Dementia Prevention, Intervention and Care

What works – and where do we need more research?

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Dr Andrew Sommerlad

Wellcome Trust Research Fellow
UCL Division of Psychiatry
Declaration of interest

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- I do not own any shares
- I have no conflicts of interest to declare
Why the commission?

- The greatest global challenge for health and social care in the 21st century
- Dementia is the most feared disease
- Currently nearly 50 million live with it
- Cost $800 billion rising to £2 trillion by 2050
- Important and relatively neglected area
Gill Livingston
Andrew Sommerlad
Vasiliki Orgeta
Sergi Costafreda
Jonathan Huntley
David Ames
Clive Ballard
Sube Banerjee
Alistair Burns
Jiska Cohen-Mansfield
Claudia Cooper
Nick Fox
Laura Gitlin
Robert Howard
Helen Kales
Eric Larson
Karen Ritchie
Kenneth Rockwood
Elizabeth Sampson
Quincy Samus
Lon Schneider
Geir Selbæk
Linda Teri
Naaheed Mukadam
The Lancet Commission on dementia

“Effective dementia prevention, intervention, and care could transform the future for society and vastly improve living and dying for individuals with dementia and their families. Acting now on what we already know can make this difference happen.”
Key messages

1. The number of people with dementia is increasing globally
2. Be ambitious about prevention
3. Treat cognitive symptoms
4. Individualise dementia care
5. Care for family carers
6. Plan for the future
7. Protect people with dementia
8. Manage neuropsychiatric symptoms
9. Consider end of life
10. The future role of technology
Key messages

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The number of people with dementia is increasing globally

- Expected to rise to 132 million by 2050
- Particularly in low and medium income countries
  - *but* incidence in some countries has *decreased*
  - *so* dementia is potentially preventable
Incidence ↓ by about 20% in past 20 years
- US, UK, Sweden, Netherlands, Canada
  - in those who are more educated
- Stable in Nigeria
- Increase in China and Japan

More dementia as more older people

<table>
<thead>
<tr>
<th>Year</th>
<th>Projection of the elderly population (aged 60+)</th>
<th>Estimate of elderly with dementia (aged 60+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>1,435,346</td>
<td>87,319</td>
</tr>
<tr>
<td>2020</td>
<td>1,504,341</td>
<td>93,506</td>
</tr>
<tr>
<td>2025</td>
<td>1,638,715</td>
<td>106,877</td>
</tr>
<tr>
<td>2030</td>
<td>1,766,528</td>
<td>122,738</td>
</tr>
<tr>
<td>2035</td>
<td>1,850,019</td>
<td>138,097</td>
</tr>
<tr>
<td>2040</td>
<td>1,888,297</td>
<td>149,882</td>
</tr>
</tbody>
</table>


We expect the prevalence of dementia in Denmark to increase by 50% in 2030 and perhaps 70% in 2040 – unless effective risk reduction strategies or curative treatments are implemented in the meantime.
Lifestyles have changed:

- Fewer people smoking
- More education
- Reduced cardiovascular risk factors and mortality

Jousilahti et al, BMJ 2016
But there is the potential for reversal of the trend:

Increased obesity

More diabetes

Increased hypertension and treatment
Be ambitious about prevention

Hand washing to prevent puerperal fever

Cleaning water sources to prevent cholera

Use of condoms to prevent AIDS

WHO 1987
Life course model for dementia prevention

- It's never too early
- It's never too late

• This is first life-course analysis
  • Defined mid life as age 45-65
  • Later life as >65

• Used NICE 2015 and NIH (Daviglus 2010) guidelines

• Calculated the population attributable fraction for dementia
PAF calculation

- Population Attributable Fraction
- Fraction theoretically prevented by eliminating risk factor
- Calculated by
  - Relative risk (how risk is increased) using meta-analyses
  - Prevalence (how common the risk is in the population)

- Used all-cause rather than AD dementia
- International data when available

- Combined risk accounting for substantial overlap
Nine factors

Early life (<45)
- Education

Mid life (45 – 65)
- Hypertension
- Obesity
- Peripheral hearing loss

Late life (>65)
- Smoking
- Depression
- Physical inactivity
- Social isolation
- Diabetes
Hearing loss

