

## ANALYSIS

## TOO MUCH MEDICINE

# Political drive to screen for pre-dementia: not evidence based and ignores the harms of diagnosis

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Current policy in many countries is aimed at increasing the rates of diagnosis of dementia and cognitive impairment.<sup>1-3</sup> This policy drive has been accompanied by research into early detection of dementia, including preclinical identification of underlying neurobiology that might later be associated with dementia.<sup>4</sup> Although the clinical features of people with established dementia are unmistakable,<sup>5-6</sup> the ability of these preclinical features to predict future disease is less clear. Nevertheless, the belief that there is value in screening for “pre-dementia” or mild cognitive impairment is creeping into clinical practice, with the resulting overdiagnosis having potential adverse consequences for individual patients, resource allocation, and research.<sup>7-8</sup>

## Trends in policy and practice

Recent government policy directives have called for screening or case finding of mild cognitive impairment and dementia.<sup>2-4,9,10</sup> In the US, under the new Affordable Care Act (the health care reform law), the Medicare insurance programme will cover an annual wellness visit to a physician that includes detection of cognitive impairment or any measurable change in thinking abilities.<sup>10</sup> In England, the government has announced that it will reward general practitioners—around £3600 (€4200; \$5600) a year per practice—for assessing patients aged over 75 years (and those over 60 years in at-risk groups, that is, those with established vascular disease or diabetes) for dementia and cognitive impairment.<sup>1-3,11</sup> In addition, it has committed to having “a memory clinic in every town and every city,” partly to increase early diagnosis.<sup>12</sup>

However, there is no sound evidence that memory clinics are beneficial. When they were first introduced in the 1980s their main aim was to recruit patients to enter clinical trials of cholinesterase inhibitors,<sup>13,14</sup> and they were later used to increase the marketing base for these drugs,<sup>14</sup> which are widely promoted to the public as a potent and effective treatment despite limited

evidence to support their use.<sup>15</sup> Little attention has been paid to the fact that attending memory clinics generates stress for patients<sup>16</sup> and their carers,<sup>17</sup> and expands the use of biomarker testing (cerebrospinal fluid measurements of amyloid and tau) and neuroimaging,<sup>18,19</sup> with associated costs and morbidity.

Although some people are positive about the value of memory clinics, there is evidence that they may be no more effective than standard care by general practitioners.<sup>20</sup>

The drive to screen for dementia and mild cognitive impairment has been questioned because dementia does not meet the World Health Organization’s Wilson-Jungner criteria<sup>21</sup> for screening and there is no evidence for the usefulness of any preventive or curative pharmacological intervention.<sup>22</sup> Screening is not recommended by the UK National Screening Committee,<sup>23</sup> the Royal Australian College of General Practitioners guidelines,<sup>24</sup> or the US Preventative Services Task Force.<sup>25</sup> Evolving definitions have been responsible for increasing prevalence.

The emphasis on early diagnosis of mild cognitive impairment stems from the assumption that people with dementia have an illness that progresses through a period when symptoms are initially mild and interventions more likely to be effective.<sup>26</sup> Historically, older people with minor memory or cognitive changes were regarded as having a relatively benign and age related problem. But over the past 15 years or so a change in terminology has resulted in people being labelled as having a disease in its own right or of having a condition that will inevitably progress to dementia.<sup>27-33</sup> As a result, there has been an apparent increase in the prevalence of mild cognitive impairment (fig 1⇓).<sup>34</sup> The effect of the recent changes in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and biomarker testing is uncertain but they are likely to increase overdiagnosis because they permit labelling of asymptomatic people as having pre-symptomatic Alzheimer’s disease or dementia.

### Summary box

*Clinical context*—Dementia is age related and with an ageing global population is predicted to become an overwhelming and costly problem

*Diagnostic change*—Introduction of broader diagnostic criteria for mild cognitive impairment and pre-dementia based on new cognitive screening tests coupled with cerebrospinal fluid biomarkers and neuroimaging

*Rationale for change*—Past neglect of services and research in dementia has fuelled international calls for action and earlier treatment

*Leap of faith*—People with mild symptoms will eventually develop dementia and interventions are more likely to be effective at an early stage

*Impact on prevalence*—The current prevalence of dementia is thought to be 10-30% in people over the age of 80, but the adoption of new diagnostic criteria will result in up to 65% of this age group having Alzheimer's disease diagnosed and up to 23% of non-demented older people being diagnosed with dementia

