

1 **The Lancet standing commission on dementia prevention,**  
2 **intervention and care**

3 Professor Gill Livingston MD \*Division of Psychiatry, University College London, UK; Camden and  
4 Islington NHS Foundation Trust, London, UK

5 Jonathan Huntley PhD Division of Psychiatry, University College London, UK; Camden and Islington  
6 NHS Foundation Trust, London, UK

7 Andrew Sommerlad PhD Division of Psychiatry, University College London, UK Camden and Islington  
8 NHS Foundation Trust, London, UK;

9 Professor David Ames MD National Ageing Research Institute and University of Melbourne Academic  
10 Unit for Psychiatry of Old Age, Parkville and Kew, Victoria, Australia

11 Professor Clive Ballard MD University of Exeter, Exeter, UK

12 Professor Sube Banerjee MD University of Plymouth Faculty of Health: Medicine, Dentistry and  
13 Human Sciences, 403 Rolle Building, Drake Circus, Plymouth PL4 8AA

14 Professor Carol Brayne MD Cambridge Institute of Public Health, University of Cambridge,  
15 Cambridge, UK

16 Professor Alistair Burns MD University of Manchester, Manchester, UK

17 Professor Jiska Cohen-Mansfield Department of Health Promotion, School of Public Health, Sackler  
18 Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; Heczeg Institute on Aging, Tel Aviv  
19 University, Tel Aviv, Israel; Minerva Center for Interdisciplinary Study of End of Life, Tel Aviv  
20 University, Tel Aviv, Israel

21 Professor Claudia Cooper PhD Division of Psychiatry, University College London, UK; Camden and  
22 Islington NHS Foundation Trust, London, UK

23 Sergi G Costafreda PhD Division of Psychiatry, University College London, UK; Camden and Islington  
24 NHS Foundation Trust, London, UK

25 Amit Dias MD Dept. of Preventive and Social Medicine, Goa Medical College, Goa, India

26 Professor Nick Fox MD Dementia Research Centre and UK Dementia Research Institute at University  
27 College London, Institute of Neurology, National Hospital for Neurology and Neurosurgery, London,  
28 UK

29 Professor Laura N Gitlin PhD Center for Innovative Care in Aging, Johns Hopkins University,  
30 Baltimore, Maryland, USA

31 Professor Robert Howard MD Division of Psychiatry, University College London, UK; Camden and  
32 Islington NHS Foundation Trust, London, UK

- 33 Professor Helen C Kales MD Department of Psychiatry and Behavioral Sciences, UC Davis School of  
34 Medicine, University of California, USA
- 35 Professor Mika Kivimäki FMedSci, Department of Epidemiology and Public Health, University College  
36 London, UK
- 37 Professor Eric B Larson MD Kaiser Permanente Washington Research Institute, Group Health  
38 Cooperative, Seattle, WA, USA
- 39 Professor Adesola Ogunniyi MBChB Professor of Medicine, University College Hospital, Ibadan,  
40 Nigeria
- 41 Vasiliki Orgeta PhD Division of Psychiatry, University College London, UK
- 42 Professor Karen Ritchie PhD Inserm, Unit 1061, Neuropsychiatry: Epidemiological and Clinical  
43 Research, La Colombière Hospital, University of Montpellier, France; Centre for Clinical Brain  
44 Sciences, University of Edinburgh UK
- 45 Professor Kenneth Rockwood MD Centre for the Health Care of Elderly People, Geriatric Medicine  
46 Dalhousie University, Halifax, Nova Scotia, Canada
- 47 Professor Elizabeth L Sampson MD Marie Curie Palliative Care Research Department, Division of  
48 Psychiatry University College London, London, UK
- 49 Quincy Samus PhD Department of Psychiatry and Behavioral Sciences, Johns Hopkins Bayview, Johns  
50 Hopkins University, Baltimore, MD, USA
- 51 Professor Lon S Schneider MD Department of Psychiatry and the Behavioural Sciences and  
52 Department of Neurology, Keck School of Medicine, Leonard Davis School of Gerontology of the  
53 University of Southern California, Los Angeles, CA, USA
- 54 Professor Geir Selbæk MD Norwegian National Advisory Unit on Ageing and Health, Vestfold  
55 Hospital Trust, Tønsberg, Norway; Institute of Clinical Medicine, Faculty of Medicine, University of  
56 Oslo, Oslo, Norway; Geriatric Department, Oslo University Hospital, Oslo, Norway
- 57 Professor Linda Teri PhD Department Psychosocial and Community Health, School of Nursing,  
58 University of Washington, Seattle, USA
- 59 Naaheed Mukadam PhD Division of Psychiatry, University College London, UK; Camden and Islington  
60 NHS Foundation Trust, London, UK

61 \* Corresponding author

62

## 63 **Executive summary**

64 The number of older people, including those living with dementia, is rising, as younger-age mortality  
65 declines. However, the age-specific incidence of dementia has fallen in many countries, probably  
66 due to improvements in education, nutrition, health-care, and lifestyle changes. Overall, there is  
67 growing evidence for the nine potentially modifiable risk factors for dementia that the Lancet 2017  
68 commission modelled previously; education, hypertension, hearing impairment, smoking, obesity,  
69 depression, exercise, diabetes and social contact. We now add three more risk factors for dementia  
70 with more recent, convincing evidence. These are higher alcohol consumption, traumatic brain injury  
71 and air pollution. We have completed new reviews and meta-analyses and incorporated these into  
72 an updated 12 risk factor life-course model of dementia prevention. Together they account for  
73 around 40% of worldwide dementias, which theoretically could be prevented or delayed by  
74 eliminating these risk factors. The potential for prevention is high and may be higher in low and  
75 middle-income countries (LMIC) where more dementias currently occur.

76 Our new life course model and evidence synthesis has important worldwide policy implications. It is  
77 never too early and never too late in the life course for dementia prevention. Early-life risks, such as  
78 less education affect cognitive reserve; midlife and old age risk factors influence reserve and  
79 triggering of neuropathological developments. Culture, poverty and inequality are important  
80 obstacles to, or drivers of, the need for change. Those who are most deprived need the changes  
81 most and will derive the highest benefit.

82 Policy should prioritise childhood education for all. Public health initiatives minimising head injury  
83 and decreasing harmful alcohol drinking could potentially reduce young-onset and late-life  
84 dementia. Mid-life systolic blood pressure control should aim for  $\leq 130$ mmHg to delay or prevent  
85 dementia. Stopping smoking, even in later life ameliorates this risk. Passive smoking is a less-  
86 considered modifiable risk factor for dementia. Many countries have restricted this exposure. Policy  
87 makers should expedite improvements in air quality, particularly in areas with high air pollution.

88 We recommend keeping cognitively, physically and socially active in mid- and late-life but there is  
89 little evidence for any single specific activity being protective against dementia. Using hearing aids  
90 appears to reduce the excess risk from hearing loss. Sustained mid-life, and possibly late-life,  
91 exercise protects from dementia, perhaps through decreasing obesity, diabetes and cardio-vascular  
92 risk. Depression may be a risk for dementia, but in later life dementia may cause depression.  
93 Although behaviour change is difficult and some associations may not be purely causal, there  
94 remains huge potential for individuals to reduce their dementia risk.

95 In LMIC, not everyone has access to secondary education; there are high rates of hypertension,  
96 obesity and hearing loss and the prevalence of diabetes is growing rapidly, so an even greater  
97 proportion of dementias are potentially preventable.

98 Amyloid beta and tau biomarkers indicate risk of progression to Alzheimer's dementia but most  
99 people with normal cognition and these biomarkers never develop AD. While accurate diagnosis is  
100 important for patients and families who have impairments and functional concerns, there is a lack of  
101 evidence to support pre-symptomatic diagnosis in everyday practice.

102 Our understanding of dementia aetiology is shifting, with recent description of new pathological  
103 causes. In the oldest old, in particular, mixed dementia is more common. Blood biomarkers may

104 hold promise for future diagnostic approaches and are more scalable than CSF and brain imaging  
105 markers.

106 Wellbeing is the goal of much dementia care. People with dementia have complex problems and  
107 symptoms in many domains. Interventions should be individualised and consider the person as a  
108 whole, as well as their family carers. Evidence is accumulating for the effectiveness, at least in the  
109 short-term, of psychosocial interventions tailored to the patient's needs to manage neuropsychiatric  
110 symptoms. Evidence based interventions for carers can reduce depressive and anxiety symptoms  
111 over years, be cost-effective and may save money.

112 Keeping people with dementia physically healthy is important for their cognition. People with  
113 dementia have more physical health problems than others of the same age but often receive less  
114 community health care, and find it particularly difficult to access and organise care. People with  
115 dementia have more hospital admissions than other older people, including for illnesses that are  
116 potentially manageable at home. Such hospitalisations are distressing and are associated with poor  
117 outcomes and high costs. Health-care professionals should consider dementia in older people  
118 without known dementia who have frequent admissions or who develop delirium. Delirium is  
119 common in people with dementia and contributes to cognitive decline. In hospital, care including  
120 appropriate sensory stimulation, ensuring fluid intake, and avoiding infections may reduce delirium  
121 incidence.

122 Acting now on dementia prevention, intervention, and care will vastly improve living and dying for  
123 individuals with dementia and their families, and thus society.

## 124 Key messages

- 125 1. There is updated evidence for adding three modifiable risk factors – excessive alcohol  
126 consumption, head injury and air pollution - to our original Lancet Commission life course  
127 model of nine factors (less education, hypertension, hearing impairment, smoking, obesity,  
128 depression, physical inactivity, diabetes, and infrequent social contact).
- 129 2. These 12 risk factors may prevent or delay up to 40% of dementias if modified.
- 130 3. Be ambitious about prevention. Prevention is about policy and individuals. Contributions to  
131 the risk and mitigation of dementia begin early and continue throughout life, so it is never too  
132 early or too late. These require both public health programmes and individually tailored  
133 interventions. In addition to population strategies, policy should address high-risk groups to  
134 increase social, cognitive and physical activity; and vascular health.
- 135 4. Specific actions for risk factors from across the lifecourse are:  
136
  - 137 i. Aim to maintain systolic BP  $\leq$ 130 mmHg in midlife from around age 40 years  
138 (antihypertensive treatment for hypertension is the only known effective preventive  
139 medication for dementia).
  - 140 ii. Encourage use of hearing aids for hearing loss and reduce hearing loss by protection  
141 of ears from high noise levels.
  - 142 iii. Reduce exposure to air pollution and second hand tobacco smoke.
  - 143 iv. Prevent head injury
  - 144 v. Limit alcohol use, as alcohol misuse and drinking >21 units (14 drinks) weekly  
145 increase the risk of dementia

- 146 vi. Avoid smoking uptake and support smoking cessation to stop smoking, as this  
147 reduces the risk of dementia even in late-life  
148 vii. Provide all children with primary and secondary education.  
149 viii. Reduce obesity and the linked condition of diabetes and thus decrease dementia.  
150 ix. Sustained mid-life, and possibly late-life physical activity is associated with reduction  
151 in the risk of dementia  
152 x. Addressing other putative risk factors for dementia, like sleep, through lifestyle  
153 interventions, will improve general health.

154 5. Clearly many risk factors cluster around inequalities and in vulnerable populations. Thus  
155 tackling them will not involve only health promotion but societal action to improve the  
156 circumstances in which people live their lives. Examples include creating environments that  
157 have physical activity as a norm, reduce the population profile of blood pressure rise with age  
158 through better patterns of nutrition, and in which there is reduced potential exposure to  
159 excessive alcohol. Dementia is rising more in LMIC than in high-income countries, because of  
160 population ageing and higher frequency of potentially modifiable risk factors. Preventative  
161 interventions may yield the largest dementia reductions in LMIC.

162 **For those with dementia recommendations are:**

- 163 6. Most people with dementia have other illnesses too and may struggle to look after their  
164 health and this may result in potentially preventable hospitalizations. Post-diagnostic care for  
165 people with dementia should address physical and mental health, social care and support.  
166 7. Specific multicomponent interventions decrease neuropsychiatric symptoms in people with  
167 dementia and are the treatments of choice. Psychotropic drugs are often ineffective and may  
168 have severe adverse effects.  
169 8. Specific interventions with family carers have long lasting effects on depression and anxiety  
170 symptoms, increase quality of life, are cost-effective and may save money.  
171

## 172 Introduction

173 Worldwide around 50 million people live with dementia, and this is projected to increase to 131  
174 million by 2050,<sup>1</sup> rising particularly in low and middle-income countries (LMIC) where around two-  
175 thirds of people with dementia live.<sup>1</sup> Dementia affects individuals, their families and the economy,  
176 with global costs estimated to exceed US\$800 billion annually.<sup>1</sup>

177 We re-convened the Lancet Commission <sup>2</sup> to identify the advances likely to have the greatest impact  
178 since our 2017 paper and build on its work. Our interdisciplinary, international group of experts  
179 presented, debated and agreed on the best available evidence. We adopted a triangulation  
180 framework evaluating the consistency of evidence from different lines of research and used that as  
181 the basis to evaluate evidence. We have summarised best evidence using, where possible, good  
182 quality systematic reviews, meta-analyses or individual studies, where these add important  
183 knowledge to this field. We performed systematic literature reviews and meta-analyses where  
184 needed to generate new evidence for our analysis of potentially modifiable risk factors for dementia.  
185 Within this framework, we present a narrative synthesis of evidence including systematic reviews  
186 and meta-analyses and explain its balance, strengths and limitations. There is updated evidence  
187 about dementia risk in LMIC; risks and protective factors for dementia; detection of Alzheimer’s  
188 dementia (AD); multimorbidity in dementia and interventions for people affected by dementia.

189 Nearly all the evidence is from studies in high-income countries (HIC), so risks may differ for other  
190 countries and interventions may require modification for different cultures and environments. This  
191 also underpins the critical need to understand the dementias related to life course disadvantage –  
192 whether in HICs or LMICs.

193 Our understanding of dementia aetiology is shifting. A consensus group, for example, has described  
194 hippocampal sclerosis associated with TDP-43 proteinopathy, as limbic-predominant age-related  
195 TDP-43 encephalopathy (LATE) dementia, usually found in people aged over 80, progressing more  
196 slowly than AD, detectable at post-mortem, often mimicking or comorbid with AD.<sup>3</sup> This reflects  
197 increasing attention to how clinical syndromes are and are not related to particular underlying  
198 pathologies and how this might change across age. More work is needed, however, before LATE can  
199 be used as a valid clinical diagnosis.

200 The fastest growing demographic group in HIC is the oldest old, those aged over 90. This represents  
201 a unique scientific opportunity to focus on both human biology, in this previously rare population, as  
202 well as on meeting their unique needs and promoting their well-being.

## 203 Prevention of dementia

204 The number of people with dementia is rising. Predictions about future trends in dementia  
205 prevalence vary depending on the underlying assumptions and geographical region, but generally  
206 suggest substantial increases in overall prevalence related to population ageing. For example,  
207 according to the Global Burden of Diseases, Injuries, and Risk Factors Study, the global age-  
208 standardised prevalence of dementia between 1990 and 2016 was relatively stable, but with an  
209 ageing and bigger population the number of people with dementia has more than doubled since  
210 1990.<sup>4</sup>

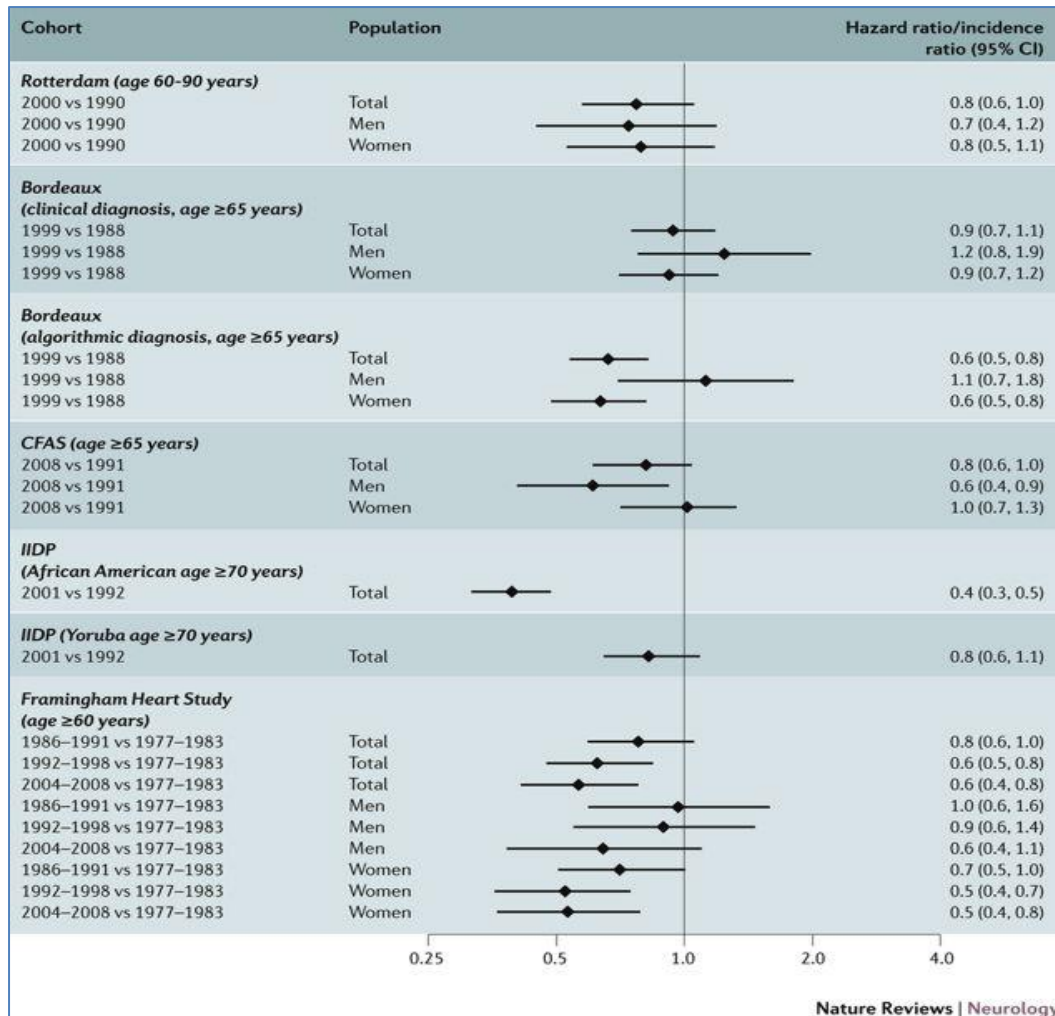
211 However, in many countries such as the US, UK and France, age-specific incidence rates are lower in  
212 recent compared to earlier cohorts collected using similar methods and target populations <sup>5</sup> (Figure

213 1) and there appears to be a decrease in age specific incidence of dementia. In, for example,  
214 England, public health models from UK population based studies suggest a declining trend in age-  
215 specific dementia incidence.<sup>6</sup> All-cause dementia incidence is lower in people born more recently,<sup>7</sup>  
216 probably due to educational, socio-economic, health care and lifestyle changes.<sup>2,5</sup> However, in  
217 these countries increasing obesity, diabetes and declining physical activity may reverse this  
218 trajectory.<sup>8,9</sup> In contrast, age-specific dementia prevalence in Japan, South Korea, Hong Kong and  
219 Taiwan looks as if it is increasing, as is AD in non-Western countries, although it is unclear  
220 whether diagnostic methods are always the same in comparison studies.<sup>5,7 6</sup>

221 Modelling the UK change, suggests a 57% increase in the numbers of people with dementia from  
222 2016 to 2040, 70% of that expected if age-specific incidence rates remained steady,<sup>10</sup> such that by  
223 2040 there will be 1.2 million UK people with dementia. Models also suggest that there will be future  
224 increases both in the number of individuals who are independent and those with complex care  
225 needs.<sup>6</sup>

226 In our first report, this commission described a life-course model for potentially modifiable risks for  
227 dementia.<sup>2</sup> Life-course is important when considering risk, for example, obesity and hypertension in  
228 mid-life predict future dementia, but both body weight and blood pressure usually fall in late-life in  
229 those with or developing dementia,<sup>9</sup> so late-life lower weight and blood pressure may signify illness  
230 not an absence of risk.<sup>11-14</sup> We consider evidence about other potential risk factors and incorporate  
231 those with good quality evidence in our model.

232



233 with permission **Figure 1: Incidence rate ratio comparing new cohorts to old cohorts from**  
 234 **five studies of dementia incidence**<sup>5</sup> Age-specific dementia prevalence is increasing in some  
 235 other countries. IIDP (Indianapolis-Ibadan Dementia Project) in USA and Nigeria; Bordeaux study  
 236 France; and Rotterdam, Netherlands study adjusted for age. Framingham Heart Study, USA adjusted  
 237 for age and sex. CFAS = Cognitive Function and Ageing Study UK; adjusted for age, sex, area and  
 238 deprivation.

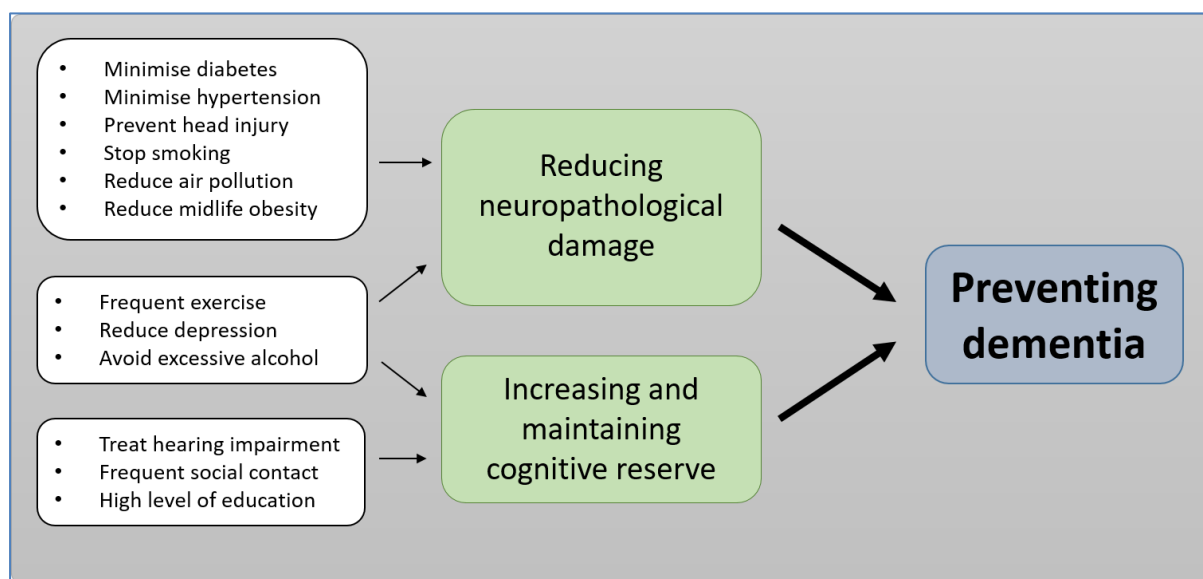
239 Figure 2 summarises possible mechanisms of protection from dementia. These involve cognitive  
 240 reserve, which allow for cognition maintenance despite pathology and neuropathological damage.  
 241 There are different terms describing the observed differential susceptibility to age- and disease-  
 242 related changes and these are not used consistently.<sup>15,16</sup> A recent consensus paper defines “reserve”  
 243 as a concept accounting for the difference between an individual’s clinical picture and their  
 244 neuropathology. It divides it into neurobiological brain reserve (for example, numbers of neurones  
 245 and synapses at a given time point), brain maintenance (as neurobiological capital at any time point,  
 246 based on genetics or lifestyle reducing brain changes and pathology development over time) and  
 247 cognitive reserve (CR) as adaptability enabling preservation of cognition or everyday functioning in  
 248 spite of brain pathology.<sup>15</sup> CR is changeable and quantifying it uses proxy measures such as  
 249 education, occupational complexity, leisure activity, residual approaches (the variance of cognition  
 250 not explained by demographic variables and brain measures) or identification of functional networks  
 251 that may underlie such reserve.<sup>15</sup>



252 Early-life factors, such as less education, affect the resulting cognitive reserve, midlife and old-age  
 253 risk factors influence age-related cognitive decline and triggering of neuropathological  
 254 developments. Consistent with the hypothesis of cognitive reserve is that older women are more  
 255 likely to develop dementia than men of the same age, probably partly because they have on average  
 256 had less education than have older men. Cognitive reserve mechanisms may include preserved  
 257 metabolism or increased connectivity in temporal and frontal brain areas.<sup>17-21</sup> People otherwise in  
 258 good physical health can sustain a higher burden of neuropathology without cognitive impairment.  
 259 <sup>22</sup> Culture, poverty and inequality are important obstacles to and drivers of the need for change.  
 260 Those who are most deprived need the changes most and will derive the highest benefit.

261 Exercise increases and smoking decreases HDL-cholesterol and docosahexaenoic acid blood levels  
 262 (DHA) which in one study were associated with reduced dementia and AD risk independently of  
 263 cardiovascular health and the allele APOEε4.<sup>23</sup> Smoking increases air particulate matter, and has  
 264 vascular and toxic effects.<sup>23</sup> Similarly air pollution may act via vascular mechanisms.<sup>24</sup> Exercise may  
 265 reduce weight and diabetes risk, improve cardiovascular function, decrease glutamine or enhance  
 266 hippocampal neurogenesis.<sup>25</sup> Higher HDL-cholesterol may protect against vascular risk and  
 267 inflammation accompanying amyloid-beta (Aβ) pathology in Mild Cognitive Impairment (MCI).<sup>26</sup>

268



269

270 **Figure 2. Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk**  
 271 **reduction of potentially modifiable risk factors in dementia**

## 272 **Dementia in Low and Middle Income Countries (LMIC)**

273 Numbers of people with dementia in LMIC are rising faster than in higher income countries because  
 274 of increases in life expectancy and greater risk factor burden. We previously calculated that nine  
 275 potentially modifiable risk factors together are associated with 35% of the population attributable  
 276 fraction (PAFs) of dementia worldwide: less education, high blood pressure, obesity, hearing loss,  
 277 depression, diabetes, physical inactivity, smoking and social isolation assuming causation.<sup>2</sup> Most  
 278 research data for this calculation came from high-income countries and review evidence shows  
 279 there is a relative lack of specific evidence of the impact of risk factors on dementia risk in LMIC,  
 280 particularly from Africa and Latin America<sup>27</sup>.

281 Calculations taking into account country-specific prevalence of the nine potentially modifiable risk  
282 factors indicates population attributable fractions of 40% in China, 41% in India and 56% in Latin  
283 America with the potential for these numbers to be even higher depending on which estimates of  
284 risk factor frequency are used.<sup>28 29</sup> There is therefore higher potential for dementia prevention in  
285 these countries than in global estimates which use data which is predominantly from higher income  
286 countries. National policies on access to education, addressing causes and management of high  
287 blood pressure, causes and treatment of hearing loss, socioeconomic and commercial drivers of  
288 obesity including influences on physical inactivity may be risk reduction strategies in many countries  
289 if not currently in place. The higher social contact observed in these three LMIC regions provide  
290 potential insights for higher income countries to influence this risk factor for dementia.<sup>30</sup> We have  
291 not been able to take into account other risk factors such as poor health in pregnancy of  
292 malnourished mothers, difficult births, early life malnutrition, survival with heavy infection burdens  
293 alongside malaria and HIV, all of which may add to the risks in LMIC.

294 Diabetes is also very common and cigarette smoking is rising in China while falling in most high-  
295 income countries.<sup>31</sup> A meta-analysis found variation of the rates of dementia within China, with a  
296 higher prevalence in the north and lower in central China, estimating there was 9.5 million people  
297 with dementia, whereas a slightly later synthesis estimated a higher prevalence of around 11 million.  
298<sup>30,32</sup> These data highlight the need for more focused work in LMIC for more accurate estimates of risk  
299 and interventions tailored to each setting.