- Three studies
  - Non-demented participants
  - > 5 years follow up
  - Objective assessment (e.g. pure tone audiometry)
- Follow-up over 9 years, 12 years, and 17 years
- Each found peripheral hearing loss increased risk
- Pooled RR of 1·94
Potentially modifiable risk factors

35%

Hearing loss 9%
Education 8%
Smoking 5%
Depression 4%
Physical inactivity 4%
ApoE ε4 7%
Increased brain cognitive reserve

Preserved hearing  Education  Cognitive training

Rich social network

Reduced obesity

Stop smoking

Reduced depression

Reduced brain damage (vascular, neurotoxic, or oxidative stress)

Treatment of diabetes, hypertension, and high serum cholesterol

Exercise

Adherence to Mediterranean diet

Reduced brain inflammation

Non-steroidal anti-inflammatories
Cognitive reserve

Increased brain anatomical substrate or greater adaptability of cognition

Some people with neuropathology do not have dementia
Can we prevent dementia?

- Randomised controlled trials have been underwhelming
- FINGER trial had small cognitive benefit
- Other multi-domain trials ineffective
- RCTs are sometimes impossible and may not be needed
  - Smoking, social contact
  - Treating hypertension

Ngandu et al 2015

Peters et al 2008
Prevention: What do we need to know?

- Causal direction

Singh-Manoux et al 2017
Other potential risk factors

- Head injury
- Pollution
- Alcohol
- Sleep disorders
- Diet
Prevention: What do we need to know?

• Causal direction

• Other potential risk factors

• **How and when** to modify risk factors
  – Worldwide FINGER study
  – Technological approaches

Singh-Manouix et al 2017
Intervention for dementia

• Treating cognitive symptoms

• Manage neuropsychiatric symptoms

• Care for family carers

• Diagnosis is a prerequisite to deliver this
Treat cognitive symptoms

- Donepezil, rivastigmine and galantamine approved for AD, DLB, PDD
- Target biochemical abnormalities
- Not neuroprotective or disease-modifying
Cholinesterase inhibitors in Alzheimer’s Disease

Cognition

Global impression
Prescription of cholinesterase inhibitors gives benefit in clinical practice

- 4.2 points/year

Perera et al, Plos One 2014
• Stopping donepezil in mod/severe AD leads to faster MMSE decline

• Continue drugs unless significant side-effects

Howard et al, 2012
# Memantine and cognition

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Memantine, N</th>
<th>Mean (SD)</th>
<th>Placebo, N</th>
<th>Mean (SD)</th>
<th>Mean difference IV, fixed (95% CI)</th>
<th>Weight %</th>
<th>Mean difference IV, fixed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9605/Reisberg 2003</td>
<td>124</td>
<td>-4 (11:34)</td>
<td>123</td>
<td>-10.1 (13:5)</td>
<td></td>
<td>17.2%</td>
<td>6.10 (2.99 to 9.21)</td>
</tr>
<tr>
<td>MD-02/Tariot 2004</td>
<td>198</td>
<td>0.9 (9.42)</td>
<td>196</td>
<td>-2.5 (9.66)</td>
<td></td>
<td>46.9%</td>
<td>3.40 (1.52 to 5.28)</td>
</tr>
<tr>
<td>MD-01</td>
<td>170</td>
<td>-1.7 (11:34)</td>
<td>165</td>
<td>-2.6 (8.61)</td>
<td></td>
<td>35.9%</td>
<td>0.90 (-1.25 to 3.05)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>492</td>
<td>484</td>
<td></td>
<td></td>
<td></td>
<td>100%</td>
<td>2.97 (1.68 to 4.26)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 7.64, df = 2$ ($p = 0.02$); $I^2 = 74$
Test for overall effect: $Z = 4.51$ ($p < 0.00001$)
Test for subgroup difference: not applicable
What do we need to know?