*Evidence of overdiagnosis*—Screening for cognitive impairment and measurement of biomarkers and neuroimaging are increasing the diagnosis of mild cognitive impairment, which in many people will improve spontaneously

*Harms from overdiagnosis*—Unnecessary investigation and treatments with side effects; adverse psychological and social outcomes; and distraction of resources and support from those with manifest dementia in whom need is greatest

*Limitations*—Current case identification and screening policy relies mostly on anecdotal and observational data from potentially biased sources, including those with vested commercial interests, rather than evidence from clinical trials. There is a lack of research focused on older people, in whom dementia is most prevalent

*Conclusions*—Current policy is rolling out untested and uncontrolled experiments in the frailest people in society without a rigorous evaluation of its benefits and harms to individuals, families, service settings, and professionals

### Evolving nomenclature and definitions related to early or mild cognitive impairment<sup>30-33</sup>

#### Early definitions of cognitive decline emphasising aging

*Benign senescent forgetfulness (1962)*—General forgetfulness; difficulty recalling factual information; preserved global knowledge; intact awareness of deficits

*Age-associated memory impairment (1989)*—For people aged 50-79 years impaired performance (>1 standard deviation below the mean) on one or more memory tests compared with young adults

*Late life forgetfulness (1989)*—Impaired memory performance (1-2 standard deviations below the mean of similarly aged peers) on at least 50% of the memory tests

*Age consistent memory impairment (1989)*—Memory performance within one standard deviation of the mean of similarly aged peers on more than 75% of memory tests

*Age associated cognitive decline (1994)*—Decline of at least one standard deviation, compared with age matched norms, in any area of cognitive functioning

#### Recent definitions of cognitive decline emphasising disease process

*Mild cognitive impairment (1992)*—Short term and long term memory impairment and impairment in one or more of abstract thinking, judgment, higher cortical functioning, changes in personality

*Cognitive impairment no dementia (1995)*—Impaired cognitive function in one or more domains, not demented

*Amnesic mild cognitive impairment (1999)*—Subjective memory complaint, objective memory impairment, intact cognitive function, intact functional ability, not demented

*Amnesic mild cognitive impairment single domain (2004)*—Subjective or proxy cognitive complaint, objective memory impairment (decline from premorbid levels), intact cognitive function, relatively intact functional ability, not demented

*Prodromal Alzheimer's disease (2010)*—Early symptomatic, pre-dementia phase of Alzheimer's disease: episodic memory loss of the hippocampal type, not sufficiently severe to affect instrumental activities of daily living, biomarker evidence from cerebrospinal fluid or neuroimaging

*Preclinical Alzheimer's disease (2010)*—Asymptomatic at-risk stage between the earliest pathogenic events/brain lesions of Alzheimer's disease and the first appearance of specific cognitive changes; identified by finding amyloid in the brain (PET scanning) or cerebrospinal fluid

*Minor neurocognitive disorder (2013)*—Modest cognitive decline from a previous level of performance in one or more domains; based on the concerns of the individual, a knowledgeable informant, or clinician; test performance in the range of 1-2 standard deviations below appropriate norms on formal testing or equivalent clinical evaluation; insufficient to interfere with independence

Nevertheless, only 5-10% of people with mild cognitive impairment will progress to dementia each year, and as many as 40-70% of people do not progress or their cognitive function may even improve.<sup>35 36</sup> Interestingly, this may also be accompanied by reversal of structural changes found in the brain.<sup>37</sup> Furthermore, many people who develop dementia do not meet definitions of mild cognitive impairment before diagnosis. Some studies have even shown that the development of dementia is higher in people who don't have symptoms of mild cognitive impairment than in those that do.<sup>29</sup> It is also evident that the neuropathology of mild cognitive impairment does not support the concept that most people with this condition are in the early stages of Alzheimer's disease.<sup>38 39</sup>

### Rise and rise of pre-dementia diagnoses

The new DSM-5 classification defines minor neurocognitive disorder as a modest decline in any cognitive domain—reported by a clinician, informant, or the patient—where any formal testing or clinical evaluation lies more than one standard deviation below appropriate norms.<sup>33</sup> Under this definition about 16% of the population will be automatically defined as having a minor neurocognitive disorder.<sup>40</sup> Exposing people to multiple testing for memory problems will further increase the risk of being labelled with the new disorder.