### 300 **Specific potentially modifiable risk factors for dementia**

301 Risk factors in early life (education), midlife (hypertension, obesity, hearing loss, traumatic brain  
302 injury, alcohol misuse) and later life (smoking, depression, physical inactivity, social isolation,  
303 diabetes, air pollution) can contribute to increased dementia risk (table 1). There is good evidence  
304 for all these risk factors although there is the possibility that some late-life factors, such as  
305 depression, have bidirectional impact and are also part of the dementia prodrome<sup>33 34</sup>

306 In the following section, we briefly describe relevant newly published and illustrative research  
307 studies that add to the Commission's evidence base, including risks and, for some, mitigation. We  
308 have chosen studies that are large and representative of the populations, or smaller studies in areas  
309 where there is very little evidence. We discussed them in lifecourse order and within the lifecourse  
310 in the order of strength of population attributable factor.

### 311 **Education, midlife and late-life cognitive stimulation**

#### 312 ***Education level reached***

313 Higher childhood education levels and lifelong higher educational attainment reduce dementia risk.  
314<sup>2,35,36 37</sup> New work suggests overall cognitive ability increases, with education, before reaching a  
315 plateau in late adolescence, when there is greatest brain plasticity; with relatively few further gains  
316 with education after age 20.<sup>38</sup> This suggests cognitive stimulation is more important in early life;  
317 much of the apparent later effect may be due to people of higher cognitive function seeking out  
318 cognitively stimulating activities and education.<sup>38</sup> It is difficult to separate activities from earlier  
319 achievements,<sup>38,39</sup> and late-life cognitive activity associated with lifelong cognitive function.<sup>39,40</sup>

### 320 *Cognitive maintenance*

321 One large study in China tried to separate cognitive activity in adulthood from activities for those  
322 with more education and by considering activities judged to appeal to people of different levels of  
323 education.<sup>40</sup> It found people aged >65 who read, played games or bet more frequently had reduced  
324 risk of dementia (n=15,882, odds ratio (OR) = 0.7; 95% confidence intervals [CI] 0.6-0.8). The study  
325 excluded people developing dementia less than three years after baseline to reduce reverse  
326 causation.

327 This is consistent with small studies of mid-life activities which find they are associated with better  
328 late-life cognition; so for example, in 205 people aged 30-64 years, followed until 66-88 years, travel,  
329 social outings, playing music, art, physical activity, reading, and speaking a second language, were  
330 associated with maintaining cognition, independent of education, occupation, late-life activities and  
331 current structural brain health.<sup>41</sup> Similarly, engaging in intellectual activity as adults, particularly  
332 problem solving, for 498 people born in 1936, was associated with cognitive ability acquisition,  
333 although not the speed of decline.<sup>42</sup>

### 334 *Cognitive decline*

335 The 'use it or lose it' hypothesis suggests that mental activity, in general, may increase cognitive  
336 activity. People in more cognitively demanding jobs tend to show less cognitive deterioration before,  
337 and sometimes after retirement than those in less demanding jobs.<sup>43,44</sup> One systematic review of  
338 retirement and cognitive decline found conflicting evidence.<sup>45</sup> Subsequently, a 12-year study of  
339 1658 people found older retirement age but not number of years working, was associated with  
340 lower dementia risk.<sup>46</sup> Those retiring because of ill health had lower verbal memory and fluency  
341 scores than those retiring for other reasons.<sup>47</sup> Another study found a two-fold increase in episodic  
342 memory loss attributable to retirement (n=18,575, mean age 66), compared to non-retirees,  
343 adjusting for health, age, sex and wealth.<sup>48</sup> Similarly, in a cohort of 3433 people retiring at mean age  
344 61 years, verbal memory declined 38% (95% CI 22-60) faster than before retirement.<sup>44</sup> In countries  
345 with younger compared to higher retirement ages, average cognitive performance drops more.<sup>49</sup>

### 346 *Cognitive interventions in normal cognition and Mild Cognitive Impairment*

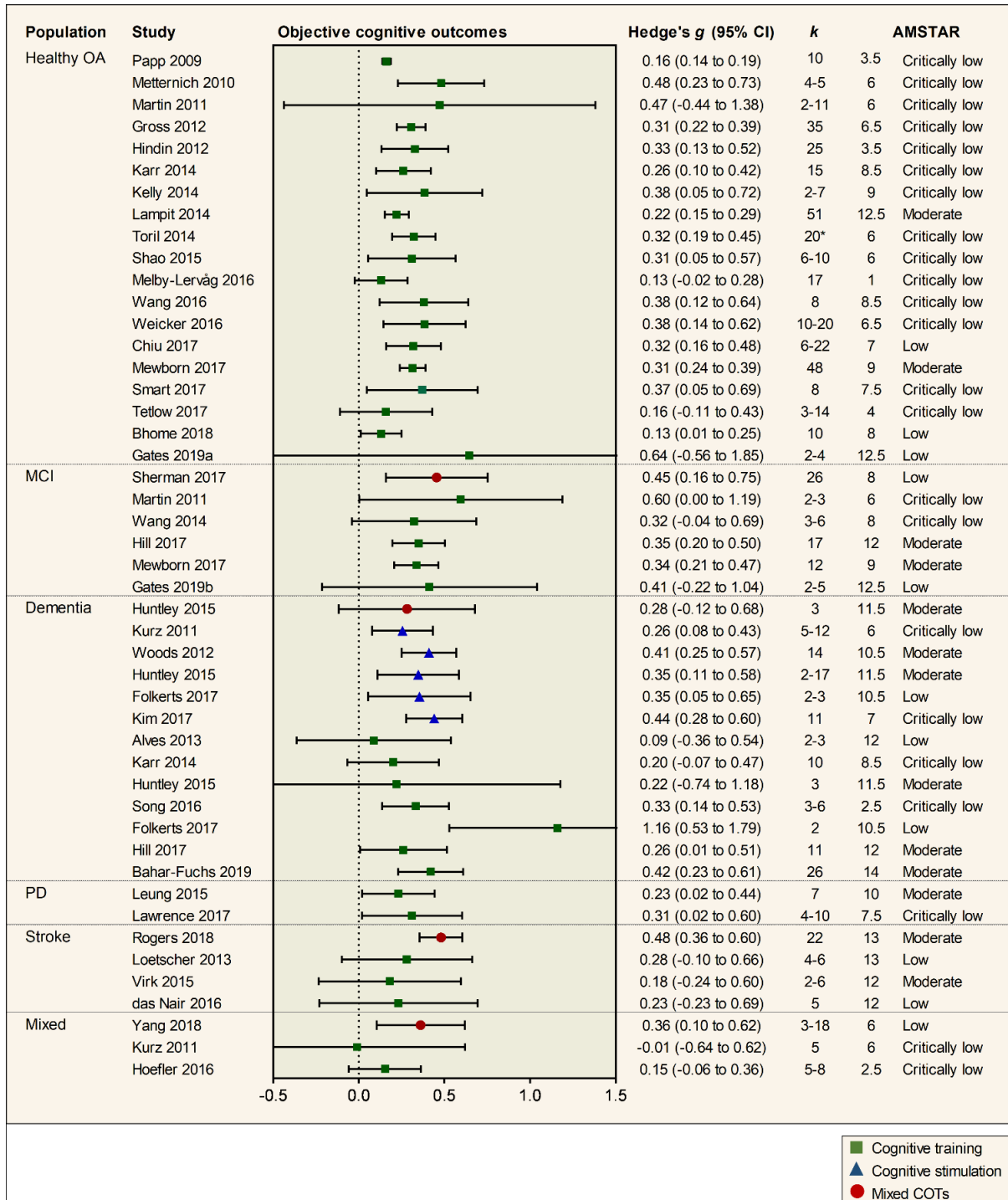
347 A cognitive intervention or cognition-orientated treatment comprises strategies or skills to improve  
348 general or specific areas of cognition.<sup>50</sup> Computerised cognitive training (CCT) programmes have  
349 increasingly replaced tasks that were originally paper-and-pencil format with computer-based tasks  
350 for practice and training.<sup>51</sup>

351 Three systematic reviews in the general population found no evidence of generalised cognition  
352 improvement from specific cognitive interventions, including computerised cognitive training (CCT),  
353 although the domain trained may improve.<sup>52-54</sup>

354 A meta-analysis of 17 controlled trials of at least 4 hours of CCT (N=351; control N=335) for Mild  
355 Cognitive Impairment (MCI), found a moderate effect post-training on general cognition (Hedges'  
356  $g=0.4$ ; 0.2-0.5)<sup>55</sup> but there were few high quality studies and there is currently no long-term high  
357 quality evidence about prevention of dementia. A meta-analysis of 30 trials of computerised,  
358 therapy-based and multimodal interventions for MCI found an effect on activities of daily living  
359 (ADL) ( $d=0.23$ ) and metacognitive outcomes ( $d=0.30$ ) compared to control.<sup>56</sup> A third systematic  
360 review identified five high quality studies, four group delivered and one by computer, and concluded  
361 the evidence for the effects of cognitive training in MCI was insufficient to draw conclusions.<sup>53</sup> A

362 comprehensive, high quality, systematic overview of meta-analyses of cognitive training in healthy  
 363 older people and those with MCI, found that most were of low standard, all were positive and  
 364 reached statistical significance but it was unclear whether results were of clinical value because of  
 365 the poor standard of the studies and heterogeneity of results (see figure 3).<sup>51</sup>

366 In the only RCT of behavioural activation (221 people) for cognition in amnesic MCI (aMCI),  
 367 behavioural activation vs supportive therapy was associated with a decreased 2-year incidence of  
 368 memory decline (relative risk (RR) 0.12; 0.02-0.74).<sup>57</sup>



370 AMSTAR= A MeaSurement Tool to Assess systematic Reviews (max score 16) **Figure 3 Pooled**  
 371 **results of meta-analyses investigating objective cognitive outcomes of cognition-oriented**  
 372 **treatment in older adults. With permission** <sup>51</sup>

### 373 **Hearing impairment**

374  
 375 Hearing loss had the highest PAF for dementia in our first report, using a meta-analysis of studies of  
 376 people with normal baseline cognition and hearing loss present at a threshold of 25 dB, which is the  
 377 World Health Organisation threshold for hearing loss. In the previous Lancet commission, we found  
 378 a RR of 1.9 for dementia in populations followed over 9-17 years, making reverse causation bias  
 379 unlikely. <sup>2</sup> Subsequent meta-analysis using the same three prospective studies measuring hearing  
 380 using audiometry at baseline, found an increased risk of dementia (OR, 1.3; 95% CI 1.0-1.6) per 10dB  
 381 of worsening of hearing loss. <sup>58</sup> A cross-sectional study of 6451 individuals designed to be  
 382 representative of the US population, with a mean age of 59.4, found a decrease in cognition with  
 383 every 10dB reduction in hearing and that continued to below the clinical threshold so that subclinical  
 384 levels of hearing impairment (below 25 dB) were significantly related to lower cognition. <sup>59</sup>  
 385 While the aetiology still needs further clarification, a small US prospective cohort study of 194 adults  
 386 without baseline cognitive impairment, (baseline mean age 54.5 years), at least two brain MRIs, with  
 387 a mean of 19 years follow-up, found that audiometry measured midlife hearing impairment, is  
 388 associated with steeper temporal lobe volume loss, including in the hippocampus and entorhinal  
 389 cortex. <sup>60</sup>

### 390 **Hearing aids**

391 A 25-year prospective study of 3,777 people aged  $\geq 65$  found increased dementia incidence in those  
 392 with self-reported hearing problems except in those using hearing aids. <sup>61</sup> Similarly, a cross-sectional  
 393 study found hearing loss was associated with worse cognition only in those not using hearing aids. <sup>62</sup>  
 394 A US nationally representative survey of 2040 people aged  $>50$ , tested two-yearly for 18 years,  
 395 found immediate and delayed recall deteriorated less after initiation of hearing aid use, adjusting for  
 396 other risk factors. <sup>63</sup> Hearing aid use remained the largest factor protecting from decline (regression  
 397 coefficient  $\beta$  for higher episodic memory = 1.53;  $p < .001$ ) adjusting for protective and harmful  
 398 factors. The long follow-up times in these prospective studies suggest hearing aid use is protective,  
 399 rather than the possibility that those developing dementia are less likely to use hearing aids. It may  
 400 be that hearing loss is a mediating factor; for example, persons with hearing loss have reduced  
 401 cognitive stimulation

### 402 **Traumatic brain injury**

403 ICD defines mild traumatic brain injury (TBI) as concussion and severe TBI as skull fracture, oedema,  
 404 brain injury or bleed. Single, severe TBI is associated in humans, and mouse models, with  
 405 widespread hyperphosphorylated tau pathology, and mice with APOE  $\epsilon 4$  compared to APOE  $\epsilon 3$  allele  
 406 have more hippocampal hyper-phosphorylated tau post-TBI. <sup>64,65</sup> TBI is usually caused by car,  
 407 motorcycle and bicycle injuries; military exposures; boxing, horse riding and other recreational  
 408 sports; firearms; and falls<sup>66</sup>. A nationwide Danish cohort study of nearly three million people aged  $\geq$   
 409 50 years, for a mean of 10 years, found an increased dementia and AD risk in people with TBI  
 410 (respectively HR 1.2; 95% CI 1.2- 1.3; HR 1.2; 95% CI 1.1- 1.2). <sup>67</sup> Dementia risk was highest in the 6  
 411 months after TBI (HR 4.1; 95% CI 3.8- 4.3) and increased with number of injuries (one TBI HR 1.2,  
 412 95% CI 1.2 - 1.3;  $\geq 5$  TBIs HR 2.8, 95% CI 2.1 - 3.8). Risk was higher for TBI than fractures in other body  
 413 areas (HR 1.3, 95% CI 1.3-1.3). It remained elevated after excluding those who developed dementia  
 414  $<2$  years after TBI, to reduce reverse causation bias. <sup>67</sup>

415 Similarly, a Swedish cohort of over 3 million people aged  $\geq 50$  years, found TBI increased one-year  
416 dementia risk (OR 3.5; 95% CI 3.2, 3.8); and risk remained elevated, albeit attenuated over 30 years  
417 (O.R 1.3; 1.1, 1.4).<sup>68</sup> ICD defined single mild TBI increased the risk of dementia less than severe and  
418 multiple TBIs increased the risk further (mild, moderate and severe respectively, OR 1.6; 95% CI 1.6-  
419 1.7; OR, 2.1; 2.0, 2.2; OR, 2.8; 2.5, 3.2 respectively). A nested case control study of early onset  
420 clinically diagnosed AD within an established cohort also found TBI was a risk factor, increasing with  
421 number and severity.<sup>69</sup> There was a stronger risk of dementia nearer the time of the TBI, leading to  
422 some people with early-onset AD.

423 Military veterans have a high risk of occupational TBI, and formal record keeping allows long-term  
424 follow up. A study of 178 779 veterans with propensity-matched veterans without TBI found  
425 dementia risk was associated with TBI severity: HR 2.4; 95% CI 2.1, 2.7 for mild TBI without loss of  
426 consciousness (LOC); HR 2.5; 95% CI 2.3-2.8 for mild TBI with LOC; and HR 3.8; 95% CI 3.6-3.9 for  
427 moderate to severe TBI.<sup>70</sup> Similarly women veterans with TBI had increased risk of dementia  
428 compared to those without TBI; HR 1.5; 95% CI 1.0-2.2.<sup>71</sup>

429 A cohort study of 28,815 older adults with concussion, found the risk of dementia doubled, with 1 in  
430 6 developing dementia over a mean follow-up of 3.9 years, although those taking statins had a 13%  
431 reduced risk of dementia compared to those who were not. They suggest further RCTs as statins  
432 may mitigate injury-related brain oedema, oxidative stress, amyloid protein aggregation, and  
433 neuroinflammation.<sup>72</sup>

434 The term chronic traumatic encephalopathy (CTE) describes sports head injury, which is not yet fully  
435 characterised and covers a broad range of neuropathologies and outcomes, with current views  
436 largely conjecture.<sup>73</sup> The evidence has subsequently been strengthened by a study on Scottish  
437 former soccer players reporting that they are more likely than controls to have AD specified on their  
438 death certificates (HR 5.1; 95% CI 2.9-8.8) and to have been prescribed any dementia-related  
439 medications (OR 4.9; 95% CI 3.8- 6.3 but not on medical records.<sup>74</sup> The study controlled for socio-  
440 economic class based on residential address, which in footballers may differ from level of education  
441 and there will be confounding factors that could not be investigated.

#### 442 Hypertension

443 Persistent mid-life hypertension is associated with increased risk of a late life dementia. In the  
444 Framingham Offspring cohort comprising 1440 people, elevated systolic blood pressure (SBP  $\geq$   
445 140mmHg in mid-life; mean age 55 years) was associated with an increased risk of developing  
446 dementia (HR 1.6; 95% CI 1.1,-2.4) over an 18 year follow-up period)<sup>12</sup>. In this study risk increased  
447 further if hypertension persisted into later life (mean age 69 years; HR 2.0; 95% CI 1.3,-3.1). In the  
448 same cohort, people in late mid-life (mean age 62 years) with ideal cardiovascular parameters  
449 (current non-smoker, body mass index 18.5 - 25 kg/m, regular physical activity, healthy diet,  
450 optimum BP <120/<80 mmHg, cholesterol, and normal fasting blood glucose) were compared to  
451 people with at least one of these risks.<sup>75</sup> They had a lower 10-year risk of all-cause dementia (HR 0.8;  
452 95% CI 0.1-1.0), vascular dementia (HR 0.5; 95% CI 0.3-0.8) and clinically diagnosed AD (HR 0.8; 95%  
453 CI 0.6-1.0). In a UK cohort study of 8639 civil servants, a single measure of BP  $\geq 130$ mmHg at age 50  
454 but not at age 60 or 70 was associated with increased risk of dementia (HR 1.4; 95% CI 1.1, 1.7).<sup>13</sup> In  
455 those with persistent SBP  $\geq 130$  mmHg, from mean age 45 to 61 years, dementia risk is increased

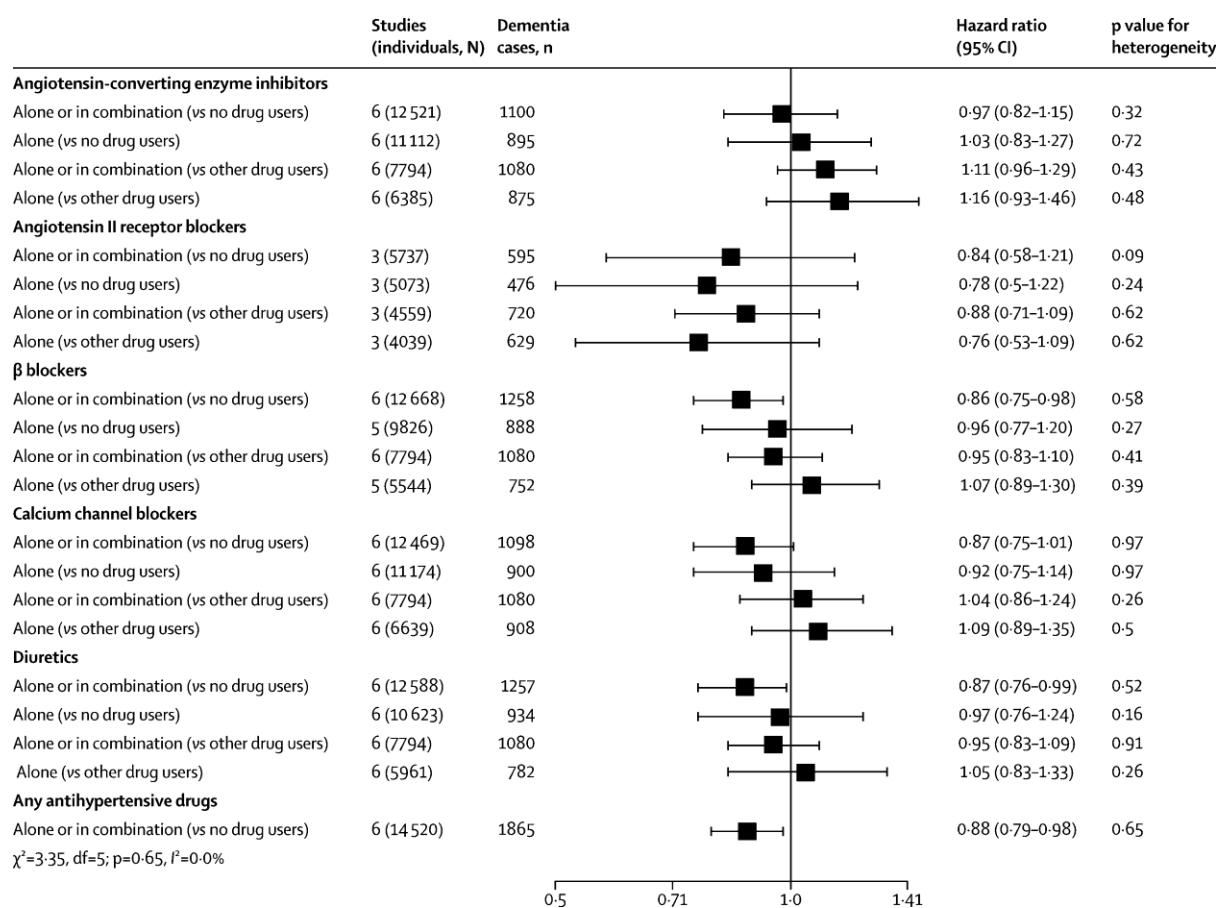
456 even if free of cardiovascular disease (CVD) relative to those without hypertension (HR 1.3; 95% CI  
457 1.0-1.7).

458 It is important to note that blood pressure declines in later life and that this decline is associated  
459 with and, potentially caused by, dementia development (HR 2.4; 95% CI 1.4- 4.2).<sup>12,13 76</sup> A further  
460 cohort study has provided potential insights into mechanisms recently, reporting that midlife  
461 hypertension, defined as from age 40, was associated with reduced brain volumes and increased  
462 white matter hyperintensity volume but not amyloid deposition.<sup>77</sup>

### 463 *Antihypertensive drugs, aspirin and statins*

464 The US and Puerto Rico Systolic Blood Pressure Intervention Trial (SPRINT) trial in 9361 hypertensive  
465 adults aged  $\geq 50$ , was stopped early as there were significantly fewer cardiovascular events and  
466 deaths in the intensive treatment arm (aiming for systolic  $< 120$ mm Hg;  $n=4678$ ) in comparison to  
467 standard treatment (systolic  $< 140$ mmHg;  $n=4683$ ).<sup>78</sup> Cognitive assessment continued after stopping  
468 the trial intervention in SPRINT MIND.<sup>79</sup> In the intensive compared to the standard treatment group,  
469 there were 7.2 dementia cases as opposed to 8.6 cases /1000 person-years (HR 0.8; 95% CI 0.7-1.0)  
470 within on average 2 years from the end of the intervention period and 5 years after baseline. Pre-  
471 specified secondary outcomes were also reduced in the intensive arm for MCI (14.6 vs 18.3  
472 cases/1000 person-years; HR, 0.8; 95% CI 0.7-1.0), combined MCI or dementia (20.2 vs 24.1  
473 cases/1000 person-years; HR, 0.9; 95% CI 0.7-1.0)<sup>79</sup> making this the first trial to suggest reduction of  
474 risk for MCI. Those who were lost to follow-up were at greater risk of dementia than those who  
475 continued but follow-up data rates did not differ according to intervention group.<sup>80</sup>

476 Four recent meta-analyses of blood pressure medications to lower high blood pressure with six  
477 studies overlap have provided combined estimates of effects. All meta-analyses suggest reduced  
478 dementia in those in the interventions arms for outcomes of any dementia as well as clinically  
479 diagnosed AD. The first included RCTs of any drugs to lower blood pressure and reported a  
480 reduction in risk of around 10% at marginal significance (relative risk [RR] 0.9; 95% CI 0.9-1.0).<sup>81</sup>  
481 Meta-regression showed risk lowered more if the achieved systolic pressure differential was larger  
482 between the intervention and control group. The second included 15 trials and observational studies  
483 of diuretics involving 52,599 people (median age 76 years) with 6.1 years median follow-up  
484 (dementia HR 0.8; 95% CI 0.8-0.9 and AD HR 0.8; 95% CI 0.7- 0.9).<sup>82</sup> The third included used  
485 individual participant data from six observational studies; (dementia HR 0.9; 95% CI 0.8 -1.0) and (AD  
486 HR 0.8; 95% CI 0.7-1.0) (see Figure 4).<sup>83</sup> The fourth focused on people prescribed calcium channel  
487 blocker only, included 10 RCTs and observational studies comprising 75,239 hypertensive older  
488 adults (median age 72 years), median follow-up 8.2 years found lowered dementia risk (RR 0.7; 95%  
489 CI 0.6-0.9).<sup>84</sup> A recent meta-analysis addressing which class of anti-hypertensive drug to use to  
490 lower risk of either incident dementia or cognitive decline, found over 50 000 participants in 27  
491 studies and reported there was no consistent difference in effect according to which class of drug  
492 was used.<sup>85</sup>



493

494 **83Figure 4 Associations of antihypertensive medication use with incident dementia in**  
 495 **those with high blood pressure with permission**

496 A Cochrane review reported good evidence that statins given to older people at risk of vascular  
 497 disease do not prevent cognitive decline or dementia.<sup>86</sup> One RCT found 100mg aspirin versus  
 498 placebo in 19,114 healthy adults aged >65 did not reduce dementia (HR 1.0; 0.8-1.2), death, physical  
 499 disability or CVD over a period of 4.7 years.<sup>87</sup>

#### 500 **Physical inactivity, exercise and fitness**

501 Studies of physical activity are complex. Patterns of physical activity change with age, generation and  
 502 are different across sex, social class, cultures and with morbidity. The studies suggest a complicated  
 503 relationship with the potential for both risk reduction and reverse causation.

504 Meta-analyses of longitudinal observational studies of 1-21 years duration showed exercise to be  
 505 associated with reduced risk of dementia.<sup>2</sup> A further overview of systematic reviews recently  
 506 concluded there was convincing evidence of physical activity protecting against clinically diagnosed  
 507 AD.<sup>88</sup>

508 Since the earlier Commission, the HUNT study of 28,916 participants aged 30-60 years has been  
 509 published, reinforcing the previous literature in this area. It was reported that at least weekly mid-  
 510 life moderate-to-vigorous physical activity (breaking into a sweat) was associated with reduced  
 511 dementia risk over a 25 year period of follow up (HR 0.8; 95% CI 0.6-1.1) but the confidence  
 512 intervals are wide.<sup>89</sup> In contrast the Whitehall Study reported on the 28-year follow-up of 10,308  
 513 people, found >2.5 hours self-reported moderate-to-vigorous physical activity/week, lowered



514 dementia risk over 10, but not 28 years.<sup>33</sup> Very long-term studies are unusual but there is one 44-  
515 year study of just 191 women (mean age 50) recruited purposively to be representative of the  
516 Swedish population. It reported that 32% of those with low measuring baseline peak fitness,, 25%  
517 with medium, and 5% with high fitness developed dementia (high versus medium HR 0.1; 95% CI  
518 0.03-0.5, low vs medium HR 1.4; 95% CI 0.7-2.8).<sup>90</sup>

519 An individual-level meta-analysis of 19 observational studies of relatively younger adults included  
520 404,840 participants' data (mean baseline age 45.5 years; mean follow-up duration 14.9 years),  
521 reporting an increased incidence of all-cause dementia (HR 1.4; 95% CI 1.2- 1.7) and clinically  
522 diagnosed AD (HR 1.4; 95% CI 1.1- 1.7) in those who were physically inactive in the 10 year period  
523 before diagnosis.<sup>91</sup> Importantly, however, no difference in dementia risk measured 10-15 years  
524 before time of dementia incidence was found except in those with comorbid cardio-metabolic  
525 disease (RR=1.3, 95% CI 0.8-2.1).