• New drug targets

• Repurposing
  – Trazodone
  – Lithium
Cognitive interventions for dementia

- **Cognitive stimulation therapy**
  - Similar effect to AChEIs
  - Other methods of administration
  - E.g. individual ineffective

- **Cognitive training**

- **Cognitive rehabilitation**
Manage neuropsychiatric symptoms

- Psychosis
- Agitation
- Depression
- Anxiety
- Sleep disturbance
- Apathy
- etc

80% persist at 18 months
Often overlap
Distressing for people with dementia and families
Psychosis

Detailed assessment

Treatable causes

Consider risk

Psychological, environmental, and social approaches

Consider carer
Step 1
Is there psychosis?
What are the symptoms?
- Talk to patient (ensure communication is optimised) and ask informant
- Need to differentiate from simple miscommunication or misremembering

Assess for causes and risk

Step 2
Are there treatable causes?
For example, delirium, sensory deficit or previous psychotic disorder, such as schizophrenia
- Treat cause of delirium
- Maximise hearing and vision
- Ensure optimal treatment of previous psychotic illness
- Activities to increase social stimulation

Is there significant risk?
Leads to potential harm to self or others
- Recommend and implement safety strategies (involve carer)
- Ensure adequate support for carer
- Short-term drug treatment if severe risk of harm to self or others

Is patient distressed by symptoms?
Ask patient and informant
Is patient distressed by symptoms? Ask patient and informant

Yes

Consider antipsychotic
- Discuss risk and benefit with patient and carer
- Begin with low-dose risperidone

Has there been a response? Reassess after 4–6 weeks

Yes

Consider withdrawal after 12 weeks Then reassess for psychosis recurrence

No

Consider antipsychotic increase, change or withdrawal After reassessing risk and distress

No

Monitor psychosis
- Explain to patient and carer
- Provide contact details for patient and carer to return if symptoms or risk worsen

Consider needs of carer
- Is carer distressed or overburdened?
- Give careful explanation of symptoms of psychosis
- Consider higher level of practical support and care for person with dementia
- Consider presence of anxiety or depression, and offer formal treatment programme
Antipsychotics and dementia

Figure 1. Rates of Death after the Initiation of Conventional and Atypical Antipsychotic Medications.
The rate of death before 10 days was not calculated, owing to insufficient data.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL® is not approved for use in patients with dementia-related psychosis. (5.1)

Donegan et al, Lancet Public Health 2017
Need for caution

• Antipsychotics effective in more severe cases
• Risperidone licensed for short-term treatment
• Withdrawal leads to higher relapse rates
• Mortality lower if treating the right people
• Smaller doses should be used in dementia

Devenand et al, NEJM 2012
Howard et al, BJPych 2016
Reeves et al, Brain, 2017
Is there agitation? What are the symptoms?
- Talk to patient (ensure communication is optimised)
- Ask key informants
Assess for causes and risk

Step 2
Are there treatable causes?
For example, pain, delirium, sensory deficits, discomfort, boredom, hunger, psychosis, or depression

- Ensure pain is adequately treated
- Treat cause of delirium
- Optimise hearing and vision
- Treat depression or psychosis*

Is there significant risk?
Leads to potential for harm to self or others

- Recommend and implement safety strategies (involve carer)
- Ensure adequate support for carer
- Short-term drug treatment if severe risk of harm to self or others

Step 3
Use evidence-based non-drug interventions which comfort and distract (e.g., activities and sensory interventions)

If patient remains significantly distressed or at risk, consider drug treatment
- Low-dose risperidone or citalopram
- Assess response by 6 weeks
- Consider withdrawal at 6–12 weeks and reassess

Consider needs of carer
- Is carer distressed or overburdened?
- Give careful explanation of symptoms of agitation
- Consider higher level of practical support and care for person with dementia
- Consider presence of anxiety or depression, and offer formal treatment programme
Step 1

Is there agitation? What are the symptoms?
• Talk to patient (ensure communication is optimised)
• Ask key informants

Assess for causes and risk

Step 2

Are there treatable causes?
For example, pain, delirium, sensory deficits, discomfort, boredom, hunger, psychosis, or depression

• Ensure pain is adequately treated
• Treat cause of delirium
• Optimise hearing and vision
• Treat depression or psychosis*

Is there significant risk?
Leads to potential for harm to self or others

• Recommend and implement safety strategies (involve carer)
• Ensure adequate support for carer
• Short-term drug treatment if severe risk of harm to self or others
Therapeutic touch
Woods et al (2009)\textsuperscript{224}
Restlessness (vs control)
Restlessness (vs placebo)

Training family caregivers in behavioural management for people with dementia living at home
Gormley et al (2001)\textsuperscript{225}

Light therapy
Ancoli-Isoel et al (2003)\textsuperscript{226}
Ancoli-Isoel et al (2003)\textsuperscript{227}
Dowling et al (2007)\textsuperscript{228}
pm light
Dowling et al (2007)\textsuperscript{228}
am light
Burns et al (2009)\textsuperscript{229}
Burns et al (2009)\textsuperscript{229}

