SCIENCE AND SOCIETY

The elephant in the room — healthy brains in later life, epidemiology and public health

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Abstract | The increasing age of the population around the world has meant that greater attention is being paid to disorders that mainly affect older people. In particular, work is focusing on ways to preserve the healthy brain and prevent dementia. Preventive studies are complex and must take into account not only simple approaches such as those used in risk and outcome studies, but also stage of life, survival and mortality, and population context before their effect can be assessed. This paper presents questions and areas which must be explored if the potential for prevention of dementia during brain ageing is to be properly understood.

'Adding life to years as well as years to life' has become something of a mantra in policy circles[1]. On an individual basis, there is great variation in the frailty experienced at the end of life. Is it possible for more of us to reach a robust, active and sharp old age, or is this to be experienced only by a small proportion of elite ageing individuals[2,3]? The brain shows a marked increase in degenerative and vascular disorders with age, but there is evidence that some factors might protect against these phenomena. It has been suggested, on the basis of observational data, that up to 50% of dementia might be preventable[4]. This topic has been widely reviewed[5,6–8]. This article does not seek to review the vast field systematically but instead provides a commentary on brain ageing with a focus on dementia research and population context. It touches on demographic projections and methods for evaluation of the health of the older population, including assessing dementia and cognitive function. Approaches to brain ageing research and the challenges of clear delineation of disorders of the most elderly are described. The complexities of identifying risk factors for dementia are discussed and whether any modification of such risk factors might be able to change the exponential increase in dementia with age. In the context of prevention of dementia, age itself seems to have been avoided or ignored and therefore might be the 'elephant in the room'. Each of the areas covered in this article are important topics in their own right and I therefore provide an overview of the field, using a selection of articles from the thousands available to illustrate these points.

Context

In order to assess the potential for prevention of the negative aspects of brain ageing, the population context must be understood, as well as ways of characterizing healthy life expectancy, rather than just life expectancy. Our global population aged over 60 is set to rise threefold to 2 billion by 2050 (REF. 9), and the numbers of those estimated to have dementia to rise from 8.1 million now to 24.3 million by 2040 (REF. 10). Life experience has changed dramatically over the last century. In many countries, the older population now faces the prospect of spending a quarter of their lives aged over 65 (REF. 1).

Measuring and monitoring health in ageing populations presents certain difficulties because of increasing combinations of morbidity and consequent impairment and disability. Methodology to assess healthy life expectancy for populations allows researchers to incorporate these diverse measures, which are highly relevant to considerations of quality of life for policy work. Data on the prevalence of health states are combined with life expectancy to allow the quantification of life expectation in particular health states. These measures are useful for policy makers and for comparison within and across countries. This approach is shown in FIG. 1, which illustrates states of health in men and women in the context of life expectancy in England and Wales[11]. This figure highlights the increasing proportion of life lived with cognitive impairment as age increases. Such analyses bring to light findings such as the marked differences between women and men in older age across these domains.

If compression of morbidity (reducing the expectation of life spent with disorders and/or in a disabled state) is occurring in populations, then increased life expectancy will not be associated with longer disability. There are some hints from data collected over the past two decades in routine National Long Term Care Surveys from medical lists that there could be reductions in severe disability[12] in the wider population in the United States, and similar findings have been reported for dementia itself[13]. Such observations, though based on limited data, provide an optimistic view that dementia might be prevented or reduced at the population level, but must be tested in more rigorous population studies. Such studies must be clear and invariable in their delineation of normal and abnormal.

The ageing brain — what is normal?

Distinguishing between normal and abnormal in an organ as complex as the human brain is a thorny task. The ageing brain is the focus of much research activity, from molecular studies to clinical and epidemiological approaches. In most of these studies, an overlap between normal ageing and pathological ageing is unavoidable as there is no clear indication of pathological ageing. In addition, the way such research is framed has implications beyond scientific interest. There are political and cultural considerations such as eligibility criteria for health insurance policies and nursing care that have arisen from the successful separation of ageing or senility from