526 People may stop exercising due to prodromal dementia so inactivity may be either a consequence or  
527 a cause or both in dementia and may be more of a risk in those with cardiovascular morbidity. As  
528 with other outcomes, exercise may be required to be sustained and continue nearer the time of  
529 risk<sup>92</sup>.

### 530 *Trials of exercise*

531 Since the original Commission several meta-analyses and systematic reviews have been published  
532 with three high quality meta-analyses which we include. The first included 39 RCTs with an unclear  
533 total number of participants examining moderate or vigorous exercise of any frequency lasting 45-  
534 60 minutes/session in cognitively normal adults aged >50 years. This reported global cognitive  
535 improvements (standard mean difference; SMD= 0.3; 95% CI 0.2-0.4) for moderate or vigorous  
536 resistance (13 studies) or aerobic exercise (18 studies) lasting 45-60 minutes per session with no  
537 difference between them but no effect found for yoga.<sup>93</sup> A second meta-analysis of RCTs in people  
538 with MCI found global cognition improved in the intervention group (SMD 0.3; 95% CI 0.1-0.5) with  
539 aerobic exercise having a higher effect (SMD: 0. 6; 95% CI 0.5-0.6). This study did not have dementia  
540 as an outcome measure. A third meta-analysis of RCTs of longer term exercise found five studies  
541 (four lasting 12 months and one 24) with 2878 participants with normal baseline cognition.<sup>94</sup> The  
542 incidence of dementia was 3.7% (n = 949) for exercisers and 6.1% (n = 1,017) for controls (random  
543 effect RR = 0.6; 95% CI = 0.3-1.1; fixed effect as no evidence of heterogeneity RR = 0.7; 95% CI = 0.4-  
544 1.0). The authors concluded that there was no significant effect of exercise for reducing dementia,  
545 MCI or clinically significant cognitive decline but the study was underpowered. WHO guidelines have  
546 been published since the first Commission, suggesting specific activity levels drawing on these, and  
547 one further systematic review which considered sex differences on the effect of exercise.<sup>93-96</sup> It  
548 concluded the evidence points towards physical activity having a small, beneficial effect on normal  
549 cognition, with a possible effect in MCI, mostly due to aerobic exercise.<sup>97</sup> There is a lack of evidence  
550 about the effect of specific types of exercise, such as progressive muscle resistance training on  
551 dementia risk.

### 552 *Diabetes mellitus*

553 In the earlier Commission we reported on diabetes as a risk factor for dementia. It is challenging to  
554 distinguish between treated and untreated diabetes as a risk factor for dementia in observational  
555 studies. In a pooled meta-analysis from over 2.3 million individuals with type 2 diabetes across 14

556 cohort studies, including 102,174 with dementia. In this diabetes was associated with an increased  
557 risk of any dementia (women: RR 1.6; 95% CI 1.5-1.8; men: RR 1.6; 95% CI 1.4,-1.8).<sup>98</sup> The risk of  
558 dementia increased with the length and severity of diabetes. The relationship with different diabetic  
559 medications on cognition or dementia outcomes remains unclear as few studies have investigated  
560 this area.<sup>99</sup> However, one meta-analysis of cohort studies of diabetes reported that, cross  
561 sectionally, people with diabetes taking metformin had lower prevalence of cognitive impairment (3  
562 studies, OR 0.6; 95% CI 0.4-0.8) and, longitudinally, reduced dementia incidence (6 studies HR 0.8;  
563 95% CI 0.4-0.9) compared with those taking other medications or no medication.<sup>101</sup> However  
564 another did not find a protective effect of metformin for incident dementia (3 studies, risk ratio (RR)  
565 1.1; 95% CI 0.5 to 2.4) with possible harm with insulin therapy (RR 1.2; 95% CI 1.1 - 1.4); but this did  
566 not account for severity of diabetes of those with type 2 diabetes on insulin.<sup>99</sup> A Cochrane review  
567 reported intensive compared to standard diabetes control trials with 5 year follow up (n = 11,140)  
568 no impact on cognitive decline (RR 1.0; 95% CI 0.9-1.1) or dementia (RR 1.3; 95% CI 0.9- 1.9).<sup>100</sup>

569 Overall type 2 diabetes is a clear risk factor for development of future dementia but it is unclear that  
570 any particular medication ameliorates this risk. Intensive diabetic control does not decrease the risk  
571 of dementia.

### 572 **Combined cardiovascular risk factors**

573 Studies of individual cardiovascular risk factors usually control for other cardiovascular risks, which  
574 cluster in individual people. This does not take into account the combinations and contexts in which  
575 risk occurs. A UK study of 7899 people aged 50 followed for 25 years, calculated a cardiovascular  
576 health score based on seven items- behavioural (smoking, diet, physical activity, body mass index)  
577 and biological (fasting glucose, blood cholesterol, blood pressure) each coded as 0, 1 or 2.<sup>101</sup> A better  
578 score was associated with a lower risk of dementia (HR 0.9 95% CI 0.9-1.0 per 1 point scale  
579 increment), for both behavioural and biological subscales (HR/ 1 point increment in subscales 0.9;  
580 95% CI 0.8-0.9) and 0.9 (95% CI 0.8-1.00), respectively), maintained in people free of cardiovascular  
581 disease over the follow-up (HR/ 1 point increment 0.9; 95% CI. 0.8- 1.0). These authors also reported  
582 an association of the score on the scale with hippocampal atrophy and total brain volume but not  
583 white matter hyperintensities. This underlines the importance of clustering of cardiovascular risk  
584 factors in midlife, as studies of individual risk factors in this sample had not shown this significant  
585 association, when controlling for other individual risks.<sup>33</sup>

### 586 **Excessive alcohol**

587 Heavy drinking is associated with brain changes, cognitive impairment and dementia, a risk known  
588 for centuries.<sup>102</sup> There is increasing evidence emerging on alcohol's complex relationship with  
589 cognition and dementia outcomes from a variety of sources including detailed cohorts and largescale  
590 record based studies. Alcohol is strongly associated with cultural patterns and other sociocultural  
591 and health related factors, making it particularly challenging to understand the evidence base.

592 A French 5-year longitudinal study of over 31 million people admitted to hospital, found alcohol use  
593 disorders (harmful use or dependence as defined in International Classification of Disease; ICD) were  
594 associated with increased dementia risk, calculated separately for men and women (women HR 3.3;  
595 95% CI 3.3-3.4; men 3.4; 95% CI 3.3- 3.4).<sup>103</sup> The relationship of dementia with alcohol use disorder  
596 was particularly clear in the earlier onset dementias (age less than 65 years) in which 56.6% had an  
597 alcohol use disorder noted in their records (n=57,353; 5.2% all dementias).

598 A systematic review incorporating 45 studies of light to moderate drinking using a variety of  
599 definitions reported a reduced risk compared to not drinking (RR 0.7; 95%CI 0.6-0.91).<sup>104</sup> Risk was  
600 not reported separately for men and women. Drinking no more than 21 units/week (equivalent to 14  
601 drinks) may be associated with a lower risk of dementia.<sup>106 105</sup> There were few heavy drinkers in a 5-  
602 year follow-up study of 13342 men and women volunteers from UK biobank aged 40-73 years old  
603 who drank and the study did not analyse abstainers.<sup>106</sup> It reported that those who drank more than  
604 one drink every day (equivalent to > 12 units/week) declined slightly more in reaction time in a  
605 perceptual matching task than those who drank less ( $\beta_2 = -0.07$ , 95% CI -0.09 – -0.04).<sup>106</sup> In the UK  
606 Whitehall study with 23 years follow-up, there were 9087 participants aged 35-55 years at baseline.  
607 <sup>107</sup> Drinking >21 units/week and long term abstinence were both associated with a 17% (95% CI 4-32  
608 and 13-23 respectively) increase in dementia compared to <14 units. Drinking >14 units was also  
609 associated with associated MRI right sided hippocampal atrophy.<sup>108</sup>

610

### 611 **Weight control and obesity**

612 Overweight is an emerging concern, given the changing BMI across the world's ageing population.  
613 There is new evidence for the relationship between increased BMI and dementia from a review of 19  
614 longitudinal studies including 589,649 people aged 35 to 65 years, followed for up to 42 years. It  
615 reported obesity (BMI  $\geq 30$ ; RR 1.3, 95% CI 1.1-1.6) but not being overweight (BMI 25- 30; RR 1.1,  
616 95% CI 1.0-1.2) was associated with late-life dementia.<sup>109</sup> In a further meta-analysis of individual  
617 level data from 1.3 million adults (aged  $\geq 18$  years), which included two studies from the meta-  
618 analysis cited above,<sup>109</sup> higher body mass measured before likely preclinical and prodromal  
619 dementia was associated with increased dementia risk (RR 1.3; 1.1-1.7/ 5-unit increase in BMI).<sup>11</sup>

### 620 **Weight loss in mid-life and dementia risk**

621 A meta-analysis of seven RCTs (468 participants) and 13 longitudinal studies (551 participants) of  
622 overweight and obese adults without dementia, mean age 50, found weight loss of  $\geq 2$ kg in people  
623 with BMI >25 was associated with a significant improvement in attention and memory. In all but one  
624 of the studies participants were aged under 65 years old. The RCTs reported memory improvement  
625 over 8-48 weeks (SMD = 0.4; 95% CI 0.2–0.6) and longitudinal studies found SMD = 0.7; 95% CI 0.5–  
626 0.8 but there is no data about the long-term effects or the effect of weight loss in preventing  
627 dementia.<sup>110</sup>

### 628 **Smoking**

629 Smokers are at higher risk of dementia than non-smokers,<sup>2</sup> and at a higher risk of premature death  
630 before the age at which they might have developed dementia, introducing some bias and  
631 uncertainty in the association between smoking and risk of dementia.<sup>111,112</sup> Stopping smoking, even  
632 when older, reduces this risk. Among 50,000 men age >60, stopping smoking for >4 years, compared  
633 to continuing, reduced dementia risk over the subsequent 8 years substantially (HR 0.9; 95% CI 0.7-  
634 1.0). Worldwide, it has been estimated that 35% of non-smoking adults and 40% of children are  
635 exposed to second-hand smoke (SHS).<sup>113</sup> There is scarce literature on the impact of this exposure  
636 and dementia risk. One study indicated that in middle-aged women aged 55-64, SHS exposure was  
637 associated with more memory deterioration and the risk increased with exposure duration even  
638 after controlling for other confounding factors.

## 639 Depression

640 Depression is associated with dementia incidence, with a variety of possible psychological or  
641 physiological mechanisms. It is also part of the prodrome and early stages of dementia. Reverse  
642 causation is also possible whereby depressive symptoms result from dementia neuropathology  
643 which occur years before clinical dementia onset. These explanations are not mutually exclusive. As  
644 in diabetes, few studies considering depression as a risk factor for dementia have distinguished  
645 between treated and untreated depression. In a meta-analysis of 32 studies, with 62 598  
646 participants, with follow-up from 2 to 17 years, a depressive episode was a risk factor for dementia  
647 (pooled effect size 2.0; 95% CI 1.7-2.3).<sup>114</sup> Meta-regression analysis revealed a non-significant trend  
648 for the association between depression and incident dementia to be weaker when the length of  
649 follow-up was longer (pooled effect size 1.97, 95% CI 1.67-2.32). In the Norwegian HUNT study,  
650 there was suggestion that symptoms of psychological distress predicted dementia 25 years later  
651 however with wide bounds of uncertainty (HR 1.3; 95% CI 1.0–1.7).<sup>89</sup> Two further studies  
652 differentiate between late-life and earlier life depressive symptoms. The UK Whitehall study, in a  
653 follow up of 10189 people, report that in late life these increase dementia risk but not at younger  
654 ages (follow-up 11 years HR 1.7; 95% CI 1.2-2.4; follow-up 22 years HR, 1.0; 95% CI, 0.7-1.4).<sup>34,115</sup> A  
655 14 year longitudinal study of 4922 initially cognitively healthy men, aged 71-89 years, found  
656 depression was associated with 1.5 (95% CI 1.2- 2.0) times the incidence of dementia but this  
657 association was accounted for by people developing dementia within 5 years of depression.<sup>120</sup> The  
658 use of antidepressants did not decrease this risk.

659 In a study of 755 people with MCI from the Australian longitudinal Alzheimer's Disease  
660 Neuroimaging Initiative (ADNI) with a history of depression, considered the effect of SSRI treatment  
661 as citalopram is known to reduce amyloid plaque generation and plaque formation in animal models.  
662 It found that >4 years SSRI treatment was associated with delayed progression to clinically diagnosed  
663 AD. It seems likely that people treated with antidepressants will differ from those who are not.  
664 Thus, the question of whether antidepressant treatment mitigates dementia risk remains open.

## 665 Social contact

666 Social contact, now an accepted protective factor, enhance cognitive reserve or encourage beneficial  
667 behaviours, although isolation may also occur as part of the dementia prodrome. Several recent  
668 studies suggest that lower social contact increases the risk of dementia. Although most people in  
669 mid and later life are married, by the time they reach older age disproportionate numbers of women  
670 are widowed as they outlive their husbands reducing their social contact. In these generations,  
671 marital status is therefore important contributor to social engagement. Additionally, most marriages  
672 are in the relatively young, and married people usually have more interpersonal contact than do  
673 single people this gives a long-term estimate of the effect of social contact A systematic review and  
674 meta-analysis including 812,047 people worldwide found dementia risk to be elevated in lifelong  
675 single (RR 1.4; 95% CI 1.1-1.9) and widowed people (RR 1.2; 95% CI 1.0-1.4), compared with married,  
676 people and the association was consistent in different socio-cultural settings. Studies adjusted for  
677 sex and we do not know if there is a differential risk between men and women. Differences persisted  
678 in studies that adjusted for education and physical health so may be attributable to married people  
679 having more social contact, although residual confounding is possible. A systematic review and  
680 meta-analysis of 51 longitudinal cohort studies of social isolation and cognition included 102,035  
681 participants aged  $\geq 50$  years at baseline, with follow-up ranging from 2-21 years.<sup>116</sup> High social  
682 contact (measured through either or both of social activity and social network) was associated with

683 better late-life cognitive function ( $r=0.05$ , 95% CI: 0.04- 0.065) and there were no differences  
684 according to sex or length of time followed-up.

685 A new meta-analysis found that in long-term studies ( $\geq 10$  years), good social engagement was  
686 modestly protective ( $n=8876$ , RR=0.9; 95% CI 0.8-1.0); but in the loneliness meta-analysis, loneliness  
687 was not associated with dementia risk.<sup>117</sup> There have been no long term ( $>10$  years) studies of  
688 loneliness and dementia outcomes.

689 A UK 28-year follow-up study of 10,308 people found that more frequent social contacts at age 60  
690 years was associated with lower dementia risk over 15 years of follow-up (HR for one standard  
691 deviation social contact frequency 0.9; 95% CI 0.8-1.0). This suggests more frequent social contact  
692 during late middle age is associated with a modest reduction in dementia risk, independent of socio-  
693 economic and other lifestyle factors.<sup>118</sup> A Japanese longitudinal cohort study of 13 984 adults aged  
694  $>65$  years old with mean 10 years follow-up calculated a five point social contact scale based on  
695 marital status, exchanging support with family members, having contact with friends, participating in  
696 community groups and engaging in paid work. It found the score to be linearly associated with  
697 reduced dementia risk; those who scored highest on the five-point scale were 46% less likely to  
698 develop incident dementia compared with those in the lowest category.<sup>119</sup>

699 Despite clear cultural variation in the meaning and perception of social isolation, findings of  
700 protective effect of more social contact are largely consistent in different settings and for either sex  
701 across the studies and meta-analyses.<sup>116,120,121</sup>

## 702 *Social interventions*

703 There is little evidence of the effects of social interventions but a systematic review of low quality  
704 RCTs of 576 adults aged  $\geq 60$  with normal cognition found facilitated meeting and discussion groups  
705 were associated with improved global cognition and increased brain volume at follow-up.<sup>120</sup>

## 706 *Air pollutants*

707 Air pollution and particulate pollutants are associated with poor health outcomes, including those  
708 related to non-communicable diseases. Attention has turned to their potential effect on the brain.  
709 Animal models suggest airborne particulate pollutants accelerate neurodegenerative processes  
710 through cerebrovascular and cardiovascular disease, A $\beta$  deposition, and Amyloid Precursor Protein  
711 (APP) processing.<sup>122,123</sup> While the higher levels of dementia from air pollutants are still subject to the  
712 potential for residual confounding, the effects on animal models are also evidence of physiological  
713 effects over and above those driven by lifecourse deprivation.

714 High nitrogen dioxide (NO<sub>2</sub>) concentration ( $>41.5$   $\mu\text{g}/\text{m}^3$ ; adjusted HR 1.2; 95% CI 1.0-1.3), fine  
715 ambient particulate matter (PM<sub>2.5</sub>) from traffic exhaust (adjusted HR 1.1; 95% CI 1.0-1.2)<sup>124-126</sup> and  
716 PM<sub>2.5</sub> from residential wood burning (HR=1.6, 95% CI 1.0–2.4 for a 1  $\mu\text{g}/\text{m}^3$  increase) are associated  
717 with increased dementia incidence. Traffic often produces NO<sub>2</sub> and PM<sub>2.5</sub> and it is hard to separate  
718 their effects, although there is evidence for additive effects of different pollutants.<sup>124-126</sup> A  
719 systematic review of studies until 2018 found 13 longitudinal studies with 1-15 years follow-up of air  
720 pollutants exposure and incident dementia, exposure to PM<sub>2.5</sub>, NO<sub>2</sub>, and carbon monoxide were all  
721 associated with increased dementia risk.<sup>24</sup> The attributable burden of dementia and excess death  
722 from PM<sub>2.5</sub> in one large 10-year US study was particularly high in black or African American

723 individuals and socioeconomically disadvantaged communities and related to particulate levels  
724 above the US guidelines.<sup>127</sup>

## 725 Sleep

726 Mechanisms by which sleep may effect dementia remain unclear, but sleep disturbance has been  
727 linked with A $\beta$  deposition,<sup>128,129</sup> reduced glymphatic clearance pathways activation,<sup>130</sup> low grade  
728 inflammation, increased Tau, hypoxia<sup>129,131</sup> and CVD.<sup>132</sup> Sleep disturbance is hypothesised to  
729 increase inflammation which raises  $\beta$ -amyloid burden leading to AD and further sleep disturbance.<sup>133</sup>

730 There are two recent meta-analyses with similar findings. The first was a synthesis of longitudinal  
731 studies with an average of 9.5 years follow-up and the second reported cross-sectional and  
732 prospective cohort studies of mixed quality with different methods of measuring sleep. They defined  
733 sleep disturbances broadly; often it was self-reported and included short and long sleep duration,  
734 poor sleep quality, circadian rhythm abnormality, insomnia and obstructive sleep apnoea (OSA).  
735 They were all associated with a higher risk of all-cause dementia (RR 1.2; 95% CI 1.1-1.3)<sup>134</sup> and  
736 clinically diagnosed AD (RR 1.6; 95% CI 1.3-1.9) compared to no sleep disturbance, though not all  
737 cohort studies excluded those with cognitive impairment or dementia at baseline from their  
738 analyses.<sup>135</sup> A U-shaped association has been reported between sleep duration and risk of MCI or  
739 dementia with higher risks of dementia with <5 hours or (HR=2.6; 95% CI 1.4-5.1) < 7 hours and >9  
740 or 10 hours sleep (HR=2.2; 95% CI 1.4-3.5) and risks for all-cause dementia and clinically diagnosed  
741 AD being similar.<sup>136 132,137,138</sup>

742 The postulated mechanisms of reduced sleep leading to accumulation of Alzheimer's Type pathology  
743 is inconsistent with the evidence that both more and less sleep are associated with increased risk of  
744 dementia. New onset late-life sleep disturbance, a few years before clinical dementia, may be part of  
745 the natural history of the dementia syndrome, appearing to be a risk factor, or reflect other  
746 disorders, for example, mood disturbances or CVD.<sup>132,139</sup> Hypnotic use may increase risks although  
747 this is unclear and a recent study suggest that findings of a connection were related to reverse  
748 causality and confounders.<sup>136 140</sup> When benzodiazepine use was considered, in one sleep length was  
749 no longer significant<sup>136</sup> but not in all studies.<sup>132</sup> Those taking hypnotics were at greater risk of  
750 dementia than those who did not whatever the sleep duration.<sup>136</sup> Medication for sleep disturbance  
751 may be harmful and benzodiazepines are associated with falls, hospital admissions and possibly  
752 dementia.<sup>141 136</sup>

## 753 Diet

754 Nutrition and dietary components are challenging to research with controversies still raging around  
755 the role of many micronutrients and health outcomes in dementia. There has been a focus on  
756 individual components ranging from folate and B vitamins, Vitamin C, D, E and selenium amongst  
757 others in observational studies as potential protective factors.<sup>88</sup> There has been a move towards  
758 considering the evidence base for whole diets in recent years, particularly high plant intake such as  
759 in the Mediterranean diet (MeDi) or the similar Nordic diet, rather than individual nutrients, which  
760 might reduce cognitive decline and dementia.<sup>142</sup> One example of this is a longitudinal cohort study  
761 of 960 participants, ages 58-99 years, in which those reporting the highest intake of green leafy  
762 vegetables, equivalent to 1.3 servings/day, declined less cognitively over 4.7 years than those  
763 reporting the lowest intake ( $\beta = 0.05$  standardized units 95%CI 0.02 - 0.07).<sup>143</sup> The authors report  
764 this difference as being equivalent to being 11 years younger. A further prospective cohort study

765 with three midlife dietary assessments in 8,255 people, followed for a mean of nearly 25 years,  
766 found neither healthy dietary pattern nor Mediterranean diet protected from dementia, except in  
767 those with CVD, suggesting that diet may influence dementia risk by protecting from the excess risk  
768 of cardiovascular risk factors.<sup>144</sup>

769

### 770 **Dietary interventions**

771 As well as whole diets, there has been some interest in multi-nutrient interventions. A systematic  
772 review and a Cochrane review including RCTs of supplements (A, B, C, D and E; calcium, zinc, copper  
773 and multivitamins trials, n-3 fatty acids, antioxidant vitamins and herbs) found a lack of evidence for  
774 supplement use to preserve cognitive function or prevent dementia in middle-aged or older  
775 people.<sup>145, 146</sup> Recent updated Cochrane reviews found no evidence for beneficial effects on  
776 cognition of those with MCI of supplementation with B vitamins for six to 24 months<sup>147</sup> or with  
777 vitamin E in preventing progression from MCI to dementia.<sup>148</sup> A 24-month RCT of 311 people of a  
778 multi-nutrient drink containing DHA, vitamins B12, B6, folic acid and other nutrients; found no  
779 significant effect on preventing cognitive deterioration in prodromal AD.<sup>149</sup> The authors comment  
780 that the control group's cognitive decline was much lower than expected, leading to an inadequately  
781 powered trial.

782 Meta-analysis of two RCTs with 471 participants with normal cognition found the MeDi diet (high  
783 intake of vegetables, legumes, fruits, nuts, cereals, and olive oil; low intake of saturated lipids and  
784 meat) improved global cognition compared to controls (SMD 0.2; 95% CI 0.0-0.4). A further meta-  
785 analysis identified five RCTs (n=1888) with a weak effect on global cognition (SMD 0.2; 95% CI 0.0 –  
786 0.5)<sup>150</sup> but no benefit of MeDi for incident cognitive impairment or dementia.

787 The WHO guidelines recommend a Mediterranean diet to reduce the risk of cognitive decline or  
788 dementia, as it may help and does not harm, but conclude Vitamins B and E, PUFA and multi-  
789 complex supplementation should *not be recommended*.<sup>97</sup>

### 790 **Trials of combination strategies to prevent dementia**

791 The FINGER RCT was a 2-year multidomain intervention to prevent cognitive decline and dementia  
792 in 1260 people with cardiovascular risk factors aged 60–77 years, recruited from a Finnish national  
793 survey. Similar multidomain studies were discussed in the earlier commission.<sup>2</sup> FINGER found a small  
794 group reduction in cognitive decline in the intervention group compared to control (comprehensive  
795 neuropsychological test battery Z score 0.02; 95% CI 0.00, 0.04) regardless of baseline  
796 sociodemographic, socioeconomic, cognitive or cardio-vascular status.<sup>151</sup> However, in a subgroup  
797 analysis, there were greater beneficial effects on processing speed in individuals with higher baseline  
798 cortical thickness in Alzheimer's disease areas.<sup>152</sup>

799 The healthy ageing through internet counselling in the elderly (HATICE) study recruited 2724 older  
800 people (≥65 years) in the Netherlands, Finland and France with two or more cardiovascular risk  
801 factors.<sup>153,154</sup> It compared an interactive internet platform plus remote support by a coach, aiming to  
802 improve self-management of vascular risk factors, with a non-interactive control platform with basic  
803 health information. There was a small improvement in the cardiovascular risk composite primary  
804 outcome in the intervention group compared to control group at 18 months, mainly through weight  
805 loss the cognition secondary outcomes, although the predicted dementia risk score was slightly

806 lower in those who received the intervention (mean difference  $-0.15$ ,  $-0.3$  to  $-0.0$ ). There was a  
807 larger effect in the younger age group (65–70 years) and those with the lowest level of education,  
808 who had a higher baseline risk, suggesting that targeting high-risk populations may be more  
809 effective. There are currently several ongoing multidomain preventative trials e.g. Worldwide  
810 Fingers.

