Preventing Dementia

What risk factors should we target and in whom?

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Overview

• The changing landscape of dementia
• Vascular risk factors and dementia
• Lifestyle and dementia
• Sleep and dementia
• Conclusions
Dementia: A Growing Health Concern

The global impact of dementia

131.5 million people will be living with dementia by 2050.

68% in low and middle income countries.

2 out of 3 people globally believe there is little or no understanding of dementia in their countries.

Every 3 seconds, someone in the world develops dementia.

Source: Dementia Alliance International
Neighbourhood Advantage & Dementia Risk

• Cross-sectional study of 4656 Australian adults aged 40 to 70 years

• Higher neighborhood-level SES was associated with better memory and lower dementia risk scores

• Findings were independent of rurality

Pase et al JAMA Open, 2022
The Average Persons Risk of Dementia Is:

1) Higher than that of their parents
2) Lower than that of their parents
3) The same as their parents
The Changing Landscape of Dementia

Projected incidence of dementia in millions based on current rates (solid lines) and assuming a decreasing trend (dashed lines)

Incidence trends per decade
\(N = 59,230; 5,133\) cases

Wolters et al Neurology. 2020
Possible risk factors for AD & dementia

- Depression
- Obesity
- Hypertension
- Physical inactivity
- Diabetes
- Poor social contact
- Alcohol consumption
- Hearing impairment
- Smoking
- Traumatic brain injury
- Air pollution
- Less education
- Poor diet
- Low social contact
- Hearing impairment
What is the Relationship between Vascular Health and Dementia?
AWARD 1 POINT FOR EACH:

1. Non Smoker
2. Optimal Cholesterol
3. Optimal BMI
4. Physically active
5. Optimal Blood Glucose
6. Optimal BP
7. Healthy Diet
A 1-point higher CVH score reduced the rate of decline in frontal brain volume to that of someone 3.4 years younger.

Methods
Over 2,500 subjects followed for 10-years with uninterrupted surveillance for dementia & multiple rounds of brain MRI, and neuropsyc testing.

Results
Higher Ideal CVH predicted a lower risk of
- Incident stroke (HR = 0.83, 95% CI 0.71-0.97)
- Incident VaD (HR = 0.61, 95% CI 0.39–0.95)
- Incident AD dementia (HR = 0.79, 95% CI 0.64–0.98)
- less cognitive decline (particularly visual memory and reasoning)
- less brain atrophy on MRI

Pase et al Stroke. 2016
5-Year Cumulative Hazards for Dementia by Genetic Risk and Ideal CVH

Peloso et al Neurology. 2020
Is the Association between Vascular & Brain Health Age Dependent?

HTN associated with 7 years of brain ageing

Mean age, 42 years

HTN associated with 2 years of brain ageing

Mean age, 62 years
Association between VRF burden and Brain Volume is Age Dependent

A lower value indicates a stronger link between vascular risk factors and smaller brain volume.

N = 2,887
What Best Predicts MRI Brain Volume at Age 85?

• Vascular risk factors measured at the same time as the MRI (i.e. age 85)
• Vascular risk factors measured 10 years ago (i.e. age 75)
• Vascular risk factors measured 20 years ago (i.e. age 65)
• Vascular risk factors measured 40 years ago (i.e. age 45)
Past VRF Burden & Brain Volume

D. Brain volume at age 85

N = 7,868
VRF Burden & Neuropathology

- **Objective:** To examine the association between VRF burden and neuropathology at autopsy (N, 129)
- **Design:** VRF burden was measured in midlife (mean, 33 years < death) and as close to death as possible (mean, 4 years < death)

Conner, Pase, et al. ACTN.2019
Association between systolic blood pressure and dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define hypertension

Jessica G. Abbé1,2, Mika Kivimäki1, Aline Dugravot1, Adam G. Tabak1,3, Aurore Fayosse1, Martin Shipley1, Séverine Sabia1,2, and Archana Singh-Manoux1,3,4,5

Singh-Manoux. EHJ, 2018 0, 1-7.
What BP lowering meds are most effective for dementia prevention?