What will be the effect of encouraging more widespread and earlier diagnosis of dementia? A meta-analysis of the diagnostic accuracy of clinical tools used by general practitioners, including 15 studies on dementia, estimated that if, a clinician saw 100 consecutive community based patients with a prevalence of

dementia of 6%, using current criteria he or she would correctly identify four of the six but would incorrectly identify dementia in a further 23 people.<sup>41</sup>

## Alzheimer's pathology and the ageing process

Definite Alzheimer's disease can be diagnosed only by examining brain tissue and finding evidence of plaques and tangles containing amyloid and tau proteins. In people under 65 the link between Alzheimer's neuropathology and dementia is strong. However, most people with dementia are over 65, and here the link between Alzheimer's neuropathology and dementia becomes complicated. In those over 85, the prevalence of Alzheimer-type brain pathology becomes similar in people with and without clinical features of dementia. Microvascular disease and evidence of oxidative injury and mitochondrial dysfunction are substantial in the brains of older people with dementia and such normal ageing changes might contribute to the symptoms as well.<sup>8 42 43</sup> This raises questions about the value of neuroimaging in diagnosis.

## Uncertainty over the diagnostic value of neuroimaging and biomarkers

Nevertheless, because current clinical methods cannot reliably detect people who may go on to develop dementia, neuroimaging and measurement of cerebrospinal fluid biomarkers to detect amyloid deposition or neurodegeneration are increasingly used in diagnosis.<sup>44</sup> It has been proposed that patients with symptoms of dementia and positive biomarkers or neuroimaging evidence can be considered to have proved Alzheimer's disease and that asymptomatic people with positive markers and abnormal neuroimaging results should be considered "at increased risk of developing Alzheimer's disease" or as having preclinical Alzheimer's disease.<sup>28 32</sup>

Currently, large scale programmes such as the worldwide Alzheimer's Disease Neuroimaging Initiative are using convenience samples of people to track biomarkers and risk of dementia, in particular Alzheimer's disease.<sup>45</sup> But there are as yet no large scale population studies that have suggested that the association between any biomarkers with dementia or underlying neuropathological abnormality is sufficiently robust to be used in clinical practice.<sup>7 46</sup> Despite the paucity of evidence<sup>47</sup> biomarkers and amyloid scans are entering everyday practice, particularly in memory clinics.<sup>18 19</sup>

## Age trumps all

The influence of old age outweighs all biomarkers and risk factors,<sup>7</sup> and biomarkers become less accurate in older people, in whom dementia is most prevalent and diagnosis is often most contentious.<sup>48</sup> About 65% of people over the age of 80 years have abnormalities on amyloid imaging and so could be diagnosed with Alzheimer's disease or pre-disease,<sup>49</sup> but the amyloid scanning does not predict cognitive function in older people.<sup>39</sup> It is assumed that asymptomatic people with evidence of amyloid deposition will eventually develop dementia with a time lag of about 17 years<sup>38 39</sup> and that older people simply do not live long enough to become demented.<sup>50</sup> Given that old age is the strongest risk factor for most diseases, we could use the same logic to confidently diagnose any pre-disease in all our older patients.

## Risks, harms, and costs of early diagnosis

Early diagnosis of cognitive impairment and dementia is argued to be beneficial because it allows healthcare professionals to give counselling about advanced care directives and patients time to organise their financial affairs and future guardianship while they are still competent and to modify risk factors and lifestyle (nutrition and physical, social, and mental activity).<sup>51</sup> However, a recent study of psychosocial intervention including counselling, education, and support in mild Alzheimer's disease did not show any benefit.<sup>52</sup>

Along with lifestyle advice it is also important to rationalise prescribing and avoid medications that impair cognition.<sup>53</sup> But this is simply good practice and does not require screening for dementia. Lifestyle, planning, and medications should be discussed with all older people—not just those with positive test results for cognitive impairment.

There are no drugs that prevent the progression of dementia or are effective in patients with mild cognitive impairment, and none is recommended for these purposes.<sup>15</sup> Once patients get labelled with disease, or pre-disease, however, they may try therapies that are marketed (in the absence of evidence) as disease modifiers, such as vitamin E, ginkgo biloba, cholinesterase inhibitors, or memantine, and run the risk of adverse effects.<sup>54</sup> The adverse effects of cholinesterase inhibitors include increased risk of hip fractures, syncope, and pacemaker insertion,<sup>55</sup> while the cost is £800 to £1000 per patient each year in the UK. One trial suggested increased mortality in people with mild cognitive impairment treated with a cholinesterase inhibitor.<sup>56</sup> Expenditure on these drugs has risen dramatically (for example, total cost in Australia rose more than fivefold over one decade<sup>57</sup>).

