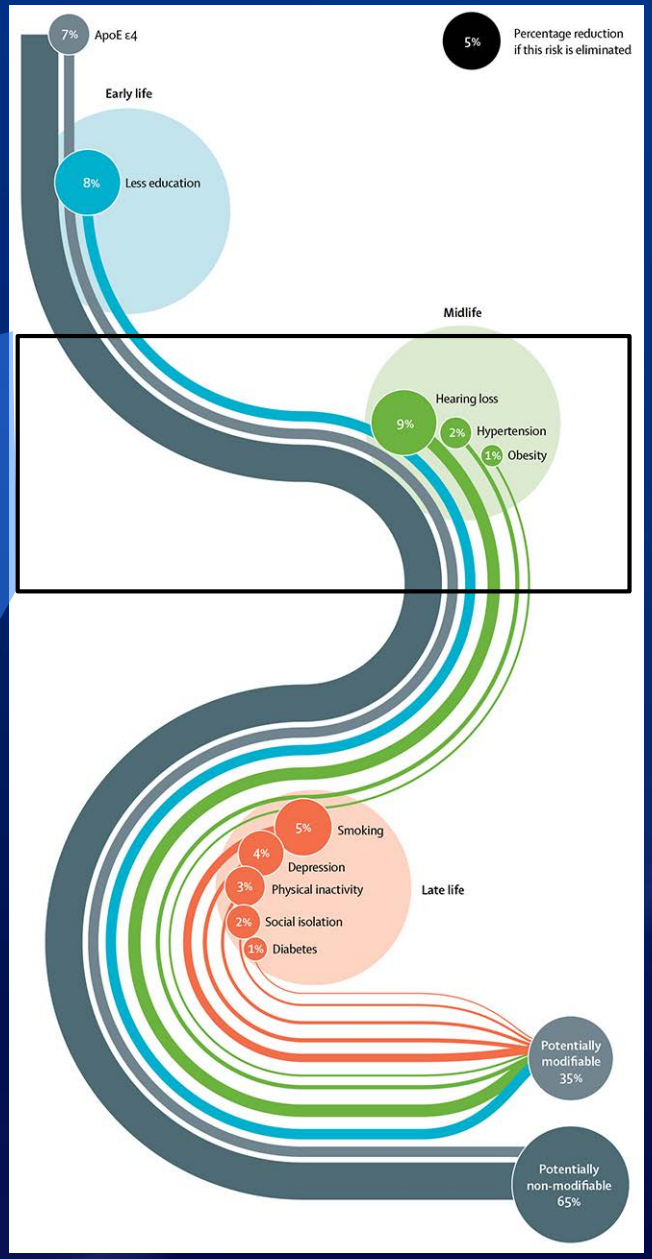

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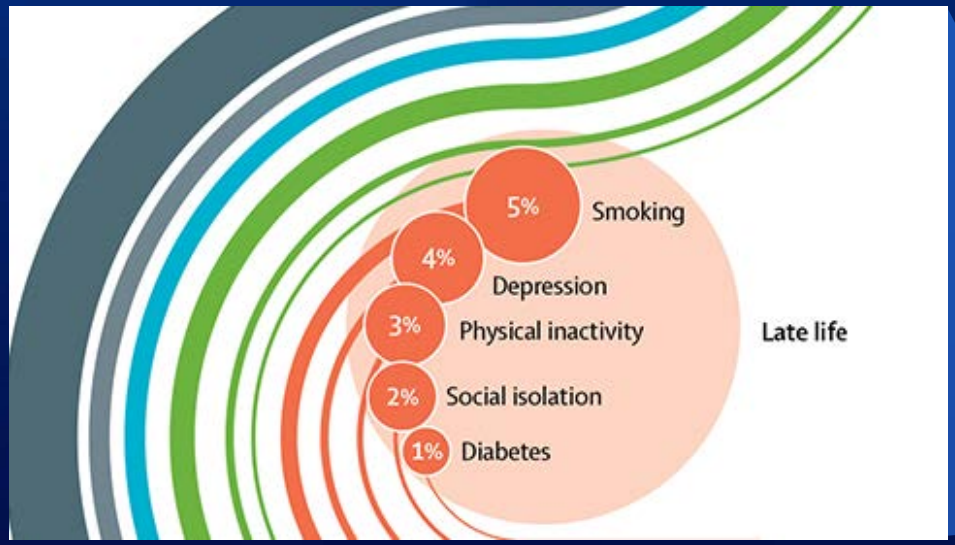