- 1) ACE Inhibitors
- 2) ARBs
- 3) Beta-blockers
- 4) CCB
- 5) Any
In people with high BP, treatment for high BP was associated with a reduced risk of developing (HR, 0.88; 95% CI 0.79-0.98)

Ding et al Lancet Neurology. 2020
What is the Relationship between Lifestyle Risk Factors and Dementia?
Light Intensity PA & Brain Volume

• **Background**: Most adults do not meet the recommended PA guidelines (150min moderate to vigorous PA/week)

• **Design**: Cross-sectional assessment of MRI brain volumes and accelerometry-derived total activity (steps/d) and intensity.

• **Results**: Each additional hour of light intensity PA was associated with larger brain volumes (equiv. to 1.1y of aging), even among persons not meeting current PA guidelines.

• **Importance**: Benefits of PA on brain aging may accrue at a lower more achievable level of intensity or duration
Sugary Drinks & Brain Aging

Pase et al. Alzheimer's & Dementia. 2017
Sugary Drinks & Brain Aging

Cumulative consumption of diet soda and event-free survival of incident dementia. Green, red, and blue lines denote intake of 0/wk, >0 to 6/wk, and ≥1/d, respectively.

Pase et al. Stroke, 2017
# MIND Diet & the Brain

Table 1
Dietary component servings and maximum scores for the DASH, Mediterranean, and MIND diet scores

<table>
<thead>
<tr>
<th>DASH® components</th>
<th>Max score</th>
<th>MedDiet† components</th>
<th>Max score</th>
<th>MIND components</th>
<th>Max score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total grains ≥7/d</td>
<td>1</td>
<td>Nonrefined Grains &gt;4/d</td>
<td>5</td>
<td>Whole Grains ≥3/d</td>
<td>1</td>
</tr>
<tr>
<td>Vegetables ≥4/d</td>
<td>1</td>
<td>Vegetables &gt;4/d</td>
<td>5</td>
<td>Green Leafy ≥6/wk</td>
<td>1</td>
</tr>
<tr>
<td>Fruits ≥4/d</td>
<td>1</td>
<td>Potatoes &gt;2/d</td>
<td>5</td>
<td>Other Vegetables ≥1/d</td>
<td>1</td>
</tr>
<tr>
<td>Dairy ≥2/d</td>
<td>1</td>
<td>Fruits &gt;3/d</td>
<td>5</td>
<td>Berries ≥2/wk</td>
<td>1</td>
</tr>
<tr>
<td>Meat, poultry and fish ≤2/d</td>
<td>1</td>
<td>Red meat ≤1/wk</td>
<td>5</td>
<td>Red Meats and products &lt;4/wk</td>
<td>1</td>
</tr>
<tr>
<td>Nuts, seeds &amp; legumes ≥4/wk</td>
<td>1</td>
<td>Fish &gt;6/wk</td>
<td>5</td>
<td>Fish ≥1/wk</td>
<td>1</td>
</tr>
<tr>
<td>Nuts, seeds &amp; legumes ≥4/wk</td>
<td>1</td>
<td>Poultry ≤3/wk</td>
<td>5</td>
<td>Poultry ≥2/wk</td>
<td>1</td>
</tr>
<tr>
<td>Nuts, seeds &amp; legumes ≥4/wk</td>
<td>1</td>
<td>Legumes, nuts &amp; beans &gt;6/wk</td>
<td>5</td>
<td>Beans ≥3/wk</td>
<td>1</td>
</tr>
<tr>
<td>Total fat ≤27% of kcal</td>
<td>1</td>
<td>Olive oil ≥1/d</td>
<td>5</td>
<td>Nuts ≥5/wk</td>
<td>1</td>
</tr>
<tr>
<td>Saturated fat ≤6% of kcal</td>
<td>1</td>
<td>Olive Oil primary oil</td>
<td>1</td>
<td>Fast/fried food &lt;1/wk</td>
<td>1</td>
</tr>
<tr>
<td>Sweets ≤5/wk</td>
<td>1</td>
<td>Butter, margarine &lt;1 T/d</td>
<td>1</td>
<td>Cheese &lt;1/wk</td>
<td>1</td>
</tr>
<tr>
<td>Sodium ≤2400 mg/d</td>
<td>1</td>
<td>Cheese &lt;1/wk</td>
<td>1</td>
<td>Pastries, sweets &lt;5/wk</td>
<td>1</td>
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<tr>
<td>Total DASH Score</td>
<td>10</td>
<td>Alcohol &lt;300 mL/d but &gt;0</td>
<td>5</td>
<td>Alcohol/wine 1/d</td>
<td>1</td>
</tr>
<tr>
<td>Total MedDiet Score</td>
<td>55</td>
<td>Total MIND Score</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MIND Diet & the Brain