There are also risks and costs associated with investigations for dementia. People with suspected dementia are usually assessed with three to four diagnostic tests,<sup>58</sup> and the one-off cost for a dementia diagnosis is \$5000 (£3200; €3800).<sup>51</sup> The diagnostic processes can be distressing, alarming, and stigmatising as well as costly.<sup>16</sup>

Dementia is the illness most feared by people over the age of 55 years,<sup>22</sup> and some patients and their families may become anxious after dementia or mild cognitive impairment is diagnosed. The diagnosis of dementia related illness affects identity, leading to feelings of loss, anger, uncertainty, and frustration.<sup>59</sup> It also affects roles and relationships within the family and in wider social networks. The distress of getting a diagnosis may also result in suicide or euthanasia.<sup>60</sup>

For many older patients with multiple comorbidities, dementia is part of their end of life process. Preventive interventions become therapeutically irrelevant. By the time someone aged 90 years or more dies, the risk of being demented is around 60%.<sup>61</sup> The emphasis on early diagnosis and Alzheimer's pathology is diverting our attention and healthcare resources from the current needs of older people, which relate to multimorbidity and palliative care.

## Ageing of the population as commercial opportunity

Expanding the diagnosis of dementia mostly increases profit for corporations and industries involved with developing screening and early-diagnosis tests, and pharmaceutical and complementary medicines marketed to maintain cognition in old age. It also provides work for clinicians specialising in dementia.<sup>62 63</sup> Pharmaceutical companies sponsored a study that

called for the UK government to provide financial rewards for increased diagnosis rates<sup>64</sup>; funded the development of, and distribute, the Seven Minute Screen for dementia<sup>65 66</sup>; and hold the licence for florbetapir F18 for amyloid positron emission tomography.<sup>67</sup> Many general practices in the UK are now using a tablet app with a shortened version of neuropsychological tests for dementia validated in secondary care. This method has not been validated in primary care for such opportunistic case finding; nor have any translational studies examined the consequences of such testing.<sup>68</sup>

## The curse of a diagnosis

The desire of politicians, dementia organisations, and academics and clinicians in the field to raise the profile of dementia is understandable, but we risk being conscripted into an unwanted “war against dementia.”<sup>69</sup> Nearly half of the people who have positive results on screening for cognitive impairment refuse subsequent diagnostic evaluation<sup>70</sup> because of concerns about harms associated with a diagnosis such as losing health insurance cover, driving privileges, or employment; anxiety and depression; stigma; and effect on family finances and emotions.<sup>71 72</sup> General practitioners have also been vocal in their opposition to screening and overdiagnosis.<sup>3 22</sup>

The strong political lead in the UK and US is increasing the numbers of people that receive a diagnosis of dementia and early dementia. Yet arguably the political rhetoric expended on preventing the burden of dementia would be much better served by efforts to reduce smoking and obesity, given current knowledge linking mid-life obesity and cigarettes with the risk of dementia.<sup>73</sup> And although increasing the diagnosis rates might raise awareness and perhaps fear of dementia in the community, there is a risk it will result in reallocating resources that are badly needed for the care of people with advanced dementia.<sup>7</sup>

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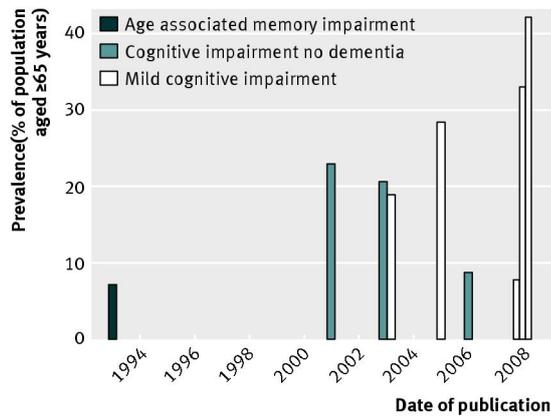
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## Figure



Influence of diagnostic criteria on prevalence of mild cognitive disorders in people aged 65 years or more.<sup>34</sup> Prevalence data presented by year of publication of studies