811



812 **Table 1: Population Attributable Fraction (PAF) for 12 dementia risk factors**

813 PAF is the relative contribution of each risk factor to the overall PAF when adjusted for communality

814

| Risk factor                    | Relative Risk for dementia (95% CI) | Risk factor prevalence (%) | Communality (%) | Unweighted PAF (%) | Weighted PAF* (%) |
|--------------------------------|-------------------------------------|----------------------------|-----------------|--------------------|-------------------|
| <b>Early life (&lt;45)</b>     |                                     |                            |                 |                    |                   |
| Less education                 | 1.6 (1.3-2.0)                       | 40.0                       | 61.2            | 19.4               | 7.1               |
| <b>Mid-life (age 45-65)</b>    |                                     |                            |                 |                    |                   |
| Hearing loss                   | 1.9 (1.4-2.7)                       | 31.7                       | 45.6            | 22.2               | 8.2               |
| Traumatic brain injury         | 1.8 (1.5-2.2)                       | 12.1                       | 55.2            | 9.2                | 3.4               |
| Hypertension                   | 1.6 (1.2-2.2)                       | 8.9                        | 68.3            | 5.1                | 1.9               |
| Alcohol >21units/week          | 1.2 (1.1-1.3)                       | 11.8                       | 73.3            | 2.1                | 0.8               |
| Obesity (Body Mass Index ≥30)  | 1.6 (1.3-1.9)                       | 3.4                        | 58.5            | 2.0                | 0.7               |
| <b>Later life (age &gt;65)</b> |                                     |                            |                 |                    |                   |
| Smoking                        | 1.6 (1.2-2.2)                       | 27.4                       | 62.3            | 14.1               | 5.2               |
| Depression                     | 1.9 (1.6-2.3)                       | 13.2                       | 69.8            | 10.6               | 3.9               |
| Social isolation               | 1.6 (1.3-1.9)                       | 11.0                       | 28.1            | 4.2                | 3.5               |
| Physical inactivity            | 1.4 (1.2-1.7)                       | 17.7                       | 55.2            | 9.6                | 1.6               |
| Diabetes                       | 1.5 (1.3-1.8)                       | 6.4                        | 71.4            | 3.1                | 1.1               |
| Air pollution                  | 1.1 (1.1-1.1)                       | 75.0                       | 13.3            | 6.3                | 2.3               |
| <b>Overall weighted PAF</b>    |                                     |                            |                 |                    | <b>39.7%</b>      |

815 **Total PAF calculation**

816 We incorporated excessive alcohol consumption, TBI and air pollution into our life-course model of  
 817 dementia because of the updated evidence. To calculate new RRs for excessive alcohol  
 818 consumption, TBI and air pollution, we systematically reviewed the literature and performed new  
 819 meta-analyses for excessive alcohol consumption and TBI. For the other nine factors, we used  
 820 values for RR and risk factors prevalence from our previous analysis and calculated communality  
 821 using the same method. <sup>2</sup>

## 822 Incorporation of the new chosen risks new systematic reviews

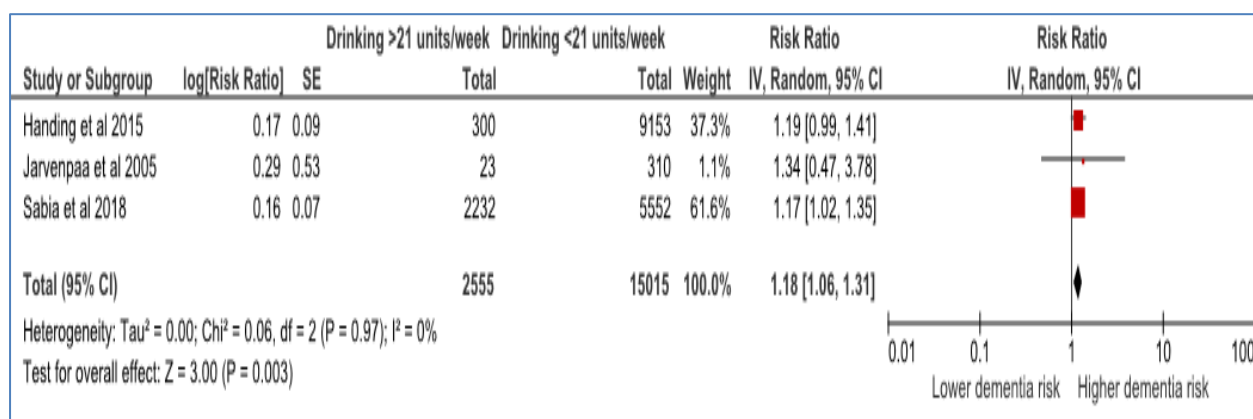
### 823 Alcohol

824 We searched, from inception to 29<sup>th</sup> October 2019, Embase, Allied and Complementary Medicine,  
825 Medline and PsycINFO terms “dementia” OR “dement\*” OR “AD” OR “VaD”, “Alzheimer\*” AND  
826 “alcohol” OR “ethanol” OR “alcohol\*” OR “drink\*” OR “drunk\*” to update an earlier review.<sup>155</sup>

#### 827 Inclusion criteria

- 828 • Original population-based cohort studies measuring drinking during midlife, as alcohol  
829 intake tends to fall with age,<sup>156</sup>
- 830 • Alcohol consumption quantified at baseline by units or number of drinks (one drink = 1.5  
831 units) per week
- 832 • All-cause dementia ascertained at follow-up using validated clinical measures.

833 We contacted authors for additional data.<sup>157</sup> Three studies met our inclusion criteria.<sup>107,157,158</sup> We  
834 converted HRs to RRs<sup>159</sup> and used raw data<sup>157</sup> to calculate RR,<sup>160</sup> for our random effects meta-  
835 analysis using Generic Inverse Variance Methods. The RR associated with drinking > 21 units (14  
836 drinks; 168g) of alcohol weekly, compared to lighter drinking was 1.18; 95% CI 1.06, 1.31 (Figure 5).  
837 We used Health Survey England (HSE) figures for heavier drinking prevalence to calculate PAF as we  
838 could not find a worldwide estimate. The weighted PAF was 0.8.



839

840 **Figure 5: Meta-analysis of relative risk of dementia associated with drinking >21 units of**  
841 **alcohol/week in midlife compared to lighter consumption of alcohol**

### 842 Traumatic brain injury

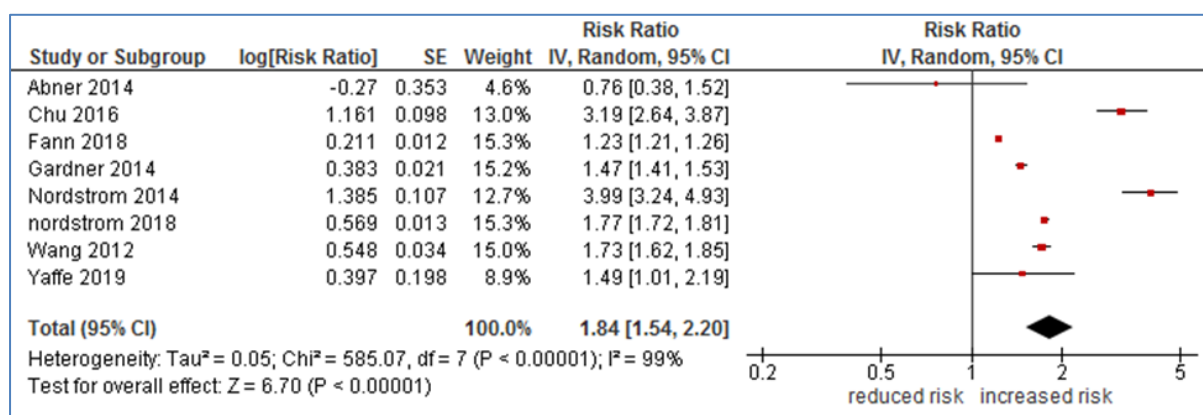
843 To estimate the RR of TBI of all severities for all cause dementia, we searched Embase, Medline and  
844 PsycINFO from 1<sup>st</sup> January 2016 to 21st October 2019, updating an earlier search,<sup>161</sup> using terms  
845 ("traumatic brain injury" or "head injury" or "brain injury" or TBI) AND (neurodegeneration or  
846 "cognitive dysfunction" or dementia or "alzheimer's disease" or "parkinson's disease" or  
847 "frontotemporal dementia"). We converted HR figures to RR.<sup>159 162</sup>

#### 848 Inclusion criteria:

- 849 • Original population-based cohort studies
- 850 • Baseline TBI of all severities reported
- 851 • All-cause dementia ascertained at follow-up using validated clinical measures.

852 We combined four new studies meeting inclusion criteria<sup>67 68 71 163</sup> with the four studies  
 853 meeting criteria from the original review in a random effects meta-analysis.<sup>161</sup> The pooled RR  
 854 was 1.84; 95% CI 1.54 -2.20 for all cause dementia from all severities of TBI (Figure 6) though  
 855 there was heterogeneity in study-specific estimates, possibly because of different populations.  
 856 We used the TBI adult population prevalence of 12.1% from a meta-analysis to calculate PAF.<sup>164</sup>  
 857 The weighted PAF was 3.4.

858



859

860 **Figure 6: Meta-analysis of relative risk of all-cause dementia associated with all severity**  
 861 **midlife Traumatic Brain Injury**

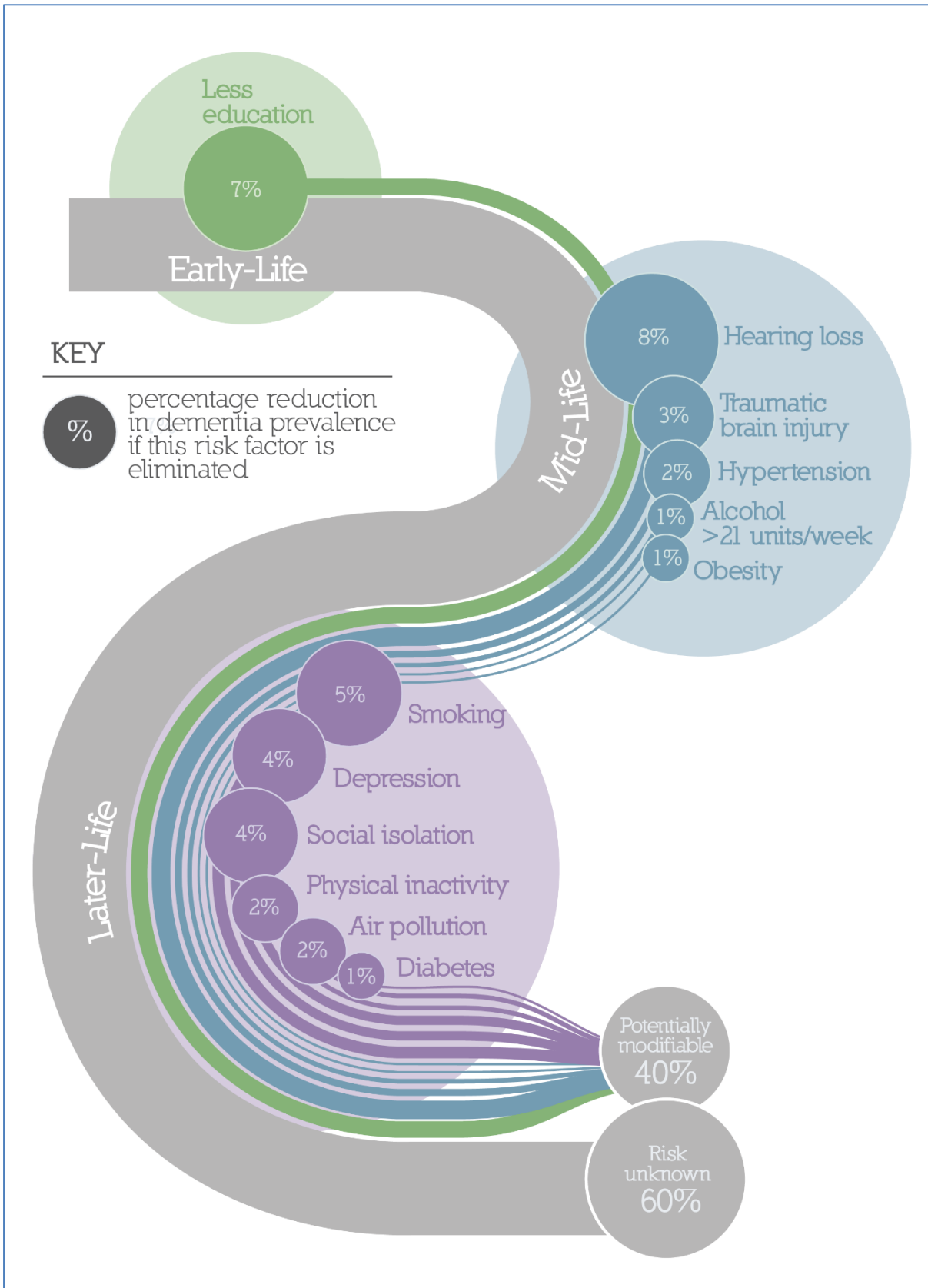
### 862 Pollution

863 A 2019 systematic review synthesised observational studies, finding consistently increased risk of  
 864 dementia from air pollution, but heterogeneous comparator groups precluded meta-analysis.<sup>24</sup> We  
 865 updated the search, using the same search terms and searching MEDLINE, Embase, and PsychINFO  
 866 from 20 September 2018 (the end date of the last search) to 22<sup>nd</sup> October 2019. We included  
 867 longitudinal studies with assessment of all cause air pollution exposure; use of formal assessment of  
 868 cognitive function at baseline; report of incident all cause dementia, data from adults (age  $\geq 18$ );  
 869 and a minimum follow up 6 months. We therefore used data from the only study of all-cause air  
 870 pollution with the outcome of all cause dementia, with low-moderate risk of bias. This population-  
 871 based, observational cohort was from Ontario, Canada, where pollutant concentrations are among  
 872 the lowest in the world and examined 2,066,639 people, with a mean baseline age of 67<sup>165</sup>. We  
 873 calculated the RR of dementia for those in the three highest quartiles compared to the lowest was  
 874 1.09 (1.07-1.11). The attributable fraction for exposure to the highest three quartiles versus the  
 875 lowest quartile of PM<sub>2.5</sub> and NO<sub>2</sub> was 6.1% (4.8-7.5). The weighted PAF was 2.3.

### 876 PAF calculation

877 We used a representative sample of over 10,000 UK community-dwelling adults, to calculate  
 878 communality (clustering of risk factors) of 11 risk factors for which data existed,<sup>166</sup> to allow  
 879 calculation of each factor's unique risk. As we could find no datasets measuring TBI, and the other 11  
 880 risk factors of interest, we could not calculate its communality. We therefore used the mean of the  
 881 other 11 communalities to calculate a weighted PAF, so we could include TBI. We used cohabitation  
 882 as a proxy measure for social contact, and urbanicity for air pollution exposure. Our analysis found  
 883 four principal components, explaining 55% of the total variance between the eleven risk factors,

884 suggesting substantial overlap. Appendix 1 shows the PAF formula and the steps in calculating  
885 communality. Table 1 displays the prevalence, communality, relative risk, unweighted and weighted  
886 PAFs adjusted for communality. We present in Figure 7 the new updated life course model of  
887 potentially modifiable risks factors for dementia. *Figure 7* the updated life course model of



889

890 **Figure 7: Population attributable fraction of potentially modifiable risk factors for dementia**

## 891 *Strengths and limitations*

892 This is the most comprehensive analysis to date and updates the earlier Lancet Commission with  
893 emerging risk factor evidence convincing enough to calculate PAF for potentially reversible risk  
894 factors. We reviewed the literature systematically for the chosen risk factors, and provided  
895 illustrative recent literature. Using this we have updated our synthesis and identified data to  
896 calculate communality. We find a hopeful picture with an updated estimate of around 40% of all  
897 cases of dementia being associated with 12 potentially modifiable risk factors.

898 We have made assumptions to calculate this new model. We used global figures for dementia risk  
899 although we know the risk factors prevalence vary between countries and most global research is  
900 from high-income countries, so LMIC are under-represented because of lack of data. We have  
901 assumed a causal relationship between risk factors and dementia, although we have been cautious  
902 and not included risk factors with less good evidence. There is no single database with all 12 risk  
903 factors together, but we found 11 in a UK database and used the mean figure for communality  
904 calculations for TBI. We calculated communality for the other 11. We do not know how far findings  
905 of communality in other geographical populations might differ, or in those with a differing  
906 distribution of age groups or sex. We found that social isolation was not explicitly measured and had  
907 to use proxies, such as cohabitation when considering prevalence, which are approximate.

908 Specifically, evidence for the association of alcohol misuse with dementia comes from high-income  
909 countries and future studies from low- and middle-income countries are need to complete the  
910 picture. Exposure to air pollution changes over a lifetime and is inextricably linked to poverty and  
911 deprivation. However, the effects on animal models suggests specific physiological effects over and  
912 above those driven by lifecourse deprivation. We also considered the overlap with education for this  
913 and other risk factors and the correction for education, strongly inversely linked to deprivation, will  
914 address at least some of the confounding. However, the results in one study which reported the  
915 effect of air pollution on incident dementia showed very little difference in estimates before and  
916 after adjustment for education and other risk factors suggests there is little residual confounding.<sup>165</sup>  
917 We were also unable to meta-analyse data on pollution and thus unlike the other relative risks the  
918 figure comes from only one study, from an area of low pollution so is likely to be an underestimate.

919 The longitudinal evidence linking potentially modifiable risk factors to dementia generally fulfils  
920 causality criteria in observational data (strength, consistency, biological plausibility, temporality,  
921 dose-response, coherence and quasi-experimental studies, for example, more education or using  
922 hearing aids). When measuring a risk nearer to the age of dementia onset, then it is more likely that  
923 prodromal change affects, or even causes it. Alternatively, a risk factor may act on preclinical  
924 pathology or even cause dementia near the time of exposure. Thus, alcohol and TBI are particularly  
925 important in young-onset dementia, although most early onset dementias relate to genetic risks.  
926 Risk factors may also matter more at a time of higher biological vulnerability, which the studies we  
927 have drawn on cannot establish. The length of exposure required for risk or protection effect, and  
928 their inter-relationships as they change across life is unclear - it seems likely that longer or more  
929 intense exposure has stronger effects. Additionally, as our communality figures show, risk factors  
930 overlap. We cannot establish from these data if having multiple risk factors has an additive or  
931 synergistic effect. Association does not prove causation, however, as already noted, the reductions  
932 in prevalence and incidence in several high income countries suggests that at least some of the risk  
933 factors estimated here do have a causal relationship with the clinical expression of dementia.

## 934 **Key points and recommendations**

935 We judge there is sufficient new evidence to add three additional modifiable risk factors for  
936 dementia to our earlier Commission model (alcohol, traumatic brain injury, and air pollution). We  
937 have been able to add updated evidence on the nine risk factors implicated in the first commission  
938 (education, hypertension, hearing impairment, smoking, obesity, depression, inactivity, diabetes and  
939 social contact). Reduction of these risk factors may be protective for people with or without a  
940 genetic risk, although study findings have not been entirely consistent.<sup>167,168 169,170</sup> As we noted in  
941 the previous Commission others have previously calculated an estimate of the risk associated with  
942 APOE4 is 7% taking into account some other risk factors and this highlights how relatively important  
943 potentially modifiable risk factors are in dementia.<sup>2,171</sup>

944 For some risk factors, the pattern of risk and the individual's other health, both physical and mental  
945 may be especially important. Currently, the evidence suggests a Mediterranean or Scandinavian diet  
946 may have value in preventing cognitive decline in people with intact cognition, particularly as one  
947 component of a healthy lifestyle, although it is unclear how long the exposure has to be or during  
948 which ages. We do not recommend taking additional vitamins, oils or mixed dietary supplements as  
949 a means of preventing dementia as extensive testing in trials has not led to signals of beneficial  
950 effects.

951 There are few data from RCTs on interventions to prevent cognitive decline, all-cause dementia or  
952 AD. For some key life influences, only observational data, particularly related to natural experiments  
953 such as changing the statutory education age, are possible. These should be investigated  
954 systematically wherever possible. Others can theoretically be investigated but the long follow-up  
955 required for midlife risk and protective factors and non-random attrition in longer studies are  
956 challenging. Using intermediate endpoints, such as cognition, and dementia onset in research  
957 remains uncertain as there are no intermediate markers that have such a close relationship with  
958 dementia outcomes that it's possible to predict with certainty for any given individual, age and sex.  
959 Overall, the evidence for treating hypertension is strongest and high blood pressure throughout mid-  
960 life increases the risk of dementia even without stroke.

961 While there is a need for more evidence, recommendations should not await this, as there are clear  
962 indications of ways to reduce the chances of developing dementia without causing harm that will  
963 also lead to other health and wellbeing benefits.

964 Our recommended strategies for dementia risk reduction include both population-wide and targeted  
965 interventions

966 Population wide:

- 967 • Prioritise childhood education for all, worldwide.
- 968 • Implement social public health policies that reduce hypertension risk in the whole  
969 population.
- 970 • Develop policies that encourage social, cognitive and physical activity across the lifecourse  
971 for all but there is no evidence for specific activities being protective.
- 972 • Scrutinise the risks for hearing loss throughout the lifecourse, in order to reduce the risk of  
973 exposure to this risk factor in later life.

- 974 • Reduce the risk of serious brain trauma in relevant settings, including occupational and  
975 transport.
- 976 • National and international policies to reduce population exposure to air pollution.
- 977 • Continue to strengthen national and international efforts to reduce exposure to smoking,  
978 both for children and adults to reduce uptake and encourage cessation.

979 Targeted on individuals

- 980 • Treat hypertension and aim for SBP <130mmHg in mid-life.
- 981 • Use hearing aids for hearing loss. We need to help people wear them as many find them  
982 unacceptable, too difficult to use or ineffective.
- 983 • Drinking 21 units (14 drinks) /week or more is a risk factor for dementia.
- 984 • Prevent head trauma where an individual is at high risk.
- 985 • Stopping smoking is beneficial regardless of age.
- 986 • Reduce obesity and the linked condition of diabetes by healthy food availability and an  
987 environment to increase movement.
- 988 • Sustained mid-life, and possibly late-life physical activity protects from dementia.

989 Although we have more to learn about effectiveness, avoiding or delaying even a proportion of  
990 potentially modifiable dementias should be a national priority for all.

### 991 **Interventions and care in dementia**

992 Not all dementia will be preventable and below we present the latest evidence about intervention  
993 and care for dementia. To date there has been an emphasis on specific subtypes of dementia. Most  
994 notably over the last decades into Alzheimer's Disease, which has been conceptualised in a variety of  
995 changing diagnostic criteria over the years, for example, DSM 1V and DSM V.<sup>172,173</sup> This implies early  
996 pre-clinical detection of the disease process before it becomes dementia, and to this end there has  
997 been an intense effort to detect biomarkers that predict clinical outcomes. Biomarkers need to show  
998 reliability and validity, and in the area of this Lancet Commission they also need to be very closely  
999 and clearly related to clinical syndrome outcomes in the way that, for example, HPV now is for  
1000 cervical cancer, and hypertension has been for stroke.

### 1001 **Biomarkers and detection of AD**

1002 Markers of neurodegeneration linked to clinical dementia include brain volume loss, including  
1003 hippocampal volume loss and entorhinal cortex and medial temporal cortical thinning seen in  
1004 structural imaging. The most studied molecular markers are in AD and are amyloid and tau, which  
1005 Positron Emission Tomography (PET) and cerebrospinal fluid (CSF) detect clinically. The prevalence of  
1006 particular pathologies at different ages is important in interpretation of such studies. So, for  
1007 example, population derived studies show there are increases in plaques in the population from less  
1008 than 3% at age 50 to 59 to around 40% at age 80 to 89.<sup>174</sup>

### 1009 **Amyloid imaging**

1010 Amyloid imaging detects amyloid in the brain with high sensitivity and specificity in both cognitively  
1011 normal and people with AD when compared to either neuropathology or clinical diagnosis  
1012 distinguishing AD from other neurodegenerative conditions.<sup>175</sup> It is not a diagnostic test for  
1013 dementia but for whether there is amyloid in the brain. A US study of randomly selected older  
1014 people from the community recruited 1671 people (mean age of 71 years).<sup>174</sup> The prevalence of



1015 PET detected amyloid positivity increased from 2.7% (95% CI 0.5-4.9) of people without cognitive  
 1016 impairment aged 50 to 59 years to 41.3% (95% CI 33.4-49.2%) aged 80 to 89 years.<sup>174</sup> In 10-year  
 1017 follow up PET positivity was associated with a higher probability of developing AD dementia  
 1018 compared to those who were amyloid negative; HR 2.6 (95% CI 1.4 -4.9). It was not very different for  
 1019 participants with aMCI who were amyloid positive vs amyloid negative, HR 1.9 (95% CI 0.9- 3.9) for  
 1020 and 1.6 (95% CI 0.8 -3.4) respectively.

1021 Similarly, an 8 year follow-up study of 599 volunteers (average age 70) in Australia found that  
 1022 cognitively normal (CN) PET amyloid positive people had an elevated risk of developing AD  
 1023 compared to amyloid negative (17.7% vs 8.1%, OR: 2.4; 95% CI 1.5- 4.0).<sup>176</sup> Over 80% of the 266  
 1024 who were PET amyloid positive did not go onto develop within eight years, showing positive status  
 1025 does not predict impairment for most people in which might be a useful prognostic window. Follow-  
 1026 up at 5-years of CN or aMCI amyloid positive participants vs amyloid negative found the same  
 1027 pattern of increased risk (OR 2.6; 95% CI 1.4- 4.9). Risk also increases with older age (HR=1.05, 95%  
 1028 CI 0.55-2.0/year), and APOEε4 status (HR=2.6, 95%CI 1.4-5.0).<sup>176</sup>

1029 Most people who are amyloid positive with no other markers have not developed AD dementia  
 1030 during their lifetime. A model of lifetime risks of people who are amyloid positive without any other  
 1031 biomarkers finds it to be 8.4% for a 90 year-old woman who is cognitively normal at baseline, 23.5%  
 1032 for a 75 year old and 29.3% for a 65 year old.<sup>177</sup> The 10-year risk is considerably less, so a 65-year-  
 1033 old woman with only amyloid biomarkers but who is cognitively normal and has no  
 1034 neurodegeneration has a 10-year AD risk of 2.5% and a man 2.3%, but the risk is somewhat higher  
 1035 with accompanying neurodegeneration (Table 2).<sup>177</sup>

1036 Overall, the knowledge of PET measured amyloid and tau status and MRI derived cortical thickness  
 1037 in a general population derived sample, only adds a small improvement for predicting memory  
 1038 decline over a model with clinical and genetic variables, which may not be clinically important.<sup>178</sup>

| Age | Normal state 1 | A state 2       | N state 3      | A & N state 4    | MCI & A & N state 5 | MCI & N state 6  |
|-----|----------------|-----------------|----------------|------------------|---------------------|------------------|
| 60  | 0.2 (0.06–0.8) | 1.3 (0.6–2.5)   | 3.6 (1.1–14.2) | 7.1 (4.5–10.9)   | 93.5 (91.1–95.0)    | 57.2 (48.2–67.9) |
| 65  | 0.5 (0.14–1.8) | 2.5 (1.2–4.9)   | 4.3 (1.4–15.0) | 10.7 (6.8–16.2)  | 91.7 (89.2–93.5)    | 55.4 (46.6–65.8) |
| 70  | 1.1 (0.34–3.5) | 4.7 (2.4–8.7)   | 5.5 (2.0–16.6) | 15.5 (10.0–22.8) | 88.6 (85.8–90.6)    | 52.2 (43.8–62.4) |
| 75  | 2.2 (0.74–6.5) | 7.8 (4.1–14.0)  | 7.3 (2.9–19.0) | 20.8 (13.7–29.7) | 83.8 (80.7–86.2)    | 47.4 (39.6–57.0) |
| 80  | 3.7 (1.3–9.8)  | 11.1 (6.0–18.7) | 9.3 (3.9–20.9) | 24.4 (16.4–33.8) | 75.8 (72.2–78.7)    | 40.0 (33.1–48.6) |
| 85  | 4.7 (1.8–11.0) | 11.5 (6.5–18.5) | 9.7 (4.3–19.3) | 23.1 (15.8–31.2) | 63.7 (59.6–67.2)    | 30.0 (24.5–37.2) |
| 90  | 3.8 (1.5–8.2)  | 8.2 (4.7–12.9)  | 7.1 (3.3–13.3) | 16.8 (11.5–22.6) | 46.7 (42.7–50.2)    | 19.1 (15.3–24.3) |

1039 **Table 2: Ten-year risks %; (95% Confidence intervals) by age of developing Alzheimer's**  
 1040 **disease dementia for females based on amyloidosis (A) by itself and in the presence of**  
 1041 **neurodegeneration (N), and mild cognitive impairment (MCI) with permission**  
 1042

1043 Using amyloid PET with patients with cognitive impairment of uncertain causes, results in changes to  
 1044 the clinical diagnosis of AD<sup>179</sup> and sometimes to medication prescription. We do not know whether

1045 PET use improves patient care or decreases care costs. Many people have a mixed cause of  
1046 dementia and a positive result does not indicate only AD.