- We studied 2092 dementia-free participants followed for 10-years
- MIND diet scores were averaged across 3 timepoints
- Higher MIND diet scores also predict superior global cognition, verbal memory, visual memory, processing speed, verbal comprehension, and larger brain volume on MRI
What is the Relationship between Sleep and Dementia?
‘The restorative function of sleep may be a consequence of the enhanced removal of potential neurotoxic waste products that accumulate in the awake CNS’ (Xie et al., 2013 Science)
• 511 participants (aged 59±9 years; 49% men) from the community with self reported insomnia symptoms and cognition 3 years later

• Increased severity of insomnia symptoms was associated with poorer global cognition and verbal episodic memory measured approximately 3 years later

• The effect was particularly apparent in APOE e4 carriers

Baril...Pase, Alzheimer’s & Dementia (2021)
Insomnia & AD biomarkers

(A) Association between Insomnia Symptom Severity (ISI) score (continuous variable) and Aβ42

(B) Association between ISI score (high vs low) and Aβ42. Models are adjusted for age and sex.

Cohen's d = 0.58
p = 0.03
Prolonged sleep duration as a marker of early neurodegeneration predicting incident dementia

ABSTRACT

Objective: To evaluate the association between sleep duration and the risk of incident dementia and brain aging.

Methods: Self-reported total hours of sleep were examined in the Framingham Heart Study (n = 2,457, mean age 72 ± 6 years, 57% women) as a 3-level variable: ≤6 hours (short), 6-9 hours (reference), and >9 hours (long), and was related to the risk of incident dementia over 10 years, and cross-sectionally to total cerebral brain volume (TCBV) and cognitive performance.

Results: We observed 234 cases of all-cause dementia over 10 years of follow-up. In multivariable analyses, prolonged sleep duration was associated with an increased risk of incident dementia (hazard ratio [HR], 2.01; 95% confidence interval [CI], 1.24-3.28). These findings were driven...
Sleep Time & Dementia Risk

Sleep time in the past (13 years earlier)

Sleeping >9 hrs: x 2↑ in risk of dementia
Always sleeping >9 hrs: no ↑ in risk of dementia
Recently sleeping >9 hrs: x2.4↑ in risk of dementia
Recently sleeping >9 hrs + having thinking problems: x 6↑ in risk of dementia

Sleep time at baseline

10-year risk of dementia

HR, 2.04 (95% CI: 1.26-3.30)
HR, 1.34 (95% CI: 0.42-4.26)
HR, 2.43 (95% CI: 1.44-4.11)
HR, 6.01 (95% CI: 1.48-24.43)

Neurology. 2017.88(12):1172-1179
# Sleep Architecture & Dementia Risk

Models are adjusted for age and sex. Results were unchanged with adjusting for BMI, education level, APOE ε4, smoking, SBP, Rx for hypertension, DM, CHD, depressive symptoms, sleeping meds, antidepressants, & anxiolytics.