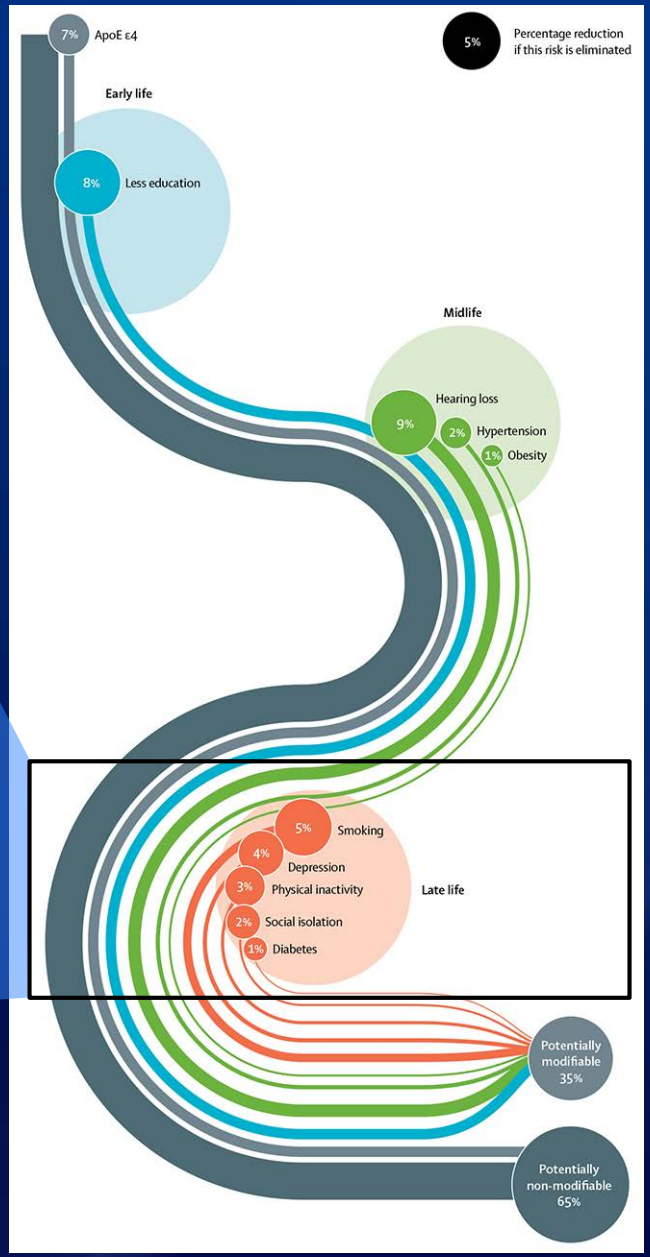

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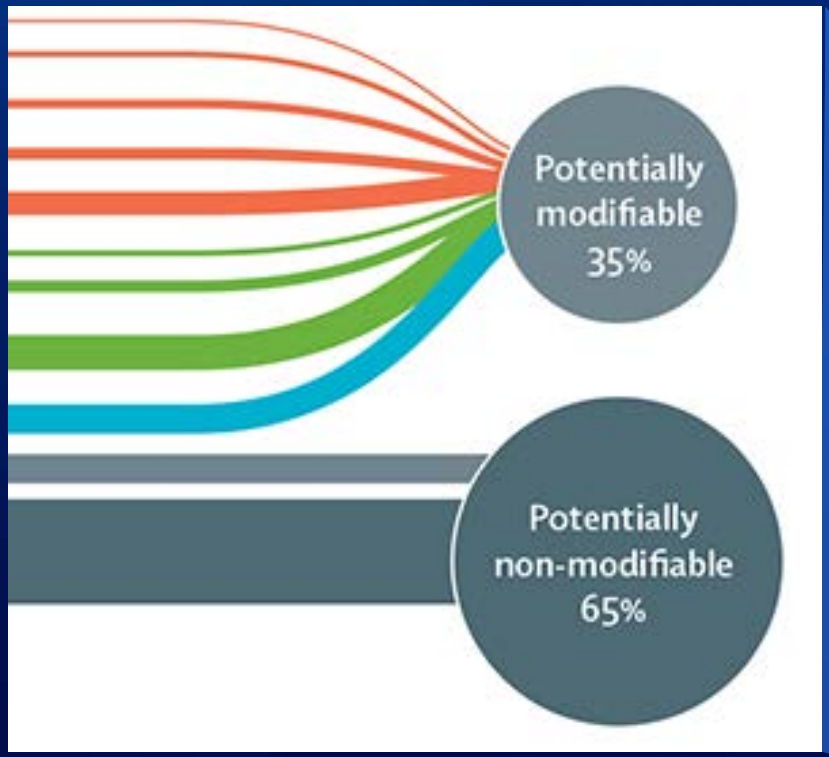