### 1047 **Fluid biomarkers**

1048 PET imaging is very costly (\$3000 in US) and although used in some clinical settings remains the topic  
1049 of research to understand its usefulness in broader populations. Fluid biomarkers, i.e. blood and  
1050 cerebrospinal fluid tests, have become a more practical focus of interest since it has become  
1051 possible to measure specific proteins linked to the proteins associated with the neuropathologies of  
1052 Alzheimer's Disease.<sup>180</sup> A composite blood biomarker for amyloid tested in a discovery dataset and  
1053 then a validation cohort of participants aged 60 to 90 for amyloid burden (areas under the receiver  
1054 operating characteristic curves (AUCs) 96.7% for discovery and 94.1% for validation who were  
1055 already taking part in studies in Japan or Australia. It had sensitivity and specificity above 80%  
1056 against amyloid PET measurement<sup>180</sup> and correlated with CSF levels of A $\beta$ 1-42. These results are  
1057 similar to other amyloid blood biomarkers<sup>181,182</sup> and harmonization to a common reference standard  
1058 is now vital. Whilst CSF A $\beta$ 1-42/1-40 ratio and amyloid PET are now considered interchangeable,<sup>183</sup>  
1059 CSF tau biomarkers have only correlated weakly with brain tau as currently measured by  
1060 radioligands.<sup>184</sup> Neurofilament light (NfL) protein is being measured in many cohorts. It is, however,  
1061 non-specific and people with Huntington's disease, multiple sclerosis, MCI and AD may have raised  
1062 blood NfL, as it is a marker of neurodegeneration.<sup>185-187</sup>

### 1063 **Key points and conclusions**

1064 To be useful in clinical practice biomarkers must be very well understood in the populations to which  
1065 they are going to be applied, including the effects of age and sex on results. There is now reasonable  
1066 evidence that PET or fluid measured amyloid and tau indicate increased risk for development of  
1067 cognitive impairment in older adults but at the individual level prognostication is not possible as  
1068 most cognitively normal people with these markers do not develop dementia within a clinically  
1069 relevant timeframe. Negative amyloid results can be useful for ruling out current Alzheimer's  
1070 pathology in people with cognitive impairment when the cause is uncertain and show an individual is  
1071 unlikely to develop AD during the next few years. High NfL levels indicate a neurodegenerative  
1072 process but not its cause. The value of biomarkers, in terms of diagnostic value, has not been  
1073 properly addressed in different representative populations and particularly not in LMICs. The  
1074 potential advantages of blood biomarkers are their low cost and their wider acceptability and  
1075 applicability in many settings. In many areas of medicine more reliable diagnostic tests have  
1076 improved research including epidemiological and public health research and trials - to help  
1077 distinguish cause from syndrome (TB from a fever) or assess risk factor and disease  
1078 (hypercholesterolaemia and ischaemic heart disease). Those developed for the underlying biology  
1079 of the dementia syndrome must be subject to the same assessment of value.

### 1080 **Principles of intervention in people with dementia**

1081 In the first Commission, we discussed the reasons that where concerns are raised by patient or  
1082 family, an accurate diagnosis is helpful. It provides a gateway to intervention and services where  
1083 available, for planning for possible futures, and support for family, as well as to facilitate research.  
1084 Unfortunately, these services are not always available. National plans for dementia support timely  
1085 diagnosis and support to individuals and their families.

1086 We did not address screening of those not presenting concerns but rigorous systematic reviews by  
 1087 the US Task Force on Prevention have found an absence of evidence of benefit and harm.<sup>188</sup> The  
 1088 first trial globally of screening took place in the US, screening 4005 primary care patients aged 65  
 1089 years or older. It found no clear benefit or harm in terms of quality of life, mood or increasing  
 1090 diagnostic rates.<sup>189</sup> Other strategies may become more valuable in time such as sensitive awareness  
 1091 of risk factors, when routine records suggest an individual may be in decline.<sup>190</sup>

1092 People with dementia have complex problems with symptoms in many domains. Those providing  
 1093 support and any interventions must consider the person as a whole, as well as their context and  
 1094 their close carers whether family or friends. This needs to balance their medical, cognitive,  
 1095 psychological, environmental, cultural and social needs.<sup>2</sup> In the context of underprovision of  
 1096 services, this is and will continue to be a challenge. Dementia, as an illness which affects cognition by  
 1097 definition, affects the ability to organise activities; and people with dementia often need help to do  
 1098 what they enjoy; for example, listen to music, or go to gardens and parks. Wellbeing is one of the  
 1099 goals of dementia care.

## 1100 **Interventions once a diagnosis has been made**

### 1101 ***Medication***

1102 Cholinesterase inhibitors have a useful, modest role in improving cognition and ADL in mild-to-  
 1103 moderate AD and memantine can be prescribed in combination or each drug used separately for  
 1104 moderate and severe AD.<sup>2,191,192</sup> However while available in most countries these are no longer  
 1105 remunerated in France because as they feel that their benefit is small and they shift clinician's  
 1106 attention from other interventions; it is unknown whether this will help patients or be detrimental  
 1107 to them.<sup>193</sup> There have been no advances in A $\beta$  therapeutics, with negative results from phase 3  
 1108 trials of monoclonal antibodies (e.g., solanezumab, crenezumab) and inhibitors of  $\beta$ -secretase 1  
 1109 (BACE1), a protease involved in the production of A $\beta$  peptides.<sup>194</sup> Aducanumab previously  
 1110 abandoned as futile now has further unpublished results. Three 5HT<sub>6</sub> antagonists and the calcium  
 1111 channel blocker nilvadipine<sup>195,196</sup> have also been ineffective. These medications also show  
 1112 substantial impact during treatments at 'therapeutic' levels on the leakiness of blood vessels. The  
 1113 long-term impact of such side effects is unknown. There is a continuing focus on anti-tau, anti-  
 1114 amyloid and anti-inflammatory drugs and some argue that pre-symptomatic interventions are  
 1115 necessary, especially if targeting A $\beta$  production, but there is no current evidence of efficacy<sup>197</sup> and  
 1116 of worsening target symptoms.<sup>198</sup>

### 1117 ***Cognitive training in people with dementia (CT)***

1118 A meta-analysis of 12 controlled trials of 389 people with mild dementia, completing  $\geq 4$  hours of  
 1119 group based computerized cognitive training (CCT), (mean age from 66 to 81 years old, 63.5% female  
 1120 participants) found a small, statistically significant beneficial effect on overall cognition, driven by  
 1121 two trials of virtual reality or Nintendo Wii (SMD=0.3; 95% CI 0.0-0.5), one with a low and one with a  
 1122 high risk of bias.<sup>55</sup>

1123 A second systematic review, a Cochrane review found 33 trials of CT, only one of which overlapped  
 1124 with the study above, with around 2,000 participants with mild-to-moderate dementia, most with a  
 1125 high or uncertain risk of bias. People completing CT, compared with usual treatment or non-specific  
 1126 activities, had small to moderate effects on overall cognition (SMD 0.4; 95% CI 0.2-0.6) and specific

1127 cognitive abilities such as verbal fluency, and improvements lasted for a few months to one year.  
1128 There was no direct evidence suggesting it was better than cognitive stimulation therapy.

### 1129 *Exercise and physical activity*

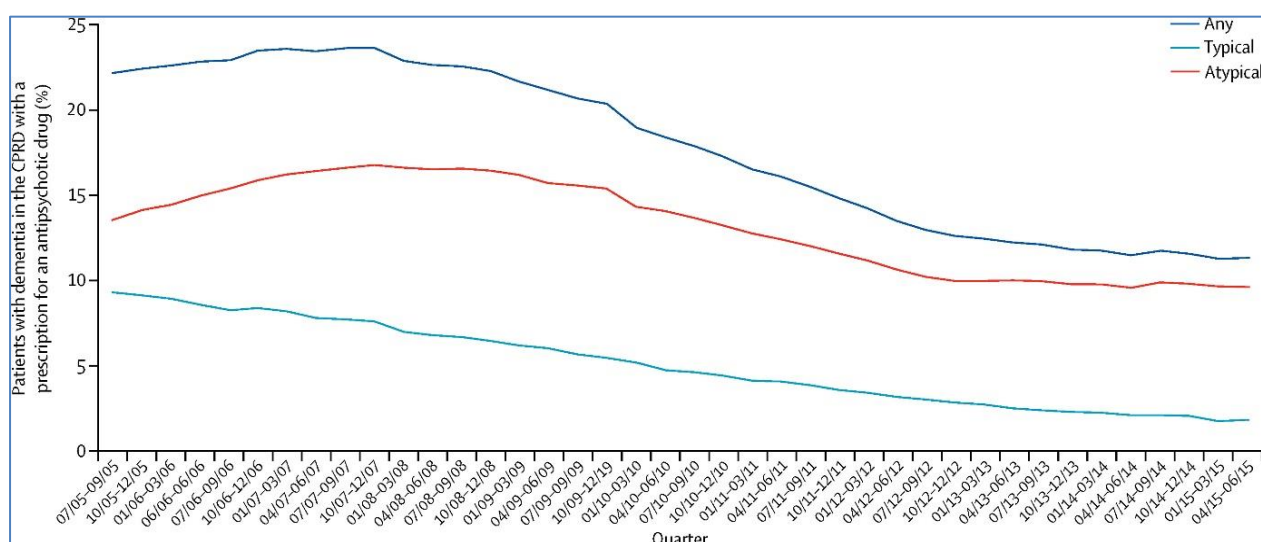
1130 The Dementia and Physical Activity (DAPA) RCT found moderate-to-high intensity aerobic and  
1131 strength exercise training did not slow cognitive impairment in people with mild-to-moderate  
1132 dementia but improved physical fitness.<sup>199</sup> The US Reducing Disability in Dementia (RDAD) study  
1133 implemented an at-home multicomponent intervention including exercise education, training to  
1134 increase pleasant events, and activator-behaviour-consequence problem-solving approach over six  
1135 weeks by case managers in 255 community dwelling people with dementia aged over 60 and their  
1136 family carer and were able to follow-up 140 (54.9%). They found increased physical activity; days of  
1137 taking  $\geq 30$  minutes of exercise; (effect size 0.6; 95% CI 0.4- 0.8; post-treatment and at 13 months  
1138 0.3; 95% CI 0.1-0.5) in a pre/post intervention comparison.

### 1139 *Interventions for neuropsychiatric symptoms (NPS) of dementia*

1140 NPS are common and often clustered in people with dementia. They may precede dementia and are  
1141 associated with tau and amyloid neuropathology.<sup>200</sup> This suggests that underlying neurobiological  
1142 mechanisms may underpin neuropsychiatric symptoms. However, there are also likely to be other  
1143 drivers which relate to the person with dementia's environment, and personal history .  
1144 Neurodegeneration could lead to increased vulnerability to stressors or triggers. Genetics, cognitive  
1145 reserve, resilience, medical comorbidities and environment may modify these relationships. Needs  
1146 and responses will also be individual and relate to a person's own social, cultural and historical  
1147 context. First-line assessment and management of NPS should focus on basic health: describe and  
1148 diagnose symptoms, look for causes such as pain (using validated pain assessments may help),  
1149 illness, discomfort, hunger, loneliness, boredom, lack of intimacy and worry that could cause the  
1150 behaviours and alleviate these while considering risks of harm.<sup>2</sup>

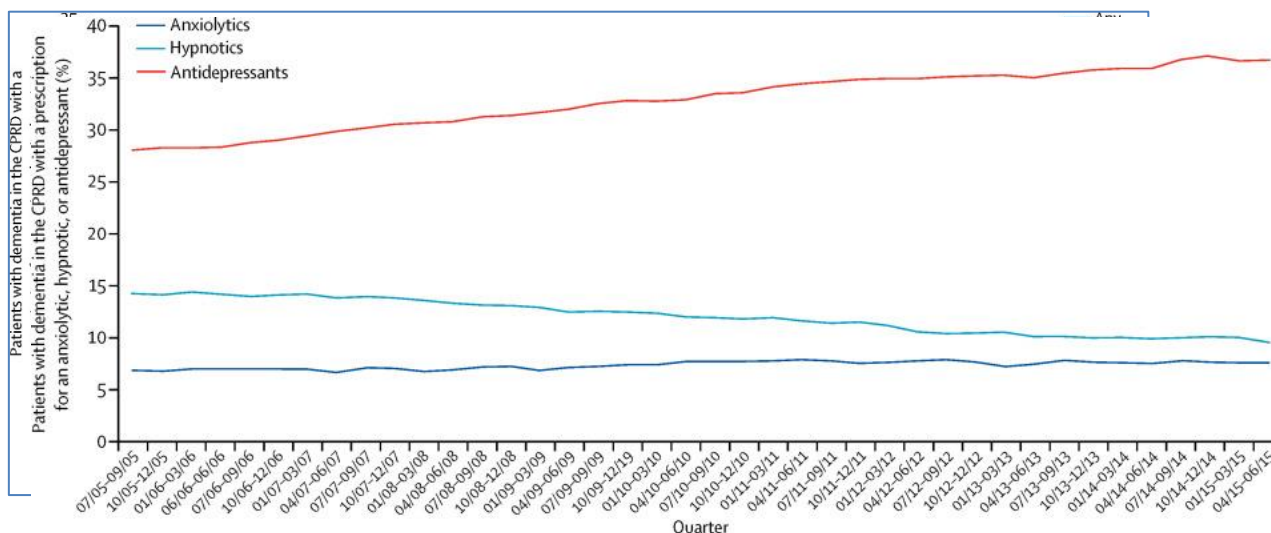
### 1151 **Figure 8a: Proportion of patients with a diagnosis for dementia living at home or in a care home 1152 prescribed an antipsychotic drug with permission**<sup>201</sup>

1153 There is no new evidence of medication effectiveness for these symptoms; risperidone in low doses  
1154 (0.5mg daily oral usually recommended) and some other antipsychotics are often ineffective and  
1155 have adverse effects.<sup>2</sup> Specific initiatives have led to a decrease in antipsychotic prescriptions for



1156 people with dementia, although they are often replaced by another psychotropics (figure 8 a, b),  
 1157 such as benzodiazepines, antidepressants and mood stabilizers.<sup>201</sup> These lack evidence of efficacy  
 1158 for neuropsychiatric symptoms but show clear evidence of possible harm; for example, trazodone  
 1159 and benzodiazepines increase fall related injuries.<sup>141</sup> It is important to carefully assess major policy  
 1160 changes carefully, within and across countries for unintended consequences (and perhaps  
 1161 unexpected benefits) and their costs.

1162



1163 **Figure 8b: Proportion of patients with a diagnosis of dementia prescribed an anxiolytic, hypnotic,**  
 1164 **or antidepressant with permission**

1165

1166 Evidence is slowly accumulating for the effectiveness, at least in the short-term, of person-centred  
 1167 psychosocial interventions tailored to individual needs. In Germany, a six-month cluster-RCT of  
 1168 nurse-delivered supervised dementia care management used a computer-assisted nurse assessment  
 1169 to determine personalised intervention modules, then a multi-disciplinary team discussion and  
 1170 agreement with the GP for 634 people (mean age 80) living with dementia at home with a primary  
 1171 carer or alone.<sup>202</sup> The mean MMSE was 23, only 38% had a formal diagnosis of dementia; the  
 1172 majority of participants had mild dementia but some had moderate and some severe. The  
 1173 intervention consisted of psychosocial management of treatment and care, medication management  
 1174 and carer support and education and discussion with a psychiatrist or neurologist. It was associated  
 1175 with better outcomes for neuropsychiatric symptoms compared to care as usual (CAU), but because  
 1176 of deterioration in CAU (Neuropsychiatric Inventory, NPI -7.5; 95% CI -11.1- -3.8; CAU NPI; increased  
 1177 from 7.2 to 15.2; intervention group NPI increased from 7.6 to 8.2). This between-group reduction in  
 1178 neuropsychiatric symptoms was greater than that expected, extrapolating from other study results,  
 1179 with antipsychotic medication. Effects on quality of life were only apparent for those people living  
 1180 with a carer.

1181 An eight-session home-based Tailored Activity Program (TAP-VA) RCT, tailored to the person with  
 1182 dementia living at home and a family member versus eight telephone-based education sessions,  
 1183 recruited 160 participants with 64% follow-up, imputing values for the rest.<sup>203</sup> Non-completers  
 1184 having more severe neuropsychiatric symptoms. It reported a large reduction in overall  
 1185 neuropsychiatric symptoms immediately after the intervention, which were better in the TAP-VA

1186 group on the neuropsychiatric inventory (mean difference in score = 24.3; 95%CI 3.1- 45.6); and in  
1187 dependence and pain but this was not sustained four months later.

### 1188 **Depression**

1189 Since the last Commission two new systematic reviews of antidepressants to treat depression in  
1190 dementia reported moderate quality evidence that antidepressant treatment for people with  
1191 dementia does not lead to better control of symptomatology compared with placebo.<sup>204,205</sup>

### 1192 **Agitation**

1193 Agitation is distressing for people with dementia and those around the patient, and contributes  
1194 significantly to the overall costs increasing as the level of agitation increases.<sup>206</sup> There is an  
1195 increasing body of evidence on this important behaviour, mostly focused on care homes settings.  
1196 These findings are important as these represent the most affected populations but as many people  
1197 with dementia reside at home this still leaves a major gap in knowledge.

1198 Care home residents with agitation often find sitting still difficult and therefore may not be included  
1199 in activities.<sup>207,208</sup> Two new cluster RCTs of professionals delivering multicomponent,  
1200 interdisciplinary, interventions in care homes successfully reduced agitation. The WHELD study  
1201 included participants with or without NPS and provided person-centred care, aiming to improve  
1202 communication with people with dementia. It implemented social, sensory experiences or other  
1203 activities; educated about antipsychotic review and addressed physical problems, finding lower  
1204 Cohen Mansfield Agitation Inventory (CMAI) at 9 months (MD -4.3points; 95% CI -7.3, -1.2).<sup>209</sup> The  
1205 TIME study for people with moderate-to-high levels of agitation consisted of a manual-based  
1206 comprehensive assessment of the resident and structured case conference for the staff and doctor,  
1207 to create a tailored plan, and then implement it. This led to reduced agitation at 8 and 12 weeks; NPI  
1208 (-1.1 points; 95% CI -0.1- -2.1; and -1.6; 95% CI -0.6- - 2.7) and CMAI (-4.7 points; 95% CI -0.6- -8.8;  
1209 and- 5.9; 95% CI -1.7- -10.1).<sup>210</sup> These effects sizes are similar to those seen for medications, but  
1210 without harmful side effects.<sup>211</sup> A further RCT of a six-session intervention with staff in groups,  
1211 teaching staff to understand agitation as related to medical, psychological or social unmet needs and  
1212 implement strategies to meet these needs, using the DICE approach<sup>212</sup> (Describe, Investigate, Create,  
1213 Evaluate) to recognise and respond to resident's unmet needs of; pleasant events and  
1214 communication strategies. The intervention did not reduce agitation symptoms, although it was  
1215 cost-effective, improving quality of life.<sup>213</sup> Overall, the current evidence for agitation in care homes  
1216 favours multi-component interventions by staff and not drug interventions. This still leaves a major  
1217 gap in knowledge about those living at home who comprise the majority of those with dementia.

### 1218 **Psychotic symptoms in dementia**

1219 People with dementia may be wrongly thought to have delusions when they misremember, and new  
1220 psychotic symptoms are often due to delirium, so thorough assessment of symptoms is essential.<sup>2</sup>  
1221 Management of psychosis in dementia should start with non-pharmacological interventions;  
1222 however, evidence for their effectiveness for psychosis in dementia is weaker than for agitation.<sup>214</sup>  
1223 Antipsychotics for psychosis in dementia should be prescribed in as low a dose and for the shortest  
1224 duration possible.<sup>2</sup> However, a Cochrane review of antipsychotics withdrawal found two trials with  
1225 participants who had responded to antipsychotic treatment. These reported that stopping  
1226 antipsychotics was associated with symptomatic relapse<sup>215</sup> suggesting the need for caution in any  
1227 medication withdrawal in this group. There was low-quality evidence that, in general,

1228 discontinuation may make little or no difference to overall NPS, adverse events, quality of life or  
1229 cognitive function.<sup>216</sup>

### 1230 **Apathy**

1231 Apathy may be conceptualised as the opposite of engagement, comprising reduced interest,  
1232 initiative and activity. Like people without dementia, those with dementia engage more in preferred  
1233 activities, but require additional support to do so.<sup>217</sup> Another study in care homes observed  
1234 engagement increased during activities in those who attended the groups.<sup>218</sup> A Cochrane review of  
1235 the few people who had been in drug RCTs of methylphenidate versus placebo for apathy in  
1236 dementia found small improvements on the apathy evaluation scale (MD -5.0; 95% CI -9.6 - -0.4, n =  
1237 145, 3 studies, low-quality evidence) but not on the NPI apathy subscale, MD -0.1; 95% CI -3.9- 3.7, n  
1238 = 85, 2 studies).<sup>219</sup>

### 1239 **Sleep**

1240 There is no evidence that medication for sleep in dementia is effective<sup>220</sup> and considerable evidence  
1241 for harm, for example, earlier death, increased hospitalisation and falls.<sup>136,141</sup> Testing of non-  
1242 pharmacological interventions is ongoing.<sup>221</sup>

### 1243 **Carers**

1244 Carer distress related to neuropsychiatric symptoms beyond dementia symptoms themselves was  
1245 associated in one study with increased use and costs of health services,<sup>222</sup> highlighting the need for  
1246 effectively identifying, educating, and supporting distressed carers. An RCT reporting six-year follow-  
1247 up after the 8 session START intervention found continuing effectiveness for carer depressive  
1248 symptoms (adjusted mean difference (MD) -2.00; 95% CI -3.3, -0.6, n=243) and risk of case-level  
1249 depression, with patient-related cost being approximately three times lower than those who did not  
1250 receive the intervention (median £5,759 versus £16,964 in the final year; p =0.07). Another US study  
1251 followed 663 people 51% with mild, 31% moderate and 18% severe dementia (any type), mean age  
1252 73, 55% with female family carer. Depression rather than symptoms of people with dementia  
1253 predicted emergency department use for people with dementia, with a 73% (95%CI 17.3-23.0)  
1254 increase when carers were depressed.

### 1255 **Functioning**

1256 A UK RCT of 14 sessions of cognitive rehabilitation focused on individual goal attainment with  
1257 therapy delivered at home by an occupational therapist or nurse to 475 participants with mild-to-  
1258 moderate dementia (MMSE  $\geq$ 18 for inclusion; mean 24) and a family carer. Individuals had two-to-  
1259 three goals; the most common was engaging in activities (21% of goals). The intervention group  
1260 reported increased goal attainment over 3 and 9 months compared to usual treatment (effect size  
1261 0.8; 95% CI 0.6 -1at both 3 and 9 months).<sup>223</sup> The treatment did not improve participants' quality of  
1262 life, mood, self-efficacy, cognition, carer stress, health status and was not cost-effective. A  
1263 systematic review of RCTs without meta-analysis for overall effect size, concluded that all  
1264 interventions which had improved functioning in people living with dementia in the community have  
1265 bene individual rather than group interventions, in-home physiotherapist delivered tailored exercise  
1266 (2 studies, larger one positive, 140 people with AD, smaller study negative, 35 people), individualised  
1267 cognitive rehabilitation (mild or moderate dementia; 2 studies; 257 CR intervention groups and 255  
1268 controls), and in-home activities-focused occupational therapy (people with mild to moderate

1269 dementia, 3 studies, 201 intervention,191 controls) reduced functional decline compared to controls  
1270 but group-exercise and reminiscence therapies were ineffective.<sup>224</sup>

### 1271 **People with dementia have other illnesses**

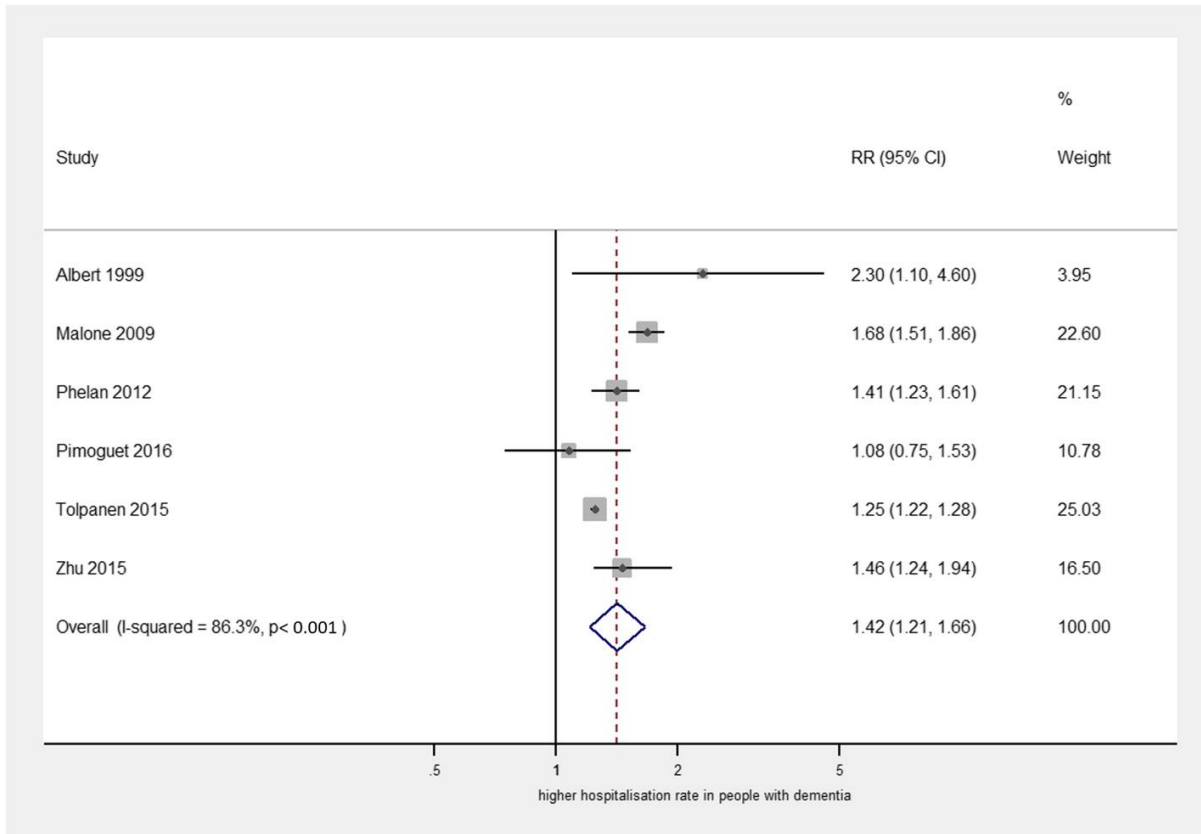
1272 Multimorbidity is a huge challenge in dementia, not only because people with dementia have  
1273 increased rates of other diseases, but also because they often find it particularly difficult to organise  
1274 care. People with dementia may forget to tell their family or health professionals of symptoms,  
1275 struggle to understand or follow agreed plans, and are more likely to forget to drink and eat,  
1276 increasing falling and infection rates.<sup>225</sup> People with dementia consult primary care less often than  
1277 those without dementia,<sup>226</sup> dental visits decline,<sup>227</sup> and family members, if involved, often feel they  
1278 lack knowledge to assist.<sup>228</sup> Healthcare professionals need education to be more comfortable,  
1279 understanding and positive in communicating with people with dementia.<sup>229</sup>

1280 Around 70-80% of people diagnosed with dementia in primary care have at least two other chronic  
1281 illnesses.<sup>230,231</sup> People who are physically more frail are more likely to have dementia, but the  
1282 relationship between pathology and symptoms in these people is comparatively weak suggesting  
1283 that dementia may be from other mechanisms.<sup>22</sup> Compared to the general older population, people  
1284 with dementia have increased rates of cerebrovascular disease,<sup>231-234</sup> stroke,<sup>235</sup> Parkinson's disease,  
1285 <sup>231,233</sup> diabetes,<sup>233</sup> <sup>235</sup>skin ulcers, anxiety and depression,<sup>231,233</sup> pneumonia, incontinence and  
1286 electrolyte disturbance.<sup>233</sup> Multi-morbidity in people with dementia is associated with faster  
1287 functional decline<sup>236</sup> and worse quality of life for people with dementia and their family carers.<sup>237</sup>

### 1288 **Hospital admissions**

1289 Hospitalisation in people with dementia is associated with adverse, unintended consequences,  
1290 including distress, functional and cognitive decline, and high economic costs.<sup>238-240</sup> People with  
1291 dementia have 1.4 to 4 times more hospital admissions than others with similar illnesses.<sup>239,241-243</sup>