## Sleep Architecture & Dementia Risk at Baseline vs. Risk of Dementia up to 19 Years Later

<table>
<thead>
<tr>
<th></th>
<th>All-Dementia</th>
<th>AD Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Stage 1, %</td>
<td>1.08 (0.99, 1.17)</td>
<td>0.10</td>
</tr>
<tr>
<td>Stage 2, %</td>
<td>1.01 (0.98, 1.04)</td>
<td>0.70</td>
</tr>
<tr>
<td>SWS, %</td>
<td>1.07 (0.82, 1.40)</td>
<td>0.61</td>
</tr>
<tr>
<td>REM, %</td>
<td>0.91 (0.86, 0.97)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Pase et al. *Neurology*. 2017;89(12):1244-1250
Slow Wave Sleep & Brain Aging

- **Methods.** N = 492 with a brain MRI and in-home overnight PSG

- **Results:** Longer SWS duration associated with higher cortical and subcortical brain volume, and lower WMHV volume. SWS duration did not associate with hippocampal volume.

- **Interpretation:** More SWS was associated with a healthier brain

<table>
<thead>
<tr>
<th></th>
<th>Absolute SWS duration</th>
<th>SWS percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (SE)</td>
<td>p</td>
</tr>
<tr>
<td>Total brain volume, % of ICV</td>
<td>0.08 (0.03)</td>
<td>0.017</td>
</tr>
<tr>
<td>Cortical GM volume, % of ICV</td>
<td>0.08 (0.03)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Subcortical GM volume, % of ICV</td>
<td>0.009 (0.005)</td>
<td>0.082</td>
</tr>
<tr>
<td>Hippocampal volume, % of ICV</td>
<td>-0.001 (0.001)</td>
<td>0.590</td>
</tr>
<tr>
<td>WMHV, % of ICV</td>
<td>-0.05 (0.02)</td>
<td><strong>0.002</strong></td>
</tr>
</tbody>
</table>
Does Treating Sleep Apnea Improve Cognition?

Treating sleep apnoea reduces daytime sleepiness but has no effect on cognition.

Pooled effects CPAP treatment on cognition

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>g</th>
<th>95% CI</th>
<th>p</th>
<th>Hedge's g</th>
<th>95% CI lower</th>
<th>95% CI upper</th>
<th>p</th>
<th>I^2 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barnes - CPAP (2004)</td>
<td>0.18</td>
<td>[-0.18; 0.54]</td>
<td>.34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dalmaes (2015)</td>
<td>-0.09</td>
<td>[-0.79; 0.61]</td>
<td>.80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kushida (2012)</td>
<td>0.24</td>
<td>[0.11; 0.38]</td>
<td>&lt; .01</td>
<td></td>
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<tr>
<td>Martínez-Garcia (2015)</td>
<td>0.88</td>
<td>[0.61; 1.16]</td>
<td>&lt; .01</td>
<td></td>
<td></td>
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<tr>
<td>McMillan (2015)</td>
<td>0.50</td>
<td>[0.25; 0.76]</td>
<td>&lt; .01</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Monasterio (2001)</td>
<td>0.41</td>
<td>[0.05; 0.76]</td>
<td>.02</td>
<td></td>
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</tr>
<tr>
<td>Pelletier-Fleury ≥30 (2004)</td>
<td>0.98</td>
<td>[0.58; 1.38]</td>
<td>&lt; .01</td>
<td></td>
<td></td>
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<tr>
<td>Pelletier-Fleury &lt;30 (2004)</td>
<td>0.81</td>
<td>[0.30; 1.33]</td>
<td>&lt; .01</td>
<td></td>
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<tr>
<td>Ponce (2019)</td>
<td>0.65</td>
<td>[0.32; 0.99]</td>
<td>&lt; .01</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Wu (2016)</td>
<td>1.41</td>
<td>[1.04; 1.79]</td>
<td>&lt; .01</td>
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</tbody>
</table>

Random effects model 0.61 [0.36; 0.86]

Heterogeneity: I^2 = 84%, p < .01
Test for overall effect: z = 4.73 (p < .01)
Summary

Dementia risk differs by age, geographic location, advantage, and time.

Maintaining a healthy heart at an early age is important for preserving brain health with advancing age.

Aspects of lifestyle, such as adequate sleep, may be involved in dementia pathogenesis.
Acknowledgements

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Ella Rowsthorn
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Lachlan Cribb
Maddie Gibson

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bachcohortstudy.com

Australian Government
NHMRC National Institute for Dementia Research

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National Institute on Aging