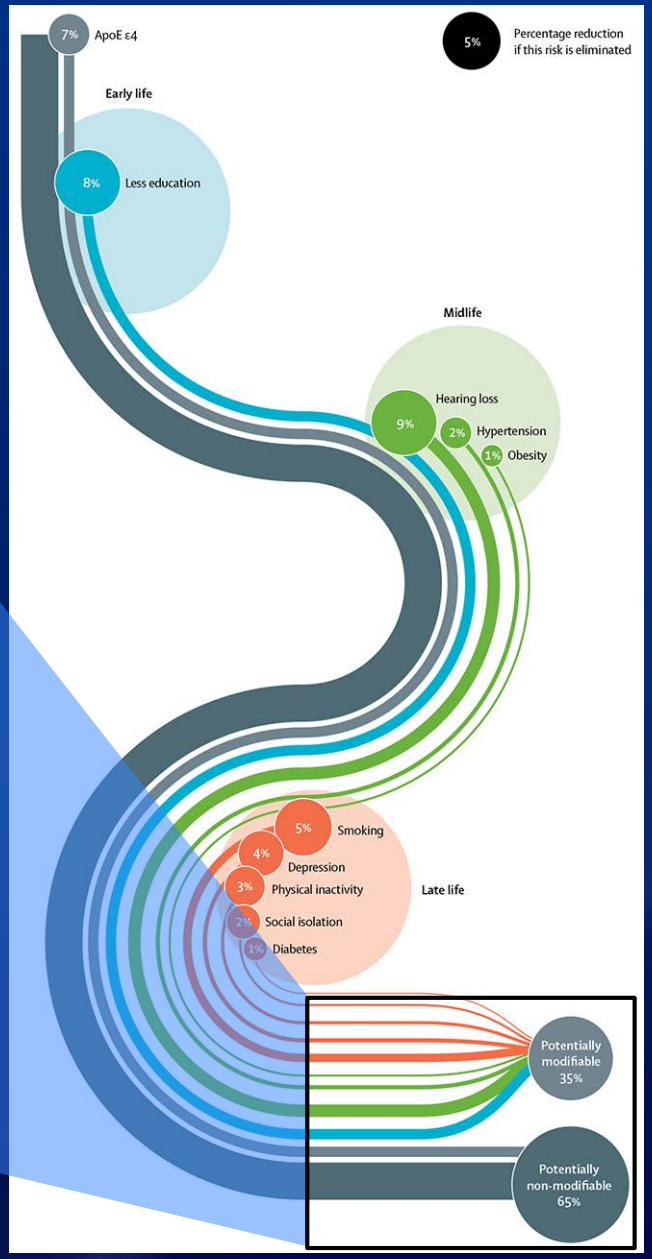

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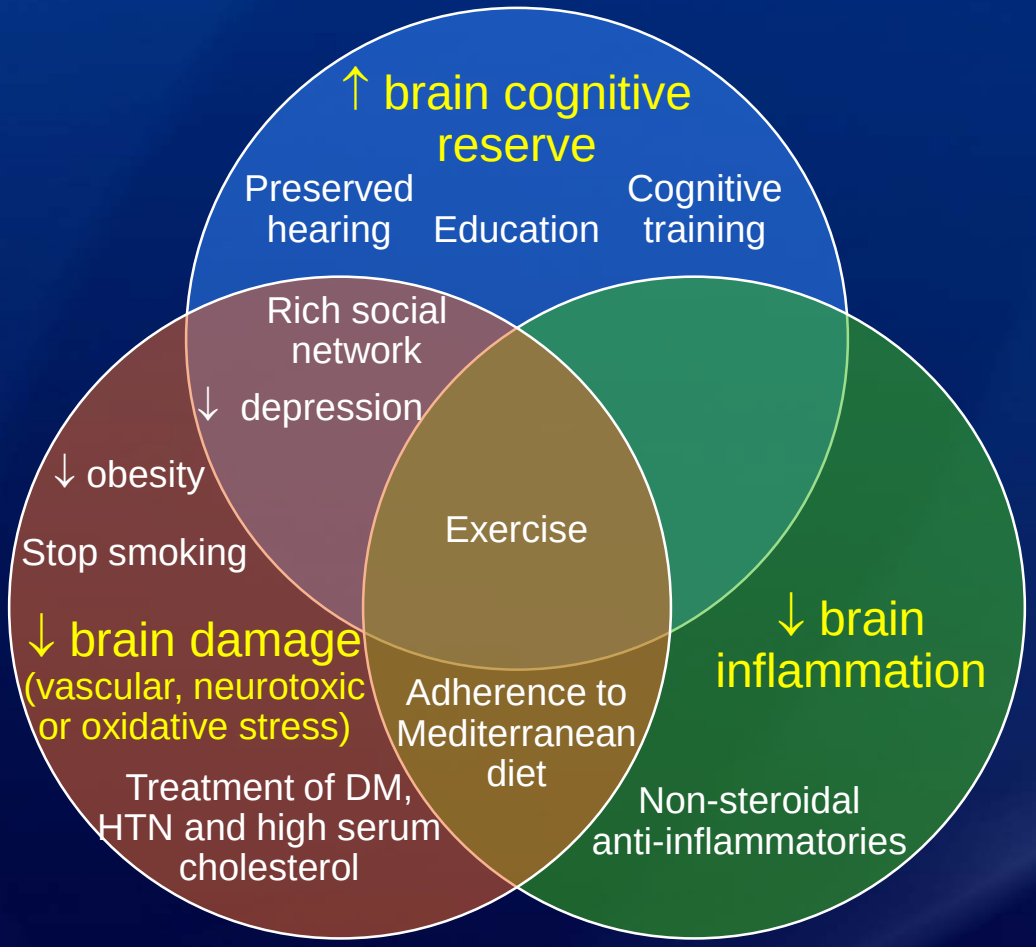
Potential Brain Mechanisms for Preventive Strategies in Dementia



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Thank You

For more information about the study, please contact:
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