1292

1293 **Figure 9 Systematic review and meta-analysis of hospitalisation rates of people with dementia**  
 1294 **compared to those without dementia controlled for age and sex (with permission)<sup>244</sup>**

1295 A systematic review and meta-analysis including 34 studies of 277,432 people with dementia, found  
 1296 that in the six studies which compared the two groups, people with dementia had increased  
 1297 hospitalisation compared to those without, after adjusting for age, sex, and physical comorbidity (RR  
 1298 1.4; 95% CI 1.2 -1.7; see figure 9).<sup>244</sup> Hospitalisation rates in people with dementia ranged from 0.37  
 1299 to 1.26/person-year in high-quality studies. Admissions are often for conditions that might be  
 1300 manageable in the community (potentially preventable hospitalisations).<sup>241</sup> People with dementia  
 1301 experience longer and more frequent admissions and readmissions; healthcare expenditure for  
 1302 people with moderate-severe dementia is around double that of people without dementia.<sup>242,245,246</sup>  
 1303 Early detection and management of physical ill health in people with dementia, particularly of pain,  
 1304 falls, diabetes, incontinence and sensory impairment, is important.<sup>191,247,248</sup> However, no  
 1305 intervention has successfully reduced hospital admissions of community-dwelling people with  
 1306 dementia,<sup>249</sup> although education, exercise, rehabilitation and telemedicine have reduced admissions  
 1307 for older people without dementia.<sup>250</sup>

1308 High quality care for people with dementia takes longer than caring for others with the same  
 1309 condition.<sup>251</sup> Recognition of dementia in hospital inpatients is necessary for optimum care,<sup>252</sup> but  
 1310 dementia is often undetected or unrecorded.<sup>253</sup> In the UK however, detection rates have increased  
 1311 over the past 10 years.<sup>254</sup>

### 1312 **Physical illness, delirium and dementia**

1313 Dementia and delirium frequently occur together. In one hospital inpatients' survey nearly 35% of  
 1314 those aged >80 experienced delirium; those with prior cognitive impairment had 15 times the risk of

1315 developing delirium than those without (OR 15.3; 95% CI 5.2- 45.4).<sup>255</sup> People with delirium are 12  
1316 times more likely to be diagnosed with dementia in the future than others, either because of pre-  
1317 existing undiagnosed dementia, or because delirium has neurotoxic effects and so precipitates  
1318 dementia.<sup>256</sup> People with similar neuropathology show faster cognitive decline if they develop  
1319 delirium than if they do not.<sup>257</sup> Additionally, older people without dementia declined cognitively  
1320 more than twice as fast after an emergency hospital admission for any cause, compared to those not  
1321 admitted, suggesting any severe illness is associated with cognitive decline.<sup>258</sup> Risk factors for  
1322 delirium in dementia include sensory impairment, pain, polypharmacy, dehydration, intercurrent  
1323 illnesses such as urinary tract infections or faecal impaction, and an unfamiliar or changing  
1324 environment.<sup>259</sup> Delirium in older people should prompt consideration of underlying dementia

1325 Most research on delirium prevention has been in people without dementia. It suggests targeting  
1326 hydration, stopping medication predisposing to delirium, monitoring the depth of anaesthesia and  
1327 sleep promotion. However, there is no evidence for medication efficacy, including cholinesterase  
1328 inhibitors, antipsychotic medication or melatonin.<sup>260-262</sup> The Hospital Elder Life Program (HELP)  
1329 intervention to prevent delirium in those admitted to hospital reduced delirium incidence and  
1330 includes people who are cognitively impaired. It is a multidisciplinary treatment consisting of daily  
1331 visits, orientation, therapeutic activities, sleep enhancement, early mobilisation, vision and hearing  
1332 adaptation, fluid repletion, infection prevention and management of constipation, pain, and  
1333 hypoxia; and feeding assistance.<sup>263</sup>

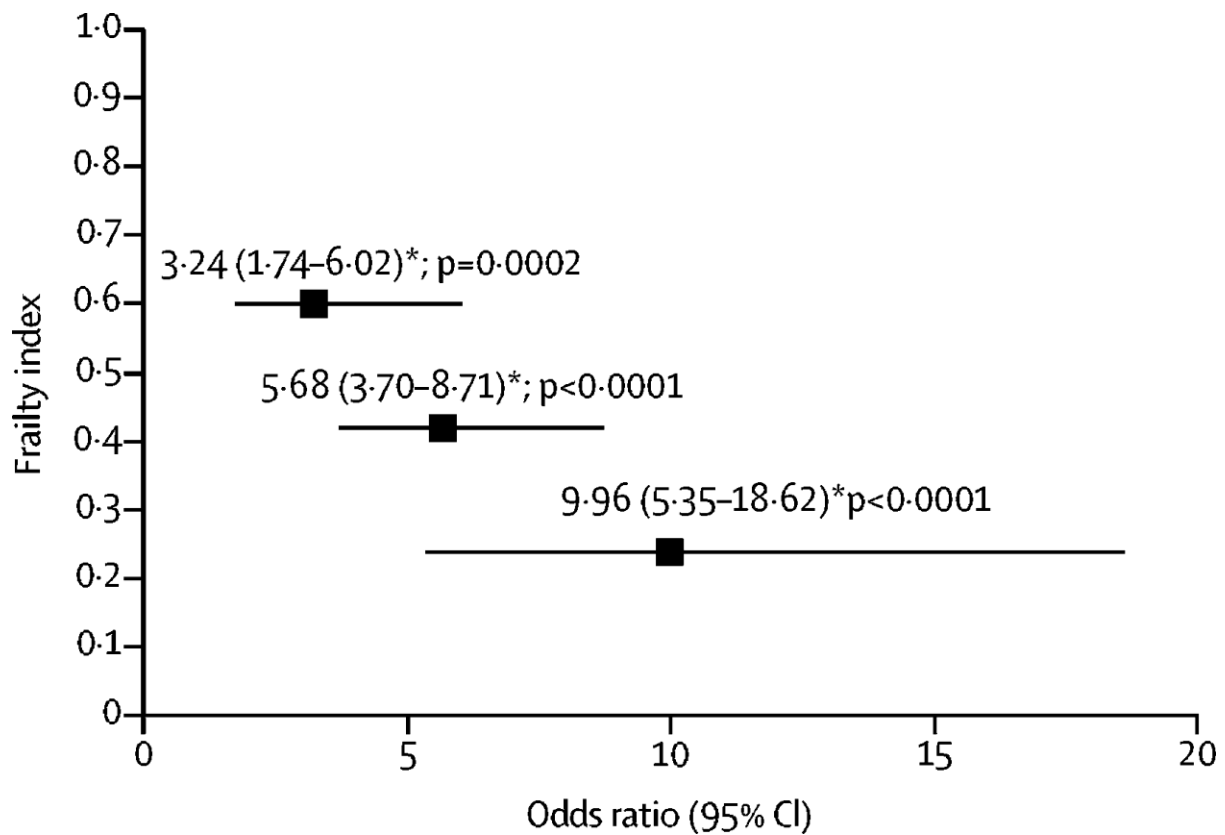
1334 A network meta-analysis of drugs for prevention and treatment of delirium did not include studies of  
1335 people with dementia, so we cannot recommend drugs for people with dementia and delirium as  
1336 this research may be inapplicable to people with dementia.<sup>264</sup>

1337 There is little high quality research on managing delirium in dementia. One RCT compared a  
1338 specialist medical and mental health unit to usual care for 600 “confused” people aged >65 years,  
1339 acutely admitted to hospital and found no difference in the primary outcome of days spent at home  
1340 or in hospital, but increased family satisfaction.<sup>265</sup> A further RCT of cognitively stimulating activities  
1341 for people with delirium in dementia did not improve the delirium.<sup>266</sup> There is currently no definitive  
1342 evidence that any medication improves delirium in people with dementia: cholinesterase inhibitors,  
1343 antipsychotics, and sedating benzodiazepines are ineffective and antipsychotics and  
1344 benzodiazepines are associated with mortality and morbidity.<sup>238,261,267-270</sup> Given the risk of dementia  
1345 in people who develop delirium, its prevention, and possibly advances in its management, may offer  
1346 a means for dementia prevention.<sup>271</sup>

### 1347 **Link between very old age, frailty and dementia**

1348 The fastest growing demographic group in most advanced countries are people 90 and over. In one  
1349 well characterized post-mortem cohort of the oldest old (n=1079; mean age 90) dying with  
1350 dementia, found that neuropathological features of Alzheimer disease account for about half of the  
1351 cognitive decline seen and people diagnosed with AD had mixed causes of dementia.<sup>272</sup> Although AD  
1352 neuropathology was the commonest cause of dementia, Alzheimer changes rarely occurred on their  
1353 own, so only 9% of people with dementia had pure AD pathology.<sup>273</sup> People who have Alzheimer  
1354 pathology without developing dementia tend to have fewer age-related health deficits than those  
1355 who develop it with even low levels of plaques and tangles.<sup>274</sup> A moderation analysis showed  
1356 that the relationship between Alzheimer’s disease pathology and dementia status differed  
1357 according to level of frailty, (adjusted for age, sex, and education), with increasing frailty

1358 weakening the relationship between AD pathology and dementia (figure 10).<sup>22</sup> As with delirium,  
 1359 some of this additional health risk may be modifiable. This approach suggests a new type of therapy  
 1360 focus on specific age-related processes that underpin many diseases of late life.



1361

1362 **Figure 10** (with permission) **Moderation analyses of the relationship between Alzheimer's**  
 1363 **disease pathology and clinical diagnosis of Alzheimer's dementia (adjusted for age, sex,**  
 1364 **and education). As frailty increased, the odds of a neuropathological diagnosis of**  
 1365 **Alzheimer disease corresponding to a clinical diagnosis decreased.**<sup>22</sup>

### 1366 End-of-life care in dementia

1367 There are increasing numbers of people dying with dementia but we lack evidence of the best end-  
 1368 of-life care. As well as more people with dementia, trends in age-standardised death rates (3.6%) for  
 1369 dementia increased slightly between 1990-2016, with pronounced increases in the US and Japan and  
 1370 decreases in Western-Europe and Central Latin America.<sup>4</sup> There is more willingness to include  
 1371 dementia on the death certificate, which accounts for some of the rise. The increase may be related  
 1372 to dementia becoming manifest at later ages and increasing physical frailty<sup>22</sup> and be related to a  
 1373 faster decline.

1374 Most people with dementia may die while still in the mild-to-moderate stages while only about a  
 1375 quarter of those dying with dementia have severe dementia.<sup>275,276</sup> The trajectory of dementia is  
 1376 often unpredictable<sup>277</sup> and palliative care initiation should reflect need not prognosis.

1377 Decision-making about end-of-life is complex and simple rules of thumb, co-designed with staff and  
 1378 carers provided clarity in some small studies.<sup>277</sup> One RCT testing decision-aids about families and  
 1379 doctors' goals of care for people with advanced dementia led to increased palliative care content in  
 1380 care plans.<sup>278,279</sup> In a 9-month UK prospective study, of 85 care home residents with advanced

1381 dementia from 14 homes, were likely to be living with distressing symptoms, specifically agitation  
1382 (54%) or pain (61% on movement).<sup>277</sup>

1383 Capacity to make abstract decisions, including about the future, may be lost early in dementia<sup>280</sup>.  
1384 Therefore, advance care planning, designed to empower people with dementia and improve quality  
1385 of dying, might theoretically be something everyone should do before developing dementia.<sup>281</sup>  
1386 However, people may not be able to predict their future wishes, this may explain why family carer  
1387 proxies show only low-to-moderate agreement with stated end-of-life treatment preferences of  
1388 people with dementia.<sup>282</sup> Advance care planning may, however, reduce carers' uncertainty in  
1389 decision-making and improve perceptions of quality of care.<sup>283</sup>

1390 Partners of people dying with dementia experience poorer mental health than those facing  
1391 bereavement from other causes. <sup>284</sup> possibly because of long and difficult caring responsibilities. This  
1392 may be ameliorated through sensitive and timely information, particularly regarding the progression  
1393 of dementia, <sup>285</sup> individually or through family and staff case-conferencing. <sup>286,287</sup>

## 1394 **Conclusions**

1395 Knowledge about risk factors and potential prevention, detection, and diagnosis of dementia is  
1396 improving although significant gaps remain.<sup>288</sup> In this report, we have specified policy and individual  
1397 changes to delay the onset of cognitive impairment and dementia and better ways to support and  
1398 treat people with dementia and their families and improve their quality of life.

1399 Interventions, including organisation of the complex physical illness and social needs, to support  
1400 people affected by dementia can have a huge effect when taken as a whole. Our ambition is for  
1401 worldwide provision of resources for an adequate level of wellbeing to persons with dementia and  
1402 their carers with a better evidence base to guide individual care and policy making alike. With good  
1403 quality care, people can live well with dementia and families can feel supported.

## 1404 **Contributors**

1405 GL, AS, JH and NM contributed to literature searches and quality assessments for systematic  
1406 reviews; JH and NM performed meta-analyses; GL, NM, JH and AS conceived the new PAF calculation  
1407 and NM led the statistical analysis. GL, JH, AS, NM, DA, CB, SB, AB, JCM, CC, SC, NF, RH, HK, EL, VO,  
1408 KR, KR, ES, QS, LS and GS attended the conference to discuss the content.

1409 ELS, EL, AS, DA, JH, GL wrote first draft of sections of the paper. GL wrote the first draft of the whole  
1410 paper and revisions of drafts. CB reviewed and contributed to revision of the final drafts. All authors  
1411 contributed to sections of the reports and all revised the paper for important intellectual content.

## 1412 **Acknowledgments**

1413 We are partnered by University College London, the Alzheimer's Society, UK, the Economic and  
1414 Social Research Council, and Alzheimer's Research UK, and would like to thank them for financial  
1415 help. These organisations funded the fares, accommodation, and food for the Commission meeting  
1416 but had no role in the writing of the manuscript or the decision to submit it for publication. We  
1417 would like to thank Bernadette Courtney, Jacques Gianino and Nuj Monowari, from University  
1418 College London, London, for their administrative help, including managing finances, booking rooms  
1419 and food, and setting up a website supported by the UCLH NIHR BRC. We would like to acknowledge  
1420 the contribution of Henrik Zetterberg for advice on biomarkers and dementia.

## 1421 References

- 1422 1. Prince M, Wimo A, Guerchet M, Ali G, Wu YT, M P. World Alzheimer Report 2015 - The  
1423 Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. London, 2015.
- 1424 2. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care.  
1425 *The Lancet* 2017; **390**(10113): 2673-734.
- 1426 3. Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43  
1427 encephalopathy (LATE): consensus working group report. *Brain* 2019.
- 1428 4. Collaborators GBDD. Global, regional, and national burden of Alzheimer's disease and other  
1429 dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*  
1430 *Neurol* 2019; **18**(1): 88-106.
- 1431 5. Wu YT, Beiser AS, Breteler MMB, et al. The changing prevalence and incidence of dementia  
1432 over time - current evidence. *Nat Rev Neurol* 2017; **13**(6): 327-39.
- 1433 6. Kingston A, Comas-Herrera A, Jagger C, project M. Forecasting the care needs of the older  
1434 population in England over the next 20 years: estimates from the Population Ageing and Care  
1435 Simulation (PACSim) modelling study. *Lancet Public Health* 2018; **3**(9): e447-e55.
- 1436 7. Gao S, Burney HN, Callahan CM, Purnell CE, Hendrie HC. Incidence of Dementia and  
1437 Alzheimer Disease Over Time: A Meta-Analysis. *Journal of the American Geriatrics Society* 2019.
- 1438 8. Friedrich MJ. Global Obesity Epidemic Worsening. *JAMA* 2017; **318**(7): 603.
- 1439 9. Singh-Manoux A, Dugravot A, Shipley M, et al. Obesity trajectories and risk of dementia: 28  
1440 years of follow-up in the Whitehall II Study. *Alzheimers Dement* 2018; **14**(2): 178-86.
- 1441 10. Ahmadi-Abhari S, Guzman-Castillo M, Bandosz P, et al. Temporal trend in dementia  
1442 incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study.  
1443 *BMJ* 2017; **358**: j2856.
- 1444 11. Kivimaki M, Luukkonen R, Batty GD, et al. Body mass index and risk of dementia: Analysis of  
1445 individual-level data from 1.3 million individuals. *Alzheimers Dement* 2018; **14**(5): 601-9.
- 1446 12. McGrath ER, Beiser AS, DeCarli C, et al. Blood pressure from mid- to late life and risk of  
1447 incident dementia. *Neurology* 2017; **89**(24): 2447-54.
- 1448 13. Abell JG, Kivimaki M, Dugravot A, et al. Association between systolic blood pressure and  
1449 dementia in the Whitehall II cohort study: role of age, duration, and threshold used to define  
1450 hypertension. *Eur Heart J* 2018.
- 1451 14. Delgado J, Bowman K, Ble A, et al. Blood Pressure Trajectories in the 20 Years Before Death.  
1452 *JAMA Intern Med* 2018; **178**(1): 93-9.
- 1453 15. Stern Y, Arenaza-Urquijo EM, Bartres-Faz D, et al. Whitepaper: Defining and investigating  
1454 cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement* 2018.
- 1455 16. Pernecky R, Kempermann G, Korczyn AD, et al. Translational research on reserve against  
1456 neurodegenerative disease: consensus report of the International Conference on Cognitive Reserve  
1457 in the Dementias and the Alzheimer's Association Reserve, Resilience and Protective Factors  
1458 Professional Interest Area working groups. *BMC Med* 2019; **17**(1): 47.
- 1459 17. Cholerton B, Larson EB, Baker LD, et al. Neuropathologic correlates of cognition in a  
1460 population-based sample. *J Alzheimers Dis* 2013; **36**(4): 699-709.
- 1461 18. Latimer CS, Keene CD, Flanagan ME, et al. Resistance to Alzheimer Disease Neuropathologic  
1462 Changes and Apparent Cognitive Resilience in the Nun and Honolulu-Asia Aging Studies. *J*  
1463 *Neuropathol Exp Neurol* 2017; **76**(6): 458-66.
- 1464 19. Arenaza-Urquijo EM, Przybelski SA, Lesnick TL, et al. The metabolic brain signature of  
1465 cognitive resilience in the 80+: beyond Alzheimer pathologies. *Brain* 2019.
- 1466 20. Franzmeier N, Duzel E, Jessen F, et al. Left frontal hub connectivity delays cognitive  
1467 impairment in autosomal-dominant and sporadic Alzheimer's disease. *Brain* 2018; **141**(4): 1186-200.
- 1468 21. Neitzel J, Franzmeier N, Rubinski A, Ewers M, Alzheimer's Disease Neuroimaging I. Left  
1469 frontal connectivity attenuates the adverse effect of entorhinal tau pathology on memory.  
1470 *Neurology* 2019; **93**(4): e347-e57.

- 1471 22. Wallace LMK, Theou O, Godin J, Andrew MK, Bennett DA, Rockwood K. Investigation of  
1472 frailty as a moderator of the relationship between neuropathology and dementia in Alzheimer's  
1473 disease: a cross-sectional analysis of data from the Rush Memory and Aging Project. *Lancet Neurol*  
1474 2019; **18**(2): 177-84.
- 1475 23. van der Lee SJ, Teunissen CE, Pool R, et al. Circulating metabolites and general cognitive  
1476 ability and dementia: Evidence from 11 cohort studies. *Alzheimers Dement* 2018; **14**(6): 707-22.
- 1477 24. Peters R, Ee N, Peters J, Booth A, Mudway I, Anstey KJ. Air Pollution and Dementia: A  
1478 Systematic Review. *Journal of Alzheimer's disease : JAD* 2019.
- 1479 25. Chieffi S, Messina G, Villano I, et al. Exercise Influence on Hippocampal Function: Possible  
1480 Involvement of Orexin-A. *Front Physiol* 2017; **8**: 85.
- 1481 26. Parbo P, Ismail R, Hansen KV, et al. Brain inflammation accompanies amyloid in the majority  
1482 of mild cognitive impairment cases due to Alzheimer's disease. *Brain* 2017; **140**(7): 2002-11.
- 1483 27. Anstey KJ, Ee N, Eramudugolla R, Jagger C, Peters R. A Systematic Review of Meta-Analyses  
1484 that Evaluate Risk Factors for Dementia to Evaluate the Quantity, Quality, and Global  
1485 Representativeness of Evidence. *Journal of Alzheimer's disease : JAD* 2019; **70**(s1): S165-S86.
- 1486 28. Prince M, Ferri CP, Acosta D, et al. The protocols for the 10/66 dementia research group  
1487 population-based research programme. *BMC public health* 2007; **7**(1): 165.
- 1488 29. Mukadam NS, N. Huntley, J. Livingston, G Population attributable fractions for risk factors for  
1489 dementia in low-income and middle-income countries: an analysis using cross-sectional survey data.  
1490 *Lancet Glob Health* 2019; **2019**; **7**: e596-603.
- 1491 30. Wu YT, Ali GC, Guerchet M, et al. Prevalence of dementia in mainland China, Hong Kong and  
1492 Taiwan: an updated systematic review and meta-analysis. *Int J Epidemiol* 2018.
- 1493 31. Hoffman SJ, Mammone J, Rogers Van Katwyk S, et al. Cigarette consumption estimates for  
1494 71 countries from 1970 to 2015: systematic collection of comparable data to facilitate quasi-  
1495 experimental evaluations of national and global tobacco control interventions. *BMJ* 2019; **365**:  
1496 l2231.
- 1497 32. Jia L, Quan M, Fu Y, et al. Dementia in China: epidemiology, clinical management, and  
1498 research advances. *The Lancet Neurology* 2019.
- 1499 33. Sabia S, Dugravot A, Dartigues JF, et al. Physical activity, cognitive decline, and risk of  
1500 dementia: 28 year follow-up of Whitehall II cohort study. *BMJ* 2017; **357**: j2709.
- 1501 34. Singh-Manoux A, Dugravot A, Fournier A, et al. Trajectories of Depressive Symptoms Before  
1502 Diagnosis of Dementia A 28-Year Follow-up Study. *Jama Psychiatry* 2017; **74**(7): 712-8.
- 1503 35. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of  
1504 Alzheimer's disease: An analysis of population-based data. *The Lancet Neurology* 2014; **13**(8): 2014-  
1505 794.
- 1506 36. Satizabal CL, Beiser AS, Chouraki V, Chene G, Dufouil C, Seshadri S. Incidence of Dementia  
1507 over Three Decades in the Framingham Heart Study. *N Engl J Med* 2016; **374**(6): 523-32.
- 1508 37. Larsson SC, Traylor M, Malik R, et al. Modifiable pathways in Alzheimer's disease: Mendelian  
1509 randomisation analysis. *BMJ* 2017; **359**: j5375.
- 1510 38. Kremen WS, Beck A, Elman JA, et al. Influence of young adult cognitive ability and additional  
1511 education on later-life cognition. *Proc Natl Acad Sci U S A* 2019; **116**(6): 2021-6.
- 1512 39. Blacker D, Weuve J. Brain Exercise and Brain Outcomes: Does Cognitive Activity Really Work  
1513 to Maintain Your Brain? *JAMA Psychiatry* 2018; **75**(7): 703-4.
- 1514 40. Lee ATC, Richards M, Chan WC, Chiu HFK, Lee RSY, Lam LCW. Association of Daily Intellectual  
1515 Activities With Lower Risk of Incident Dementia Among Older Chinese Adults. *JAMA Psychiatry* 2018;  
1516 **75**(7): 697-703.
- 1517 41. Chan D, Shafto M, Kievit R, et al. Lifestyle activities in mid-life contribute to cognitive reserve  
1518 in late-life, independent of education, occupation, and late-life activities. *Neurobiol Aging* 2018; **70**:  
1519 180-3.
- 1520 42. Staff RT, Hogan MJ, Williams DS, Whalley LJ. Intellectual engagement and cognitive ability in  
1521 later life (the "use it or lose it" conjecture): longitudinal, prospective study. *BMJ* 2018; **363**: k4925.

- 1522 43. Kajitani S, Sakata K, McKenzie C. Occupation, retirement and cognitive functioning. *Ageing*  
1523 *Soc* 2017; **37**(8): 1568-96.
- 1524 44. Xue B, Cadar D, Fleischmann M, et al. Effect of retirement on cognitive function: the  
1525 Whitehall II cohort study. *Eur J Epidemiol* 2018; **33**(10): 989-1001.
- 1526 45. Meng A, Nexo MA, Borg V. The impact of retirement on age related cognitive decline - a  
1527 systematic review. *BMC geriatrics* 2017; **17**(1): 160.
- 1528 46. Grotz C, Meillon C, Amieva H, et al. Why Is Later Age at Retirement Beneficial for Cognition?  
1529 Results from a French Population-based Study. *J Nutr Health Aging* 2016; **20**(5): 514-9.
- 1530 47. Denier N, Clouston SAP, Richards M, Hofer SM. Retirement and Cognition: A Life Course  
1531 View. *Adv Life Course Res* 2017; **31**: 11-21.
- 1532 48. Clouston SA, Denier N. Mental retirement and health selection: Analyses from the U.S.  
1533 Health and Retirement Study. *Soc Sci Med* 2017; **178**: 78-86.
- 1534 49. Rohwedder S, Willis RJ. Mental Retirement. *J Econ Perspect* 2010; **24**(1): 119-38.
- 1535 50. Gates NJ, Sachdev PS, Fiatarone Singh MA, Valenzuela M. Cognitive and memory training in  
1536 adults at risk of dementia: a systematic review. *BMC geriatrics* 2011; **11**: 55.
- 1537 51. Gavelin HL, A; Hallock, H; Sabates, J; Bahar-Fuchs, A. Cognition-oriented treatments for older  
1538 adults: A systematic overview of systematic reviews. *Neuropsychology Review* 2019 in press.
- 1539 52. Kane RL, BM, Fink HA, Brasure M, Davila H, desai P, Jutkowitz E, McCreedy E, Nelson VA,  
1540 McCarten JR, Calvert C, Ratner E, Hemmy LS, Barclay T. Interventions to Prevent Age-Related  
1541 Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia. Rockville  
1542 (MD), 2017.
- 1543 53. Butler M, McCreedy E, Nelson VA, et al. Does Cognitive Training Prevent Cognitive Decline?:  
1544 A Systematic Review. *Ann Intern Med* 2018; **168**(1): 63-8.
- 1545 54. Gates NJ, Rutjes AW, Di Nisio M, et al. Computerised cognitive training for maintaining  
1546 cognitive function in cognitively healthy people in midlife. *The Cochrane database of systematic*  
1547 *reviews* 2019; **3**: CD012278.
- 1548 55. Hill NT, Mowszowski L, Naismith SL, Chadwick VL, Valenzuela M, Lampit A. Computerized  
1549 Cognitive Training in Older Adults With Mild Cognitive Impairment or Dementia: A Systematic  
1550 Review and Meta-Analysis. *Am J Psychiatry* 2017; **174**(4): 329-40.
- 1551 56. Chandler MJ, Parks AC, Marsiske M, Rotblatt LJ, Smith GE. Everyday Impact of Cognitive  
1552 Interventions in Mild Cognitive Impairment: a Systematic Review and Meta-Analysis. *Neuropsychol*  
1553 *Rev* 2016; **26**(3): 225-51.
- 1554 57. Rovner BW, Casten RJ, Hegel MT, Leiby B. Preventing Cognitive Decline in Black Individuals  
1555 With Mild Cognitive Impairment: A Randomized Clinical Trial. *JAMA Neurol* 2018; **75**(12): 1487-93.
- 1556 58. Loughrey DG, Kelly ME, Kelley GA, Brennan S, Lawlor BA. Association of Age-Related Hearing  
1557 Loss With Cognitive Function, Cognitive Impairment, and Dementia: A Systematic Review and Meta-  
1558 analysis. *JAMA Otolaryngol Head Neck Surg* 2018; **144**(2): 115-26.
- 1559 59. Golub JS, Brickman AM, Ciarleglio AJ, Schupf N, Luchsinger JA. Association of Subclinical  
1560 Hearing Loss With Cognitive Performance. *JAMA Otolaryngol Head Neck Surg* 2019.
- 1561 60. Armstrong NM, An Y, Doshi J, et al. Association of Midlife Hearing Impairment With Late-Life  
1562 Temporal Lobe Volume Loss. *JAMA Otolaryngol Head Neck Surg* 2019.
- 1563 61. Amieva H, Ouvrard C, Meillon C, Rullier L, Dartigues JF. Death, Depression, Disability and  
1564 Dementia Associated with Self-Reported Hearing Problems: a 25-Year Study. *J Gerontol A Biol Sci*  
1565 *Med Sci* 2018.
- 1566 62. Ray J, Popli G, Fell G. Association of Cognition and Age-Related Hearing Impairment in the  
1567 English Longitudinal Study of Ageing. *JAMA Otolaryngol Head Neck Surg* 2018.
- 1568 63. Maharani A, Dawes P, Nazroo J, Tampubolon G, Pendleton N, group SE-CW. Longitudinal  
1569 Relationship Between Hearing Aid Use and Cognitive Function in Older Americans. *J Am Geriatr Soc*  
1570 2018; **66**(6): 1130-6.
- 1571 64. Zanier ER, Bertani I, Sammali E, et al. Induction of a transmissible tau pathology by traumatic  
1572 brain injury. *Brain* 2018: awy193-awy.