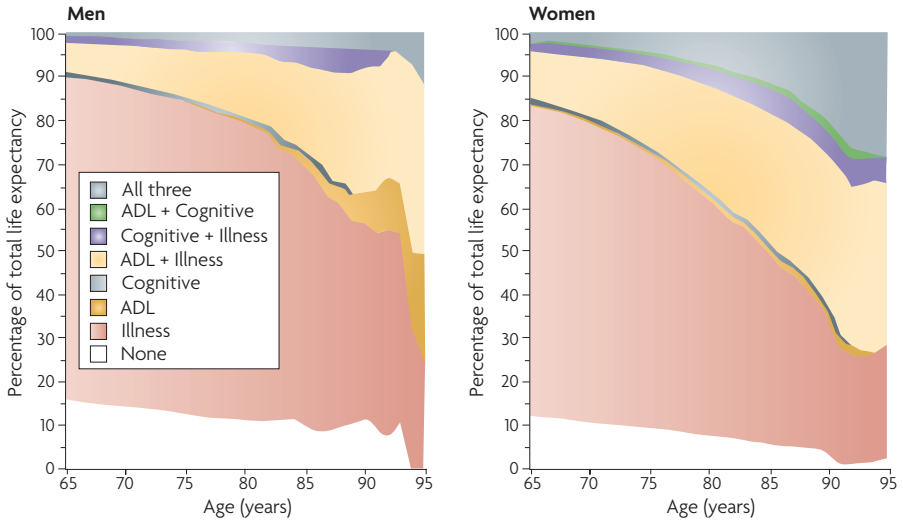

Figure 1 | **Health states during later stages of life.** Categories of ill health are plotted against age for men and women. Ill health is defined as severe cognitive deficit (Cognitive), severe impairment in activities of daily living (ADL) and chronic illness including vascular disorders (Illness). The studies represented in this graph were carried out in five population-representative samples based on 13,000 individuals. The graphs illustrate a dramatic decline of health in old age in all three subcategories of ill health, with differences between men and women becoming more marked as age progresses. 'Percentage of total life expectancy' is, for a given age, the proportion of remaining life that can be expected to be lived in different health states. Reproduced, with permission, from REF. 11 © (2001) Oxford Univ. Press.

Alzheimer's disease, which many regarded as 'normal' for old age in the last century. Similarly, potential eligibility for medication is made on the basis of a judgement about the stage of disease in Alzheimer's disease, which itself could be subject to change. Normal ageing is defined as the absence of an increasing number of conditions, the boundaries of which are changing as a result of research findings. These findings are based on research in a variety of settings, including populations. But who should be included in population studies? Such decisions can be critically important. Is it right to include only those people who have no disorders and are much healthier than the typical aged person, or is it right to include those who are representative of that particular age group, disorders and all? If biological age is different from chronological age and is considered normal, the samples which exclude those with age-related pathology will not be representative, as only a minority of the older age groups are unaffected by chronic disease (as illustrated in FIG. 1). For example, any study that excludes people with hypertension will exclude more than 30% of many older populations[14]. It also follows that such selection will exacerbate the potential bias caused by selective survival in studies of risk, leading to distortions of risk estimates — potentially including reverse causality. Should controls be the young? The literature is full of results derived from diverse approaches[15,16]. Which results are relevant to true populations? Will they be of any relevance to future populations and populations with diverse sociocultural as well as 'risk' exposure histories?

Despite these concerns, there is some consensus about the effects of age on the brain. Most empirical research findings, particularly from groups of fit volunteers followed over prolonged periods, report changes in cognition with age. These studies show a greater deterioration in tests requiring flexibility (fluidity) in neuropsychological processes, such as abstract reasoning and problem solving, than in tests of 'crystallized intelligence', which rely more on knowledge and experience, such as vocabulary[17–21], although some debate continues over terminology. The changes reported in studies of biological brain ageing seem to vary according to sample selection[22]. Clinicopathological studies show that rare individuals reach advanced ages with little neuropathological change, but most show increasing atrophy, plaques, Lewy bodies and vascular changes with age. Many researchers have interpreted such findings as representing early pathological changes rather than ageing itself[23]. This interpretation arises because there are no firm biological criteria to make a clear-cut diagnosis. At present, researchers and clinicians use loose syndromal descriptions in conjunction with supporting biological findings.

Disorders of the ageing brain

This section highlights the key disorders affecting the ageing brain and the classical research approaches used to study these diseases. Of the neurological diseases associated with ageing, Alzheimer's disease attracts the most attention, followed by vascular disease, Parkinson's disease, Lewy body dementia and frontotemporal dementia. Alzheimer's disease shows a marked increase in incidence with age, whereas the other conditions show less marked rises[24] (sometimes interpreted as age-related in contrast to age-dependent). Most research into the biological mechanisms that underlie these disorders has relied on a case control approach, in which patients are compared with unaffected people. This works well for diseases with clear-cut diagnostic criteria, but is more problematic when there is overlap between disease and normal changes in ageing, and also when the subtype such as Alzheimer's disease or Lewy Body dementia is not confirmed neuropathologically[25,26]. Many of the basic mechanisms that have been proposed to produce the clinicopathological entities mentioned above are the same (for example, oxidation, glycation, mitochondrial dysfunction and lipid dysregulation). Furthermore, such studies are more problematic in older than in younger samples, because of selective survival (as mentioned above) and the difficulty in obtaining an unbiased measurement of earlier risk or exposures.