Dementia care mapping
Chenoweth et al (2009)\textsuperscript{230}
Chenoweth et al (2009)\textsuperscript{230}

Person-centred care and communication skills
Chenoweth et al (2009)\textsuperscript{231}
Chenoweth et al (2009)\textsuperscript{231}
Dudon et al (2009)\textsuperscript{232}
Dudon et al (2009)\textsuperscript{232}
McCallion et al (1999)\textsuperscript{233}
McCallion et al (1999)\textsuperscript{233}
McCallion et al (1999)\textsuperscript{233}
Physical aggression
McCallion et al (1999)\textsuperscript{233}
Physical aggression
McCallion et al (1999)\textsuperscript{233}
Verbal aggression
McCallion et al (1999)\textsuperscript{233}
Verbal aggression
McCallion et al (1999)\textsuperscript{233}
Physical non-aggression
McCallion et al (1999)\textsuperscript{233}
Physical non-aggression

Music therapy with a specific protocol
Lin et al (2011)\textsuperscript{234}
Sung et al (2012)\textsuperscript{235}

Activities
Kolansowski et al (2011)\textsuperscript{236}
Matched to interests
Matched to functional level
Matched to both

\[ -8 \quad -6 \quad -4 \quad -2 \quad 0 \quad 2 \quad 4 \]
- Long-term effect
Interventions worsen agitation
Interventions improve agitation
**Step 3**

Use evidence-based non-drug interventions which comfort and distract (e.g., activities and sensory interventions).

If patient remains significantly distressed or at risk, consider drug treatment:
- Low-dose risperidone or citalopram
- Assess response by 6 weeks
- Consider withdrawal at 6–12 weeks and reassess

**Consider needs of carer**
- Is carer distressed or overburdened?
- Give careful explanation of symptoms of agitation
- Consider higher level of practical support and care for person with dementia
- Consider presence of anxiety or depression, and offer formal treatment programme

- Ensure pain is adequately treated
- Treat cause of delirium
- Optimise hearing and vision

- Treat depression or psychosis*

- Recommend and implement safety strategies (involve carer)
- Ensure adequate support for carer
- Short-term drug treatment if severe risk of harm to self or others
Depression in dementia
- May be a symptom of dementia
- May be a pre-existing condition
- May be a consequence of dementia

Are there treatable causes?
For example, pain, hypoactive delirium, sensory deficits, or social isolation
- Treat cause of delirium or pain and explain to patient and carer
- Optimise hearing and vision
- Discuss and implement plan to reduce social isolation

Is there significant risk
- Leads to potential harm to self or others
- Recommend and implement safety strategies (possibly including hospital admission)
- Ensure adequate support for carer

Tailor treatment to depression severity and patient’s needs and wishes

**Mild**
- Watchful waiting
  - Discuss and address possible contributory factors
  - Reassess after 4-6 weeks

**Moderate**
- Psychosocial treatment—eg.
  - Improve communication eg. treat sensory impairment
  - Psychological therapy eg. behavioral activation

Has there been a response?
- Reassess after 4-6 weeks
  - No
  - Reassess (step 1)
  - Monitor depression
    - Explain to patient and carer
    - Provide contact details for patient and carer to return if symptoms or risk worsen
  - Change or withdraw antidepressant after reassessing
  - Consider needs of carer
    - Is carer distressed or overburdened?
    - Explain patient’s symptoms of depression
    - Consider higher level of practical support and care for person with dementia
    - Consider presence of anxiety or depression, offer formal treatment programme

**Severe**
- Ensure psychological treatment is optimised—eg.
  - Improve communication eg. treat sensory impairment
  - Consider psychological therapy eg. behavioural activation (need to assess patient’s cognitive ability to engage with treatment)

And
- Consider antidepressant
  - Discuss risk and benefit with patient and carer
  - Begin with SSRI, or previously effective treatment if past history of depression

Has there been a response?
- Reassess after 4-6 weeks
  - No
  - Consider needs of carer
    - Is carer distressed or overburdened?
    - Explain patient’s symptoms of depression
    - Consider higher level of practical support and care for person with dementia
    - Consider presence of anxiety or depression, offer formal treatment programme

Has there been a response?
- Reassess after 4-6 weeks
  - Yes
  - Continue antidepressant for at least 6 months and monitor
Depression