- 1573 65. Cao J, Gaamouch FE, Meabon JS, et al. ApoE4-associated phospholipid dysregulation  
1574 contributes to development of Tau hyper-phosphorylation after traumatic brain injury. *Sci Rep* 2017;  
1575 **7**(1): 11372.
- 1576 66. Bruns J, Jr., Hauser WA. The epidemiology of traumatic brain injury: a review. *Epilepsia* 2003;  
1577 **44**(s10): 2-10.
- 1578 67. Fann JR, Ribe AR, Pedersen HS, et al. Long-term risk of dementia among people with  
1579 traumatic brain injury in Denmark: a population-based observational cohort study. *Lancet Psychiatry*  
1580 2018; **5**(5): 424-31.
- 1581 68. Nordstrom A, Nordstrom P. Traumatic brain injury and the risk of dementia diagnosis: A  
1582 nationwide cohort study. *PLoS Med* 2018; **15**(1): e1002496.
- 1583 69. Tolppanen AM, Taipale H, Hartikainen S. Head or brain injuries and Alzheimer's disease: A  
1584 nested case-control register study. *Alzheimers Dement* 2017; **13**(12): 1371-9.
- 1585 70. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of Mild  
1586 Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military  
1587 Veterans. *JAMA Neurol* 2018; **75**(9): 1055-61.
- 1588 71. Yaffe K, Lwi SJ, Hoang TD, et al. Military-related risk factors in female veterans and risk of  
1589 dementia. *Neurology* 2019; **92**(3): e205-e11.
- 1590 72. Redelmeier DA, Manzoor F, Thiruchelvam D. Association Between Statin Use and Risk of  
1591 Dementia After a Concussion. *JAMA Neurol* 2019.
- 1592 73. Smith DH, Johnson VE, Trojanowski JQ, Stewart W. Chronic traumatic encephalopathy -  
1593 confusion and controversies. *Nat Rev Neurol* 2019; **15**(3): 179-83.
- 1594 74. Mackay DF, Russell ER, Stewart K, MacLean JA, Pell JP, Stewart W. Neurodegenerative  
1595 Disease Mortality among Former Professional Soccer Players. *N Engl J Med* 2019.
- 1596 75. Pase MP, Beiser A, Enserro D, et al. Association of Ideal Cardiovascular Health With Vascular  
1597 Brain Injury and Incident Dementia. *Stroke* 2016; **47**(5): 1201-6.
- 1598 76. Walker KA, Sharrett AR, Wu A, et al. Association of Midlife to Late-Life Blood Pressure  
1599 Patterns With Incident Dementia. *JAMA* 2019; **322**(6): 535-45.
- 1600 77. Lane CA, Barnes J, Nicholas JM, et al. Associations between blood pressure across adulthood  
1601 and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth  
1602 cohort (Insight 46): an epidemiological study. *Lancet Neurology* 2019; **18**(10): 942-52.
- 1603 78. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs Standard Blood Pressure  
1604 Control and Cardiovascular Disease Outcomes in Adults Aged  $\geq 75$  Years: A Randomized Clinical  
1605 Trial. *JAMA* 2016; **315**(24): 2673-82.
- 1606 79. Group SMIftSR, Williamson JD, Pajewski NM, et al. Effect of Intensive vs Standard Blood  
1607 Pressure Control on Probable Dementia: A Randomized Clinical Trial. *JAMA* 2019.
- 1608 80. Yaffe K. Prevention of Cognitive Impairment With Intensive Systolic Blood Pressure Control.  
1609 *JAMA* 2019.
- 1610 81. Peters R, Warwick J, Anstey KJ, Anderson CS. Blood pressure and dementia: What the  
1611 SPRINT-MIND trial adds and what we still need to know. *Neurology* 2019; **92**(21): 1017-8.
- 1612 82. Tully PJ, Hanon O, Cosh S, Tzourio C. Diuretic antihypertensive drugs and incident dementia  
1613 risk: a systematic review, meta-analysis and meta-regression of prospective studies. *J Hypertens*  
1614 2016; **34**(6): 1027-35.
- 1615 83. Ding J, Davis-Plourde KL, Sedaghat S, et al. Antihypertensive medications and risk for  
1616 incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from  
1617 prospective cohort studies. *Lancet Neurol* 2019.
- 1618 84. Hussain S, Singh A, Rahman SO, Habib A, Najmi AK. Calcium channel blocker use reduces  
1619 incident dementia risk in elderly hypertensive patients: A meta-analysis of prospective studies.  
1620 *Neurosci Lett* 2018; **671**: 120-7.
- 1621 85. Peters R, Yasar S, Anderson CS, et al. An investigation of antihypertensive class, dementia,  
1622 and cognitive decline: A meta-analysis. *Neurology* 2019.



- 1623 86. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. *The*  
1624 *Cochrane database of systematic reviews* 2016; (1): CD003160.
- 1625 87. McNeil JJ, Woods RL, Nelson MR, et al. Effect of Aspirin on Disability-free Survival in the  
1626 Healthy Elderly. *N Engl J Med* 2018.
- 1627 88. Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D. Risk factors associated with the  
1628 onset and progression of Alzheimer's disease: A systematic review of the evidence. *Neurotoxicology*  
1629 2017; **61**: 143-87.
- 1630 89. Zotcheva E, Bergh S, Selbaek G, et al. Midlife Physical Activity, Psychological Distress, and  
1631 Dementia Risk: The HUNT Study. *Journal of Alzheimer's disease : JAD* 2018.
- 1632 90. Horder H, Johansson L, Guo X, et al. Midlife cardiovascular fitness and dementia: A 44-year  
1633 longitudinal population study in women. *Neurology* 2018; **90**(15): e1298-e305.
- 1634 91. Kivimaki M, Singh-Manoux A, Pentti J, et al. Physical inactivity, cardiometabolic disease, and  
1635 risk of dementia: an individual-participant meta-analysis. *BMJ* 2019; **365**: l1495.
- 1636 92. Saint-Maurice PF, Coughlan D, Kelly SP, et al. Association of Leisure-Time Physical Activity  
1637 Across the Adult Life Course With All-Cause and Cause-Specific Mortality. *JAMA Netw Open* 2019;  
1638 **2**(3): e190355.
- 1639 93. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive  
1640 function in adults older than 50: a systematic review with meta-analysis. *Br J Sports Med* 2018; **52**(3):  
1641 154-60.
- 1642 94. de Souto Barreto P, Demougeot L, Vellas B, Rolland Y. Exercise Training for Preventing  
1643 Dementia, Mild Cognitive Impairment, and Clinically Meaningful Cognitive Decline: A Systematic  
1644 Review and Meta-analysis. *J Gerontol A Biol Sci Med Sci* 2018; **73**(11): 1504-11.
- 1645 95. Barha CK, Davis JC, Falck RS, Nagamatsu LS, Liu-Ambrose T. Sex differences in exercise  
1646 efficacy to improve cognition: A systematic review and meta-analysis of randomized controlled trials  
1647 in older humans. *Front Neuroendocrinol* 2017; **46**: 71-85.
- 1648 96. Song D, Yu DSF, Li PWC, Lei Y. The effectiveness of physical exercise on cognitive and  
1649 psychological outcomes in individuals with mild cognitive impairment: A systematic review and  
1650 meta-analysis. *Int J Nurs Stud* 2018; **79**: 155-64.
- 1651 97. Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva, 2019.
- 1652 98. Chatterjee S, Peters SA, Woodward M, et al. Type 2 Diabetes as a Risk Factor for Dementia in  
1653 Women Compared With Men: A Pooled Analysis of 2.3 Million People Comprising More Than  
1654 100,000 Cases of Dementia. *Diabetes Care* 2016; **39**(2): 300-7.
- 1655 99. McMillan JM, Mele BS, Hogan DB, Leung AA. Impact of pharmacological treatment of  
1656 diabetes mellitus on dementia risk: systematic review and meta-analysis. *BMJ Open Diabetes Res*  
1657 *Care* 2018; **6**(1): e000563.
- 1658 100. Areosa Sastre A, Vernooij RW, Gonzalez-Colaco Harmand M, Martinez G. Effect of the  
1659 treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia.  
1660 *The Cochrane database of systematic reviews* 2017; **6**: CD003804.
- 1661 101. Sabia S, Fayosse A, Dumurgier J, et al. Association of ideal cardiovascular health at age 50  
1662 with incidence of dementia: 25 year follow-up of Whitehall II cohort study. *BMJ* 2019; **366**: l4414.
- 1663 102. Rehm J, Hasan OSM, Black SE, Shield KD, Schwarzing M. Alcohol use and dementia: a  
1664 systematic scoping review. *Alzheimers Res Ther* 2019; **11**(1): 11.
- 1665 103. Schwarzing M, Pollock BG, Hasan OSM, Dufouil C, Rehm J, QalyDays Study G. Contribution  
1666 of alcohol use disorders to the burden of dementia in France 2008-13: a nationwide retrospective  
1667 cohort study. *Lancet Public Health* 2018; **3**(3): e124-e32.
- 1668 104. Ilomaki J, Jokanovic N, Tan ECK, Lonnroos E. Alcohol consumption, dementia and cognitive  
1669 decline: An overview of systematic reviews. *Current Clinical Pharmacology* 2015; **10**(3): 204-12.
- 1670 105. Koch M, Fitzpatrick AL, Rapp SR, et al. Alcohol Consumption and Risk of Dementia and  
1671 Cognitive Decline Among Older Adults With or Without Mild Cognitive Impairment. *JAMA Netw*  
1672 *Open* 2019; **2**(9): e1910319.

- 1673 106. Piumatti G, Moore SC, Berridge DM, Sarkar C, Gallacher J. The relationship between alcohol  
1674 use and long-term cognitive decline in middle and late life: a longitudinal analysis using UK Biobank. *J*  
1675 *Public Health (Oxf)* 2018; **40**(2): 304-11.
- 1676 107. Sabia S, Fayosse A, Dumurgier J, et al. Alcohol consumption and risk of dementia: 23 year  
1677 follow-up of Whitehall II cohort study. *BMJ* 2018; **362**: k2927.
- 1678 108. Topiwala A, Allan CL, Valkanova V, et al. Moderate alcohol consumption as risk factor for  
1679 adverse brain outcomes and cognitive decline: longitudinal cohort study. *BMJ* 2017; **357**: j2353.
- 1680 109. Albanese E, Launer LJ, Egger M, et al. Body mass index in midlife and dementia: Systematic  
1681 review and meta-regression analysis of 589,649 men and women followed in longitudinal studies.  
1682 *Alzheimers Dement (Amst)* 2017; **8**: 165-78.
- 1683 110. Veronese N, Facchini S, Stubbs B, et al. Weight loss is associated with improvements in  
1684 cognitive function among overweight and obese people: A systematic review and meta-analysis.  
1685 *Neurosci Biobehav Rev* 2017; **72**: 87-94.
- 1686 111. Chang CC, Zhao Y, Lee CW, Ganguli M. Smoking, death, and Alzheimer disease: a case of  
1687 competing risks. *Alzheimer Dis Assoc Disord* 2012; **26**(4): 300-6.
- 1688 112. Debanne SM, Bielefeld RA, Cheruvu VK, Fritsch T, Rowland DY. Alzheimer's disease and  
1689 smoking: bias in cohort studies. *Journal of Alzheimer's disease : JAD* 2007; **11**(3): 313-21.
- 1690 113. Oberg M, Jaakkola MS, Woodward A, Peruga A, Pruss-Ustun A. Worldwide burden of disease  
1691 from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. *Lancet*  
1692 2011; **377**(9760): 139-46.
- 1693 114. Prince MJA, E. Guerchet, M Prina, M. The World Alzheimer Report 2014, Dementia and Risk  
1694 Reduction: An analysis of protective and modifiable factors. London, 2014.
- 1695 115. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Flicker L. Depression as a modifiable factor to  
1696 decrease the risk of dementia. *Transl Psychiatry* 2017; **7**(5): e1117.
- 1697 116. Evans IEM, Martyr A, Collins R, Brayne C, Clare L. Social Isolation and Cognitive Function in  
1698 Later Life: A Systematic Review and Meta-Analysis. *Journal of Alzheimer's disease : JAD* 2019; **70**(s1):  
1699 S119-S44.
- 1700 117. Penninkilampi R, Casey AN, Singh MF, Brodaty H. The Association between Social  
1701 Engagement, Loneliness, and Risk of Dementia: A Systematic Review and Meta-Analysis. *Journal of*  
1702 *Alzheimer's disease : JAD* 2018; **66**(4): 1619-33.
- 1703 118. Sommerlad A, Sabia S, Singh-Manoux A, Lewis G, Livingston G. Association of social contact  
1704 with dementia and cognition: 28-year follow-up of the Whitehall II cohort study. *PLoS Med* 2019;  
1705 **16**(8): e1002862.
- 1706 119. Saito T, Murata C, Saito M, Takeda T, Kondo K. Influence of social relationship domains and  
1707 their combinations on incident dementia: a prospective cohort study. *J Epidemiol Community Health*  
1708 2018; **72**(1): 7-12.
- 1709 120. Kelly ME, Duff H, Kelly S, et al. The impact of social activities, social networks, social support  
1710 and social relationships on the cognitive functioning of healthy older adults: a systematic review.  
1711 *Syst Rev* 2017; **6**(1): 259.
- 1712 121. Sommerlad A, Ruegger J, Singh-Manoux A, Lewis G, Livingston G. Marriage and risk of  
1713 dementia: systematic review and meta-analysis of observational studies. *J Neurol Neurosurg*  
1714 *Psychiatry* 2018; **89**(3): 231-8.
- 1715 122. Power MC, Adar SD, Yanosky JD, Weuve J. Exposure to air pollution as a potential  
1716 contributor to cognitive function, cognitive decline, brain imaging, and dementia: A systematic  
1717 review of epidemiologic research. *Neurotoxicology* 2016; **56**: 235-53.
- 1718 123. Chen H, Kwong JC, Copes R, et al. Living near major roads and the incidence of dementia,  
1719 Parkinson's disease, and multiple sclerosis: a population-based cohort study. *Lancet* 2017.
- 1720 124. Oudin A, Segersson D, Adolfsson R, Forsberg B. Association between air pollution from  
1721 residential wood burning and dementia incidence in a longitudinal study in Northern Sweden. *PLoS*  
1722 *One* 2018; **13**(6): e0198283.

- 1723 125. Oudin A, Forsberg B, Adolfsson AN, et al. Traffic-Related Air Pollution and Dementia  
1724 Incidence in Northern Sweden: A Longitudinal Study. *Environ Health Perspect* 2016; **124**(3): 306-12.
- 1725 126. Carey IM, Anderson HR, Atkinson RW, et al. Are noise and air pollution related to the  
1726 incidence of dementia? A cohort study in London, England. *BMJ Open* 2018; **8**(9): e022404.
- 1727 127. Bowe B, Xie Y, Yan Y, Al-Aly Z. Burden of Cause-Specific Mortality Associated With PM2.5 Air  
1728 Pollution in the United States. *JAMA Netw Open* 2019; **2**(11): e1915834.
- 1729 128. Spira AP, Gamaldo AA, An Y, et al. Self-reported sleep and beta-amyloid deposition in  
1730 community-dwelling older adults. *JAMA Neurol* 2013; **70**(12): 1537-43.
- 1731 129. Macedo AC, Balouch S, Tabet N. Is Sleep Disruption a Risk Factor for Alzheimer's Disease?  
1732 *Journal of Alzheimer's disease : JAD* 2017; **58**(4): 993-1002.
- 1733 130. Musiek ES, Xiong DD, Holtzman DM. Sleep, circadian rhythms, and the pathogenesis of  
1734 Alzheimer disease. *Exp Mol Med* 2015; **47**: e148.
- 1735 131. Yaffe K, Falvey CM, Hoang T. Connections between sleep and cognition in older adults.  
1736 *Lancet Neurol* 2014; **13**(10): 1017-28.
- 1737 132. Sindi S, Kareholt I, Johansson L, et al. Sleep disturbances and dementia risk: A multicenter  
1738 study. *Alzheimers Dement* 2018.
- 1739 133. Irwin MR, Vitiello MV. Implications of sleep disturbance and inflammation for Alzheimer's  
1740 disease dementia. *Lancet Neurol* 2019; **18**(3): 296-306.
- 1741 134. Shi L, Chen SJ, Ma MY, et al. Sleep disturbances increase the risk of dementia: A systematic  
1742 review and meta-analysis. *Sleep Med Rev* 2018; **40**: 4-16.
- 1743 135. Bubu OM, Brannick M, Mortimer J, et al. Sleep, Cognitive impairment, and Alzheimer's  
1744 disease: A Systematic Review and Meta-Analysis. *Sleep* 2017; **40**(1).
- 1745 136. Ohara T, Honda T, Hata J, et al. Association Between Daily Sleep Duration and Risk of  
1746 Dementia and Mortality in a Japanese Community. *J Am Geriatr Soc* 2018.
- 1747 137. Li J, Ogrodnik M, Kolachalama VB, Lin H, Au R. Assessment of the Mid-Life Demographic and  
1748 Lifestyle Risk Factors of Dementia Using Data from the Framingham Heart Study Offspring Cohort.  
1749 *Journal of Alzheimer's disease : JAD* 2018; **63**(3): 1119-27.
- 1750 138. Lutsey PL, Misialek JR, Mosley TH, et al. Sleep characteristics and risk of dementia and  
1751 Alzheimer's disease: The Atherosclerosis Risk in Communities Study. *Alzheimers Dement* 2018; **14**(2):  
1752 157-66.
- 1753 139. Lu Y, Sugawara Y, Zhang S, Tomata Y, Tsuji I. Changes in Sleep Duration and the Risk of  
1754 Incident Dementia in the Elderly Japanese: the Ohsaki Cohort 2006 Study. *Sleep* 2018.
- 1755 140. Richardson K, Mattishent K, Loke YK, et al. History of Benzodiazepine Prescriptions and Risk  
1756 of Dementia: Possible Bias Due to Prevalent Users and Covariate Measurement Timing in a Nested  
1757 Case-Control Study. *Am J Epidemiol* 2019; **188**(7): 1228-36.
- 1758 141. Bronskill SE, Campitelli MA, Iaboni A, et al. Low-Dose Trazodone, Benzodiazepines, and Fall-  
1759 Related Injuries in Nursing Homes: A Matched-Cohort Study. *J Am Geriatr Soc* 2018; **66**(10): 1963-71.
- 1760 142. Pistollato F, Iglesias RC, Ruiz R, et al. Nutritional patterns associated with the maintenance of  
1761 neurocognitive functions and the risk of dementia and Alzheimer's disease: A focus on human  
1762 studies. *Pharmacol Res* 2018; **131**: 32-43.
- 1763 143. Morris MC, Wang Y, Barnes LL, Bennett DA, Dawson-Hughes B, Booth SL. Nutrients and  
1764 bioactives in green leafy vegetables and cognitive decline: Prospective study. *Neurology* 2018; **90**(3):  
1765 e214-e22.
- 1766 144. Akbaraly TN, Singh-Manoux A, Dugravot A, Brunner EJ, Kivimaki M, Sabia S. Association of  
1767 Midlife Diet With Subsequent Risk for Dementia. *JAMA* 2019; **321**(10): 957-68.
- 1768 145. D'Cunha NM, Georgousopoulou EN, Dadigamuwage L, et al. Effect of long-term nutraceutical  
1769 and dietary supplement use on cognition in the elderly: a 10-year systematic review of randomised  
1770 controlled trials. *Br J Nutr* 2018; **119**(3): 280-98.
- 1771 146. Rutjes AW, Denton DA, Di Nisio M, et al. Vitamin and mineral supplementation for  
1772 maintaining cognitive function in cognitively healthy people in mid and late life. *The Cochrane*  
1773 *database of systematic reviews* 2018; **12**: CD011906.

- 1774 147. McCleery J, Abraham RP, Denton DA, et al. Vitamin and mineral supplementation for  
1775 preventing dementia or delaying cognitive decline in people with mild cognitive impairment. *The*  
1776 *Cochrane database of systematic reviews* 2018; **11**: CD011905.
- 1777 148. Farina N, Llewellyn D, Isaac M, Tabet N. Vitamin E for Alzheimer's dementia and mild  
1778 cognitive impairment. *The Cochrane database of systematic reviews* 2017; **4**: CD002854.
- 1779 149. Soininen H, Solomon A, Visser PJ, et al. 24-month intervention with a specific multinutrient  
1780 in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled  
1781 trial. *Lancet Neurol* 2017; **16**(12): 965-75.
- 1782 150. Radd-Vagenas S, Duffy SL, Naismith SL, Brew BJ, Flood VM, Fiatarone Singh MA. Effect of the  
1783 Mediterranean diet on cognition and brain morphology and function: a systematic review of  
1784 randomized controlled trials. *Am J Clin Nutr* 2018; **107**(3): 389-404.
- 1785 151. Rosenberg A, Ngandu T, Rusanen M, et al. Multidomain lifestyle intervention benefits a large  
1786 elderly population at risk for cognitive decline and dementia regardless of baseline characteristics:  
1787 The FINGER trial. *Alzheimers Dement* 2018; **14**(3): 263-70.
- 1788 152. Stephen R, Liu Y, Ngandu T, et al. Brain volumes and cortical thickness on MRI in the Finnish  
1789 Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER). *Alzheimers Res*  
1790 *Ther* 2019; **11**(1): 53.
- 1791 153. Richard E, Jongstra S, Soininen H, et al. Healthy Ageing Through Internet Counselling in the  
1792 Elderly: the HATICE randomised controlled trial for the prevention of cardiovascular disease and  
1793 cognitive impairment. *BMJ Open* 2016; **6**(6): e010806.
- 1794 154. Richard EMvC, EP. Hoevenaar-Blom, MP. Coley, N. Barbera, M. van der Groep, A. et al.  
1795 Healthy ageing through internet counselling in the elderly (HATICE): a multinational, randomised  
1796 controlled trial. *Lancet Digital Health* 2019; **1**(8): e424-e34.
- 1797 155. Xu W, Wang H, Wan Y, et al. Alcohol consumption and dementia risk: a dose-response meta-  
1798 analysis of prospective studies. *Eur J Epidemiol* 2017; **32**(1): 31-42.
- 1799 156. Britton A, Ben-Shlomo Y, Benzeval M, Kuh D, Bell S. Life course trajectories of alcohol  
1800 consumption in the United Kingdom using longitudinal data from nine cohort studies. *BMC Med*  
1801 2015; **13**: 47.
- 1802 157. Järvenpää T, Rinne JO, Koskenvuo M, Rähä I, Kaprio J. Binge drinking in midlife and  
1803 dementia risk. *Epidemiology* 2005: 766-71.
- 1804 158. Handing EP, Andel R, Kadlecova P, Gatz M, Pedersen NL. Midlife alcohol consumption and  
1805 risk of dementia over 43 years of follow-up: A population-based study from the Swedish Twin  
1806 Registry. *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences* 2015;  
1807 **70**(10): 1248-54.
- 1808 159. Shor E, Roelfs D, Vang ZM. The "Hispanic mortality paradox" revisited: Meta-analysis and  
1809 meta-regression of life-course differentials in Latin American and Caribbean immigrants' mortality.  
1810 *Social Science & Medicine* 2017; **186**: 20-33.
- 1811 160. Altman DG. Practical statistics for medical research: CRC press; 1990.
- 1812 161. Huang CH, Lin CW, Lee YC, et al. Is traumatic brain injury a risk factor for  
1813 neurodegeneration? A meta-analysis of population-based studies. *BMC Neurol* 2018; **18**(1): 184.
- 1814 162. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort  
1815 studies of common outcomes. *JAMA* 1998; **280**(19): 1690-1.
- 1816 163. Chu SF, Chiu WT, Lin HW, Chiang YH, Liou TH. Hazard Ratio and Repeat Injury for Dementia  
1817 in Patients With and Without a History of Traumatic Brain Injury: A Population-Based Secondary  
1818 Data Analysis in Taiwan. *Asia Pac J Public Health* 2016; **28**(6): 519-27.
- 1819 164. Frost RB, Farrer TJ, Primosch M, Hedges DW. Prevalence of traumatic brain injury in the  
1820 general adult population: a meta-analysis. *Neuroepidemiology* 2013; **40**(3): 154-9.
- 1821 165. Chen H, Kwong JC, Copes R, et al. Exposure to ambient air pollution and the incidence of  
1822 dementia: A population-based cohort study. *Environ Int* 2017; **108**: 271-7.
- 1823 166. NHS Digital. Health Survey for England 2014 : health, social care and lifestyles : summary of  
1824 key findings, 2014.