Standardization of clinical and pathological criteria for individual diseases has provided a common language, but can restrict research. For many years, the criteria for the diagnosis of Alzheimer's disease dictated that certain vascular features were excluded[27]. Findings regarding vascular features in a given subtype of dementia would therefore be interpreted with respect to the vascular condition and not by underlying neurobiology. Additionally, the use of age-related criteria that specified the presence and quantity of particular neuropathological markers of Alzheimer's disease[28] precluded unbiased investigation of age effects. The difficulties inherent in these approaches and the finding of combined pathologies in the brains of older demented individuals has led to a re-emergence of studies looking at risk for all dementias[29,30]. This approach is helpful, as most global research on descriptive epidemiology examines dementia of all types.

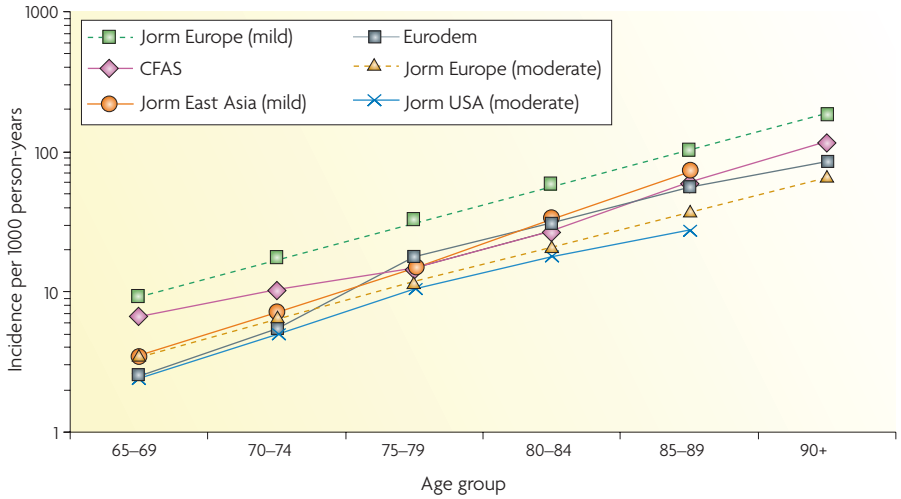

Figure 2 | **Incidence rates of dementia in the United Kingdom compared with meta-analysis results in Europe and worldwide.** The rates by which incidence of dementia increases with age across populations are similar. The Medical Research Council Cognitive Function and Ageing Study (CFAS) is a longitudinal population study of people aged 65 years and over in England and Wales. Eurodem is the combination of incidence studies in Europe (not including CFAS). A. Jorm conducted a systematic review of world literature on incidence, providing combined incidence estimates for different world areas that are separated according to severity. Each individual without dementia followed for a year contributes a person year of observation to the age group that they are in during the study, at risk of developing dementia. If they develop dementia they no longer contribute to the denominator. Reproduced from REF. 95.

Epidemiology of dementia

The epidemiology of dementia has been well described by several systematic and combined analytical reviews of prevalence and incidence[10] in different populations around the world, using internationally accepted criteria such as, or similar to, the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, revised[31] (FIG. 2). No strong evidence of variation across developed countries (including those with different ancestry such as European and Japanese) emerges. A Delphi review (defined as the "iterative circulation to a panel of experts of question and responses that are progressively refined in light of responses to each round of questions"[32]) of the literature on dementia prevalence around the world reveals considerable variation (perhaps because of patchy data), with lower estimates in Asia and Africa. However, these conclusions seem likely to be influenced not only by variation in methods and samples but also by variation in life expectancy and survival, which affect interpretation and comparison. Differences between countries in mortality in relation to specific risks will affect prevalence[33] and might not reflect true variation in dementia. In the same age group, mortality is higher in people with dementia than without. In diverse countries and regions, mortality rates in related age groups and for those with dementia will be different, which can also affect prevalence[99]. Gene–environment interactions are another possible factor. One example that indicates differences across populations is the marked difference in risk associated with different alleles of apolipoprotein E (APOE); in African Americans, the allele APOE*ε4 confers high risk, whereas in Nigerians it is not associated with increased risk[34,35].

The decision as to whether someone of a particular age in a given culture and context has dementia is dependent on the careful assessment of the individual and often a collateral source. The data generated, whether cognitive, functional or behavioural, are usually dimensional and not categorical. Examples of areas that must be measured to make a diagnosis of dementia are cognition, mood and function. All of these are usually measured using scales that produce a continuous measurement, hereafter defined as 'dimensional', rather than a categorical normal or abnormal result. In every study the same problem occurs, namely deciding where normal ageing stops and dementia starts. Clinical judgement is an empirical case by case phenomenon. Some studies have circumvented this by using algorithmic methods to assess the answers to standardized questions.