**Step 1**
- Are there depressive symptoms?
  - Discuss with patient (ensure that communication is optimised) and informants
  - Assess severity of symptoms
  - Ask if patient had depression before onset of dementia

**Step 2**
- Assess for causes and risk

**Are there treatable causes?**
- For example, pain, hypoactive delirium, sensory deficits, or social isolation
- **Treat cause of delirium or pain and explain to patient and carer**
- **Optimise hearing and vision**
- **Discuss and implement plan to reduce social isolation**

**Is there significant risk**
- Leads to potential harm to self or others
- **Recommend and implement safety strategies** (possibly including hospital admission)
- **Ensure adequate support for carer**
Step 3

Tailor treatment to depression severity and patient's needs and wishes

Mid

- Watchful waiting
  - Discuss and address possible contributory factors
  - Reassess after 4-6 weeks

- If no improvement, consider psychosocial treatments—e.g.,
  - Improve communication
  - Behavioural activation

  - Has there been a response?
    - Yes: Reassess after 4-6 weeks
    - No: Reassess (step 1)

Moderate

- Psychosocial treatment—e.g.,
  - Improve communication
e.g. treat sensory impairment
  - Psychological therapy
    - e.g. behavioural activation

  - Has there been a response?
    - Yes: Reassess after 4-6 weeks
    - No: Monitor depression
      - Explain to patient and carer
      - Provide contact details for patient and carer to return if symptoms or risk worsen

Severe

- Ensure psychological treatment is optimised—e.g.,
  - Improve communication
e.g. treat sensory impairment
  - Consider psychological therapy
    - e.g. behavioural activation (need to assess patient's cognitive ability to engage with treatment)

  - Consider antidepressant
    - Discuss risk and benefit with patient and carer
    - Begin with SSRI, or previously effective treatment if past history of depression

  - Has there been a response?
    - Yes: Continue antidepressant for at least 6 months and monitor
    - No: Change or withdraw antidepressant after reassessing

Consider needs of carer
- Is carer distressed or overburdened?
- Explain patient's symptoms of depression
- Consider higher level of practical support and care for person with dementia
- Consider presence of anxiety or depression, offer formal treatment programme
What do we need to know?

• How to manage agitation in care homes

• Understanding causality in depression
  – Allow targeting of currently effective depression treatments

• Less harmful drugs for psychosis
• Targeting to those who will benefit
Care for family carers

• Family members are the most important resource for people with dementia
  – Advocates
  – Carers
  – Decision makers

• 40% of family carers have anxiety or depression
Structured interventions

• Care for family carers is provided in diverse settings
  – But there is limited evidence as to effectiveness
  – With limited resources we should focus on effective approaches

• Effective interventions are
  – Individually tailored
  – Multi-component
  – Focus on individual carers making active choices
  – Principle: the carer can make changes which improve the situation but that the person with dementia cannot.
Strategies for Relatives (START)

- 8 session manual-based therapy
  - Targets coping with specific problems
  - Pleasurable activities
  - Planning for the future
  - Carer keeps a manual of strategies
START

- Reduced anxiety and depressive symptoms at 2 y
- Prevented and treated depression
- Cost-effective
- Many carers continuing to use it at 2 y

Livingston et al 2013
Sommerlad et al 2014

After 6 years
- OR depression = 0.2
- 2 points difference on HADS
- May reduce care home admission
What do we need to know?

- Post-diagnostic support
- Implementing research on supporting carers
- Who else can deliver it to allow roll-out to whole population
- Change for groups; young-onset, ethnic groups
- Electronic approaches: deliver to different groups
Future work: Lancet Commission 2019

Prevention

• Expanding PAF findings to LMICs
• Elucidating other potential risk factors
• Examining resilience and cognitive reserve

Intervention

• Consider new information on biomarkers for diagnosis

Care

• Physical healthcare of people with dementia
• End of life care
Key messages

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3. Treat cognitive symptoms
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7. Protect people with dementia
8. Manage neuropsychiatric symptoms
9. Consider end of life
10. The future role of technology
Thank you

Livingston et al. Dementia prevention, intervention and care. Lancet 2017
http://www.thelancet.com/pdfs/journals/lancet/P刊IIS0140-6736(17)31363-6.pdf

Partners UCL, AS, ESRC, ARUK