- 1825 167. Lourida I, Hannon E, Littlejohns TJ, et al. Association of Lifestyle and Genetic Risk With  
1826 Incidence of Dementia. *JAMA* 2019.
- 1827 168. Solomon A, Turunen H, Ngandu T, et al. Effect of the Apolipoprotein E Genotype on  
1828 Cognitive Change During a Multidomain Lifestyle Intervention: A Subgroup Analysis of a Randomized  
1829 Clinical Trial. *JAMA Neurol* 2018; **75**(4): 462-70.
- 1830 169. Licher S, Ahmad S, Karamujic-Comic H, et al. Genetic predisposition, modifiable-risk-factor  
1831 profile and long-term dementia risk in the general population. *Nat Med* 2019; **25**(9): 1364-9.
- 1832 170. Rockwood K, Wallace LMK, Davis DH. Genetic predisposition and modifiable risks for late-life  
1833 dementia. *Nat Med* 2019; **25**(9): 1331-2.
- 1834 171. Ritchie K, Carriere I, Ritchie CW, Berr C, Artero S, Ancelin ML. Designing prevention  
1835 programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors.  
1836 *BMJ* 2010; **341**: c3885.
- 1837 172. American Psychiatric Association. DSM-IV Sourcebook. Washington: American Psychiatric  
1838 Press; 1996.
- 1839 173. American Psychiatric Association, American Psychiatric Association. DSM-5 Task Force.  
1840 Diagnostic and statistical manual of mental disorders : DSM-5. 5th ed. Washington, D.C.: American  
1841 Psychiatric Association; 2013.
- 1842 174. Roberts RO, Aakre JA, Kremers WK, et al. Prevalence and Outcomes of Amyloid Positivity  
1843 Among Persons Without Dementia in a Longitudinal, Population-Based Setting. *JAMA Neurol* 2018;  
1844 **75**(8): 970-9.
- 1845 175. Rice L, Bisdas S. The diagnostic value of FDG and amyloid PET in Alzheimer's disease-A  
1846 systematic review. *Eur J Radiol* 2017; **94**: 16-24.
- 1847 176. Dang C, Harrington KD, Lim YY, et al. Relationship Between Amyloid-beta Positivity and  
1848 Progression to Mild Cognitive Impairment or Dementia over 8 Years in Cognitively Normal Older  
1849 Adults. *J Alzheimers Dis* 2018.
- 1850 177. Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using  
1851 biomarkers for preclinical disease. *Alzheimers Dement* 2018; **14**(8): 981-8.
- 1852 178. Jack CR, Jr., Wiste HJ, Therneau TM, et al. Associations of Amyloid, Tau, and  
1853 Neurodegeneration Biomarker Profiles With Rates of Memory Decline Among Individuals Without  
1854 Dementia. *JAMA* 2019; **321**(23): 2316-25.
- 1855 179. Rabinovici GD, Gatzonis C, Apgar C, et al. Association of Amyloid Positron Emission  
1856 Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With  
1857 Mild Cognitive Impairment or Dementia. *JAMA* 2019; **321**(13): 1286-94.
- 1858 180. Nakamura A, Kaneko N, Villemagne VL, et al. High performance plasma amyloid-beta  
1859 biomarkers for Alzheimer's disease. *Nature* 2018; **554**(7691): 249-54.
- 1860 181. Ovod V, Ramsey KN, Mawuenyega KG, et al. Amyloid beta concentrations and stable isotope  
1861 labeling kinetics of human plasma specific to central nervous system amyloidosis. *Alzheimers*  
1862 *Dement* 2017; **13**(8): 841-9.
- 1863 182. Janelidze S, Stomrud E, Palmqvist S, et al. Plasma beta-amyloid in Alzheimer's disease and  
1864 vascular disease. *Sci Rep* 2016; **6**: 26801.
- 1865 183. Blennow K, Mattsson N, Scholl M, Hansson O, Zetterberg H. Amyloid biomarkers in  
1866 Alzheimer's disease. *Trends Pharmacol Sci* 2015; **36**(5): 297-309.
- 1867 184. Herukka SK, Simonsen AH, Andreasen N, et al. Recommendations for cerebrospinal fluid  
1868 Alzheimer's disease biomarkers in the diagnostic evaluation of mild cognitive impairment.  
1869 *Alzheimers Dement* 2017; **13**(3): 285-95.
- 1870 185. Byrne LM, Rodrigues FB, Blennow K, et al. Neurofilament light protein in blood as a potential  
1871 biomarker of neurodegeneration in Huntington's disease: a retrospective cohort analysis. *Lancet*  
1872 *Neurol* 2017; **16**(8): 601-9.
- 1873 186. Disanto G, Barro C, Benkert P, et al. Serum Neurofilament light: A biomarker of neuronal  
1874 damage in multiple sclerosis. *Ann Neurol* 2017; **81**(6): 857-70.

- 1875 187. Mattsson N, Andreasson U, Zetterberg H, Blennow K, Alzheimer's Disease Neuroimaging I.  
1876 Association of Plasma Neurofilament Light With Neurodegeneration in Patients With Alzheimer  
1877 Disease. *JAMA Neurol* 2017; **74**(5): 557-66.
- 1878 188. Patnode CP, LA. Rossom, RC. Rushkin, MC. Redmond, N. Thomas, RG. Lin, JS. Screening for  
1879 Cognitive Impairment in Older Adults: An Evidence Update for the U.S. Preventive Services Task  
1880 Force. US: AHRQ Publication; 2019.
- 1881 189. Fowler NR, Perkins AJ, Gao S, Sachs GA, Boustani MA. Risks and Benefits of Screening for  
1882 Dementia in Primary Care: The Indiana University Cognitive Health Outcomes Investigation of the  
1883 Comparative Effectiveness of Dementia Screening (IU CHOICE) Trial. *J Am Geriatr Soc* 2019.
- 1884 190. Fowler NR, Perkins AJ, Gao S, Sachs GA, Uebelhor AK, Boustani MA. Patient characteristics  
1885 associated with screening positive for Alzheimer's disease and related dementia. *Clin Interv Aging*  
1886 2018; **13**: 1779-85.
- 1887 191. National Institute for Health and Care Excellence. Dementia: Assessment, management and  
1888 support for people living with dementia and their carers. 2018.
- 1889 192. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. *The Cochrane*  
1890 *database of systematic reviews* 2018; **6**: CD001190.
- 1891 193. Walsh S, King E, Brayne C. France removes state funding for dementia drugs. *BMJ* 2019; **367**:  
1892 l6930.
- 1893 194. Egan MF, Kost J, Tariot PN, et al. Randomized Trial of Verubecestat for Mild-to-Moderate  
1894 Alzheimer's Disease. *N Engl J Med* 2018; **378**(18): 1691-703.
- 1895 195. Lawlor B, Segurado R, Kennelly S, et al. Nilvadipine in mild to moderate Alzheimer disease: A  
1896 randomised controlled trial. *PLoS Med* 2018; **15**(9): e1002660.
- 1897 196. Andrews M, Tousi B, Sabbagh MN. 5HT6 Antagonists in the Treatment of Alzheimer's  
1898 Dementia: Current Progress. *Neurol Ther* 2018; **7**(1): 51-8.
- 1899 197. Voytyuk I, De Strooper B, Chavez-Gutierrez L. Modulation of gamma- and beta-Secretases as  
1900 Early Prevention Against Alzheimer's Disease. *Biol Psychiatry* 2018; **83**(4): 320-7.
- 1901 198. Egan MF, Kost J, Voss T, et al. Randomized Trial of Verubecestat for Prodromal Alzheimer's  
1902 Disease. *N Engl J Med* 2019; **380**(15): 1408-20.
- 1903 199. Lamb SE, Sheehan B, Atherton N, et al. Dementia And Physical Activity (DAPA) trial of  
1904 moderate to high intensity exercise training for people with dementia: randomised controlled trial.  
1905 *BMJ* 2018; **361**: k1675.
- 1906 200. Ehrenberg AJ, Suemoto CK, de Paula Franca Resende E, et al. Neuropathologic Correlates of  
1907 Psychiatric Symptoms in Alzheimer's Disease. *Journal of Alzheimer's disease : JAD* 2018.
- 1908 201. Donegan K, Fox N, Black N, Livingston G, Banerjee S, Burns A. Trends in diagnosis and  
1909 treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective  
1910 cohort study. *Lancet Public Health* 2017; **2**(3): e149-e56.
- 1911 202. Thyrian JR, Hertel J, Wucherer D, et al. Effectiveness and Safety of Dementia Care  
1912 Management in Primary Care: A Randomized Clinical Trial. *JAMA Psychiatry* 2017; **74**(10): 996-1004.
- 1913 203. Gitlin LN, Arthur P, Piersol C, et al. Targeting Behavioral Symptoms and Functional Decline in  
1914 Dementia: A Randomized Clinical Trial. *J Am Geriatr Soc* 2018; **66**(2): 339-45.
- 1915 204. Dudas R, Malouf R, McCleery J, Dening T. Antidepressants for treating depression in  
1916 dementia. *The Cochrane database of systematic reviews* 2018; **8**: CD003944.
- 1917 205. Orgeta V, Tabet N, Nilforooshan R, Howard R. Efficacy of Antidepressants for Depression in  
1918 Alzheimer's Disease: Systematic Review and Meta-Analysis. *Journal of Alzheimer's disease : JAD*  
1919 2017; **58**(3): 725-33.
- 1920 206. Panca M, Livingston G, Barber J, et al. Healthcare resource utilisation and costs of agitation  
1921 in people with dementia living in care homes in England - The Managing Agitation and Raising  
1922 QUality of Life in Dementia (MARQUE) study. *PLoS one* 2019; **14**(2): e0211953.
- 1923 207. Livingston G, Barber J, Marston L, et al. Prevalence of and associations with agitation in  
1924 residents with dementia living in care homes: MARQUE cross-sectional study. *BJPsych Open* 2017;  
1925 **3**(4): 171-8.

- 1926 208. Cooper C, Marston L, Barber J, et al. Do care homes deliver person-centred care? A cross-  
1927 sectional survey of staff-reported abusive and positive behaviours towards residents from the  
1928 MARQUE (Managing Agitation and Raising Quality of Life) English national care home survey. *PLoS*  
1929 *One* 2018; **13**(3): e0193399.
- 1930 209. Ballard C, Corbett A, Orrell M, et al. Impact of person-centred care training and person-  
1931 centred activities on quality of life, agitation, and antipsychotic use in people with dementia living in  
1932 nursing homes: A cluster-randomised controlled trial. *PLoS Med* 2018; **15**(2): e1002500.
- 1933 210. Lichtwarck B, Selbaek G, Kirkevold O, et al. Targeted Interdisciplinary Model for Evaluation  
1934 and Treatment of Neuropsychiatric Symptoms: A Cluster Randomized Controlled Trial. *Am J Geriatr*  
1935 *Psychiatry* 2018; **26**(1): 25-38.
- 1936 211. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for  
1937 dementia: Meta-analysis of randomized, placebo-controlled trials. *American Journal of Geriatric*  
1938 *Psychiatry* 2006; **14**(3): 191-210.
- 1939 212. Kales HC, Gitlin LN, Lyketsos CG, Detroit Expert Panel on A, Management of Neuropsychiatric  
1940 Symptoms of D. Management of neuropsychiatric symptoms of dementia in clinical settings:  
1941 recommendations from a multidisciplinary expert panel. *J Am Geriatr Soc* 2014; **62**(4): 762-9.
- 1942 213. Livingston G, Barber J, Marston L, et al. Clinical and cost-effectiveness of the Managing  
1943 Agitation and Raising Quality of Life (MARQUE) intervention for agitation in people with dementia in  
1944 care homes: a single-blind, cluster-randomised controlled trial. *The Lancet Psychiatry* 2019.
- 1945 214. Kales HC, Lyketsos CG, Miller EM, Ballard C. Management of behavioral and psychological  
1946 symptoms in people with Alzheimer's disease: an international Delphi consensus. *Int Psychogeriatr*  
1947 2018: 1-8.
- 1948 215. Van Leeuwen E, Petrovic M, van Driel ML, et al. Withdrawal versus continuation of long-term  
1949 antipsychotic drug use for behavioural and psychological symptoms in older people with dementia.  
1950 *The Cochrane database of systematic reviews* 2018; **3**: CD007726.
- 1951 216. Cossette B, Bruneau MA, Couturier Y, et al. Optimizing Practices, Use, Care and Services-  
1952 Antipsychotics (OPUS-AP) in Long-term Care Centers in Quebec, Canada: A Strategy for Best  
1953 Practices. *J Am Med Dir Assoc* 2019.
- 1954 217. Cohen-Mansfield J. Do Reports on Personal Preferences of Persons with Dementia Predict  
1955 Their Responses to Group Activities? *Dement Geriatr Cogn Disord* 2018; **46**(1-2): 100-8.
- 1956 218. Cohen-Mansfield J. The impact of group activities and their content on persons with  
1957 dementia attending them. *Alzheimers Res Ther* 2018; **10**(1): 37.
- 1958 219. Ruthirakuhan MT, Herrmann N, Abraham EH, Chan S, Lanctot KL. Pharmacological  
1959 interventions for apathy in Alzheimer's disease. *The Cochrane database of systematic reviews* 2018;  
1960 **5**: CD012197.
- 1961 220. Kinnunen KM, Vikhanova A, Livingston G. The management of sleep disorders in dementia:  
1962 an update. *Curr Opin Psychiatry* 2017; **30**(6): 491-7.
- 1963 221. Livingston G, Barber JA, Kinnunen KM, et al. DREAMS-START (Dementia RElAted Manual for  
1964 Sleep; STRAtegies for RelaTives) for people with dementia and sleep disturbances: a single-blind  
1965 feasibility and acceptability randomized controlled trial. *Int Psychogeriatr* 2018: 1-15.
- 1966 222. Maust DT, Kales HC, McCammon RJ, Blow FC, Leggett A, Langa KM. Distress Associated with  
1967 Dementia-Related Psychosis and Agitation in Relation to Healthcare Utilization and Costs. *Am J*  
1968 *Geriatr Psychiatry* 2017; **25**(10): 1074-82.
- 1969 223. Clare L, Kudlicka A, Oyebode JR, et al. Goal-oriented cognitive rehabilitation for early-stage  
1970 Alzheimer's and related dementias: the GREAT RCT. *Health Technol Assess* 2019; **23**(10): 1-242.
- 1971 224. Scott I, Cooper C, Leverton M, et al. Effects of nonpharmacological interventions on  
1972 functioning of people living with dementia at home: A systematic review of randomised controlled  
1973 trials. *Int J Geriatr Psychiatry* 2019.
- 1974 225. Sharma S, Mueller C, Stewart R, et al. Predictors of falls and fractures leading to  
1975 hospitalization in people with dementia: A representative cohort study. *Journal of the American*  
1976 *Medical Directors Association* 2018.

- 1977 226. Cooper C, Lodwick R, Walters K, et al. Inequalities in receipt of mental and physical  
1978 healthcare in people with dementia in the UK. *Age and Ageing* 2017; **46**(3): 393-400.
- 1979 227. Fereshtehnejad SM, Garcia-Ptacek S, Religa D, et al. Dental care utilization in patients with  
1980 different types of dementia: A longitudinal nationwide study of 58,037 individuals. *Alzheimers*  
1981 *Dement* 2018; **14**(1): 10-9.
- 1982 228. Bunn F, Goodman C, Reece Jones P, et al. What works for whom in the management of  
1983 diabetes in people living with dementia: a realist review. *BMC Med* 2017; **15**(1): 141.
- 1984 229. Banerjee S, Farina N, Daley S, et al. How do we enhance undergraduate healthcare  
1985 education in dementia? A review of the role of innovative approaches and development of the Time  
1986 for Dementia Programme. *Int J Geriatr Psychiatry* 2017; **32**(1): 68-75.
- 1987 230. Browne J, Edwards DA, Rhodes KM, Brimicombe DJ, Payne RA. Association of comorbidity  
1988 and health service usage among patients with dementia in the UK: a population-based study. *BMJ*  
1989 *open* 2017; **7**(3): e012546.
- 1990 231. Poblador-Plou B, Calderón-Larrañaga A, Marta-Moreno J, et al. Comorbidity of dementia: a  
1991 cross-sectional study of primary care older patients. *BMC psychiatry* 2014; **14**(1): 84.
- 1992 232. Rait G, Walters K, Bottomley C, Petersen I, Iliffe S, Nazareth I. Survival of people with clinical  
1993 diagnosis of dementia in primary care: cohort study. *BMJ* 2010; **341**.
- 1994 233. Bauer K, Schwarzkopf L, Graessel E, Holle R. A claims data-based comparison of comorbidity  
1995 in individuals with and without dementia. *BMC geriatrics* 2014; **14**: 10.
- 1996 234. Bunn F, Burn A-M, Goodman C, et al. Comorbidity and dementia: a scoping review of the  
1997 literature. *BMC medicine* 2014; **12**(1): 192.
- 1998 235. Bennett HQ, Norton S, Bunn F, et al. The impact of dementia on service use by individuals  
1999 with a comorbid health condition: a comparison of two cross-sectional analyses conducted  
2000 approximately 10 years apart. *BMC Med* 2018; **16**(1): 114.
- 2001 236. Melis RJ, Marengoni A, Rizzuto D, et al. The influence of multimorbidity on clinical  
2002 progression of dementia in a population-based cohort. *PloS one* 2013; **8**(12): e84014.
- 2003 237. Martin-Garcia S, Rodriguez-Blazquez C, Martinez-Lopez I, Martinez-Martin P, Forjaz MJ.  
2004 Comorbidity, health status, and quality of life in institutionalized older people with and without  
2005 dementia. *International psychogeriatrics* 2013; **25**(7): 1077-84.
- 2006 238. White N, Leurent B, Lord K, Scott S, Jones L, Sampson EL. The management of behavioural  
2007 and psychological symptoms of dementia in the acute general medical hospital: a longitudinal cohort  
2008 study. *International journal of geriatric psychiatry* 2017; **32**(3): 297-305.
- 2009 239. Malone DC, McLaughlin TP, Wahl PM, et al. Burden of Alzheimer's disease and association  
2010 with negative health outcomes. *American Journal of Managed Care* 2009; **15**(8): 481-8.
- 2011 240. Sager MA, Rudberg MA, Jalaluddin M, et al. Hospital admission risk profile (HARP):  
2012 identifying older patients at risk for functional decline following acute medical illness and  
2013 hospitalization. *Journal of the American Geriatrics Society* 1996; **44**(3): 251-7.
- 2014 241. Phelan EA, Borson S, Grothaus L, Balch S, Larson EB. Association of incident dementia with  
2015 hospitalizations. *JAMA* 2012; **307**(2): 165-72.
- 2016 242. Zhao Y, Kuo TC, Weir S, Kramer MS, Ash AS. Healthcare costs and utilization for Medicare  
2017 beneficiaries with Alzheimer's. *BMC Health Services Research* 2008; **8**: 108.
- 2018 243. Bynum JP, Rabins PV, Weller W, Niefeld M, Anderson GF, Wu AW. The relationship between  
2019 a dementia diagnosis, chronic illness, medicare expenditures, and hospital use. *Journal of the*  
2020 *American Geriatrics Society* 2004; **52**(2): 187-94.
- 2021 244. Shepherd H, Livingston G, Chan J, Sommerlad A. Hospitalisation rates and predictors in  
2022 people with dementia: a systematic review and meta-analysis. *BMC Medicine* 2019; **17**(1): 130.
- 2023 245. Zhu CW, Cosentino S, Ornstein K, Gu Y, Andrews H, Stern Y. Use and cost of hospitalization in  
2024 dementia: longitudinal results from a community-based study. *International Journal of Geriatric*  
2025 *Psychiatry* 2015; **30**(8): 833-41.



- 2026 246. Zhu CW, Cosentino S, Ornstein KA, Gu Y, Andrews H, Stern Y. Interactive Effects of Dementia  
2027 Severity and Comorbidities on Medicare Expenditures. *Journal of Alzheimer's disease : JAD* 2017;  
2028 **57**(1): 305-15.
- 2029 247. Vroomen JM, Bosmans JE, Eekhout I, et al. The cost-effectiveness of two forms of case  
2030 management compared to a control group for persons with dementia and their informal caregivers  
2031 from a societal perspective. *PloS one* 2016; **11**(9): e0160908.
- 2032 248. Intrator O, Zinn J, Mor V. Nursing home characteristics and potentially preventable  
2033 hospitalizations of long-stay residents. *J Am Geriatr Soc* 2004; **52**(10): 1730-6.
- 2034 249. Phelan EA, Debnam KJ, Anderson LA, Owens SB. A systematic review of intervention studies  
2035 to prevent hospitalizations of community-dwelling older adults with dementia. *Medical care* 2015;  
2036 **53**(2): 207.
- 2037 250. Naylor MD, Brooten D, Campbell R, et al. Comprehensive discharge planning and home  
2038 follow-up of hospitalized elders: a randomized clinical trial. *Jama* 1999; **281**(7): 613-20.
- 2039 251. Handley M, Bunn F, Goodman C. Dementia-friendly interventions to improve the care of  
2040 people living with dementia admitted to hospitals: a realist review. *BMJ open* 2017; **7**(7): e015257.
- 2041 252. Department of Health. Using the Commissioning for Quality and Innovation (CQUIN)  
2042 payment framework Guidance on new national goals for 2012-13. Department of Health; 2012.
- 2043 253. Wilkinson T, Ly A, Schnier C, et al. Identifying dementia cases with routinely collected health  
2044 data: A systematic review. *Alzheimer's & Dementia* 2018.
- 2045 254. Sommerlad A, Perera G, Singh-Manoux A, Lewis G, Stewart R, Livingston G. Accuracy of  
2046 general hospital dementia diagnoses in England: Sensitivity, specificity, and predictors of diagnostic  
2047 accuracy 2008&#x2013;2016. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*  
2048 2018.
- 2049 255. Ryan DJ, O'Regan NA, Caoimh RÓ, et al. Delirium in an adult acute hospital population:  
2050 predictors, prevalence and detection. *BMJ open* 2013; **3**(1): e001772.
- 2051 256. Jackson TA, MacLulich AM, Gladman JR, Lord JM, Sheehan B. Undiagnosed long-term  
2052 cognitive impairment in acutely hospitalised older medical patients with delirium: a prospective  
2053 cohort study. *Age Ageing* 2016; **45**(4): 493-9.
- 2054 257. Davis DHJ, Muniz-Terrera G, Keage HAD, et al. Association of Delirium With Cognitive Decline  
2055 in Late Life: A Neuropathologic Study of 3 Population-Based Cohort Studies. *JAMA psychiatry* 2017;  
2056 **74**(3): 244-51.
- 2057 258. James BD, Wilson RS, Capuano AW, et al. Cognitive decline after elective and nonelective  
2058 hospitalizations in older adults. *Neurology* 2019; **92**(7): e690-e9.
- 2059 259. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK. The interface between delirium  
2060 and dementia in elderly adults. *The Lancet Neurology* 2015; **14**(8): 823-32.
- 2061 260. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised  
2062 non-ICU patients. *The Cochrane database of systematic reviews* 2016; **3**: CD005563.
- 2063 261. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic medication for  
2064 prevention and treatment of delirium in hospitalized adults: A systematic review and meta-analysis.  
2065 *Journal of the American Geriatrics Society* 2016; **64**(4): 705-14.
- 2066 262. Barbateskovic M, Krauss SR, Collet MO, et al. Pharmacological interventions for prevention  
2067 and management of delirium in intensive care patients: a systematic overview of reviews and meta-  
2068 analyses. *BMJ open* 2019; **9**(2): e024562.
- 2069 263. Hshieh TT, Yang T, Gartaganis SL, Yue J, Inouye SK. Hospital Elder Life Program: Systematic  
2070 Review and Meta-analysis of Effectiveness. *Am J Geriatr Psychiatry* 2018; **26**(10): 1015-33.
- 2071 264. Wu YC, Tseng PT, Tu YK, et al. Association of Delirium Response and Safety of  
2072 Pharmacological Interventions for the Management and Prevention of Delirium: A Network Meta-  
2073 analysis. *JAMA Psychiatry* 2019.
- 2074 265. Goldberg SE, Bradshaw LE, Kearney FC, et al. Care in specialist medical and mental health  
2075 unit compared with standard care for older people with cognitive impairment admitted to general  
2076 hospital: randomised controlled trial (NIHR TEAM trial). *BMJ* 2013; **347**: f4132.

- 2077 266. Kolanowski A, Fick D, Litaker M, et al. Effect of cognitively stimulating activities on symptom  
2078 management of delirium superimposed on dementia: A randomized controlled trial. *Journal of the*  
2079 *American Geriatrics Society* 2016; **64**(12): 2424-32.
- 2080 267. Burry L, Mehta S, Perreault MM, et al. Antipsychotics for treatment of delirium in  
2081 hospitalised non-ICU patients. *The Cochrane database of systematic reviews* 2018; **6**: Cd005594.
- 2082 268. Yu A, Wu S, Zhang Z, et al. Cholinesterase inhibitors for the treatment of delirium in non-ICU  
2083 settings. *Cochrane Database Syst Rev* 2018; **6**: CD012494.
- 2084 269. Lonergan E, Luxenberg J, Areosa Sastre A, Wyller T. Benzodiazepines for delirium. *The*  
2085 *Cochrane database of systematic reviews* 2009; **4**.
- 2086 270. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate  
2087 Medication Use in Older Adults. *J Am Geriatr Soc* 2015; **63**(11): 2227-46.
- 2088 271. Jackson TA, Gladman JR, Harwood RH, et al. Challenges and opportunities in understanding  
2089 dementia and delirium in the acute hospital. *PLoS medicine* 2017; **14**(3): e1002247.
- 2090 272. Boyle PA, Yu L, Leurgans SE, et al. Attributable risk of Alzheimer's dementia attributed to  
2091 age-related neuropathologies. *Ann Neurol* 2019; **85**(1): 114-24.
- 2092 273. Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA. Person-specific  
2093 contribution of neuropathologies to cognitive loss in old age. *Ann Neurol* 2018; **83**(1): 74-83.
- 2094 274. Wallace L, Theou O, Rockwood K, Andrew MK. Relationship between frailty and Alzheimer's  
2095 disease biomarkers: A scoping review. *Alzheimers Dement (Amst)* 2018; **10**: 394-401.
- 2096 275. Aworinde JW, N. Lewis,G. Livingston,G. Sommerlad,A. Dementia severity at death: a register-  
2097 based cohort study. *BMC psychiatry* 2018.
- 2098 276. Meeussen K, Van den Block L, Echteld M, et al. Older people dying with dementia: a  
2099 nationwide study. *International psychogeriatrics* 2012; **24**(10): 1581-91.
- 2100 277. Sampson EL, Candy B, Davis S, et al. Living and dying with advanced dementia: A prospective  
2101 cohort study of symptoms, service use and care at the end of life. *Palliat Med* 2018; **32**(3): 668-81.
- 2102 278. Rosemond C, Hanson LC, Zimmerman S. Goals of Care or Goals of Trust? How Family  
2103 Members Perceive Goals for Dying Nursing Home Residents. *J Palliat Med* 2017; **20**(4): 360-5.
- 2104 279. Hanson LC, Zimmerman S, Song MK, et al. Effect of the Goals of Care Intervention for  
2105 Advanced Dementia: A Randomized Clinical Trial. *JAMA Intern Med* 2017; **177**(1): 24-31.
- 2106 280. Dening KH, King M, Jones L, Sampson EL. Healthcare decision-making: past present and  
2107 future, in light of a diagnosis of dementia. *Int J Palliat Nurs* 2017; **23**(1): 4-11.
- 2108 281. Gaster B, Larson EB, Curtis JR. Advance Directives for Dementia: Meeting a Unique  
2109 Challenge. *JAMA* 2017; **318**(22): 2175-6.
- 2110 282. Harrison Dening K, King M, Jones L, Vickestaff V, Sampson EL. Advance Care Planning in  
2111 Dementia: Do Family Carers Know the Treatment Preferences of People with Early Dementia? *PLoS*  
2112 *One* 2016; **11**(7): e0159056.
- 2113 283. Brazil K, Carter G, Cardwell C, et al. Effectiveness of advance care planning with family carers  
2114 in dementia nursing homes: A paired cluster randomized controlled trial. *Palliat Med* 2018; **32**(3):  
2115 603-12.
- 2116 284. Shah SM, Carey IM, Harris T, DeWilde S, Victor CR, Cook DG. The mental health and mortality  
2117 impact of death of a partner with dementia. *Int J Geriatr Psychiatry* 2016; **31**(8): 929-37.
- 2118 285. Moore KJ, Davis S, Gola A, et al. Experiences of end of life amongst family carers of people  
2119 with advanced dementia: longitudinal cohort study with mixed methods. *BMC Geriatr* 2017; **17**(1):  
2120 135.
- 2121 286. Agar M, Lockett T, Luscombe G, et al. Effects of facilitated family case conferencing for  
2122 advanced dementia: A cluster randomised clinical trial. *PLoS One* 2017; **12**(8): e0181020.
- 2123 287. Lockett T, Chenoweth L, Phillips J, et al. A facilitated approach to family case conferencing  
2124 for people with advanced dementia living in nursing homes: perceptions of palliative care planning  
2125 coordinators and other health professionals in the IDEAL study. *International psychogeriatrics / IPA*  
2126 2017; **29**(10): 1713-22.

- 2127 288. Pickett J, Bird C, Ballard C, et al. A roadmap to advance dementia research in prevention,  
2128 diagnosis, intervention, and care by 2025. *Int J Geriatr Psychiatry* 2018; **33**(7): 900-6.
- 2129