Cognitive decline and societal attitudes

There is real tension between dimensionality and the need for categorical criteria for the assessment of the dementia syndrome. Clinicians need a categorical decision for management and treatment, but research shows dimensionality. Cognitive measures can be related to *in vivo* biological measurement and to post-mortem pathological measurement but are strongly culturally influenced. The point at which an individual will be labelled as needing medical or social care is socially determined[36,37]. The move to define people in marginal or borderline states as having medical conditions, recently discussed for many areas such as weight, sexuality and childhood behaviour, also applies to the grey area between abnormal and normal ageing[38]. Societal issues here include questions such as who sets the agenda for our expectations of ageing[39–41]. Although tests such as IQ can take into account the decline in test performance with age, memory impairment is increasingly seen in the West as a potential indicator for future dementia. Previously, and in many areas of the world, various degrees of memory impairment have been accepted as part of older age. There are several ways in which the aforementioned tension could be resolved, including carrying out studies with more clearly defined groups, for example with individuals who have a sudden onset of extreme changes in cognition; comparing clearly non-impaired groups with obvious dementia sufferers; and tracking change over time, including groups with a particularly high risk of developing dementia.

High risk groups in later life

Some research provides evidence of particular risk groups for dementia. Some patient groups are undoubtedly at increased risk of dementia, including both dementia overall and specifically clinically diagnosed subtypes. Parkinson's disease, although not highly prevalent itself (1% prevalence in Western populations aged 65 and over), confers a marked increase in risk[42,43]. The lifetime risk of stroke is 1 in 3 in the United States, and this constitutes an important risk factor for dementia[44]. The potential benefit at the population level for dementia from a reduction in vascular risk is not known[45]. Will those individuals who survive stroke because of improved timely treatment, when they would previously have died, be at increased risk of dementia[46,47]? One recent report suggests that survivors are indeed at increased risk[48]. These studies have shown that brain pathologies associated with these

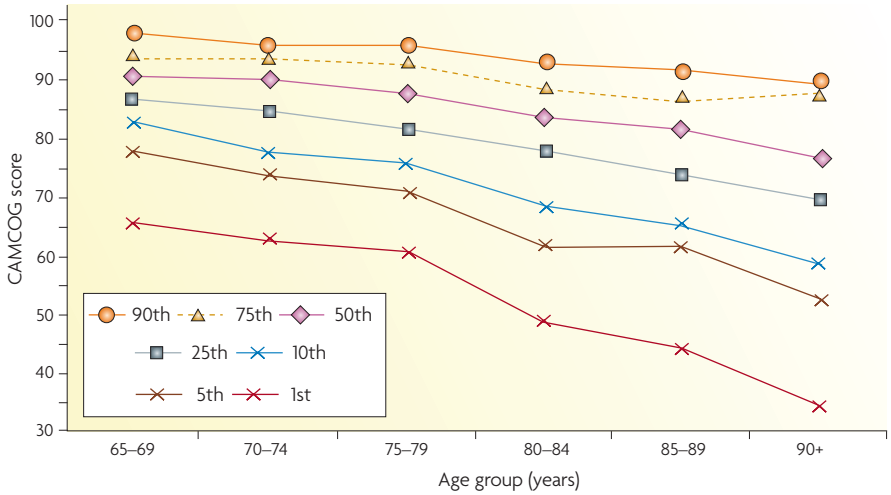

Figure 3 | **Population distribution using percentiles of the neuropsychological scale CAMCOG in the Cognitive Function and Ageing Study (CFAS).** The percentiles show the widening distribution of cognitive scores across the age groups in a population sample. CAMCOG is a neuropsychological test from CAMDEX, the standard clinically based interview. CAMCOG covers key neuropsychological domains for assessment of cognitive function in the older population including attention, orientation, memory, language, praxis and calculation, with a potential maximum of 104 (as used in CFAS). The key shows percentiles, which indicate the proportion of the population that fall below a given level of performance for a particular age. Reproduced, with permission, from REF. 16 © (2003) John Wiley & Sons.

disorders might contribute substantially to the expression of dementia and cognitive impairment even if the expression of these pathologies are below the threshold to cause this particular disorder[49]. Again, a dimensional approach seems to be useful for seeing the full picture.

Dimensions and early detection

Is it possible to use assessment of cognition to predict whether early intervention could prevent the extreme manifestation of brain failure? Although predictors for dementia and its subtypes have been the subject of research for at least two decades, it is only in recent years that this has become a mainstream activity. Early detection might permit early intervention. Current work on the milder stages of dementia is largely based on patients from memory clinics or volunteers, and tends to concentrate on people at high risk of conversion to dementia, those who have mild dementia already or the 'worried well'. They are not representative of the full population and provide a biased estimate of the positive predictive value that would be found in any true population. Screening for dementia in the population is not formally advocated. There are many possible biomarkers[50,51] for subtypes of dementia, but none has been sufficiently closely linked to observed decline in populations to suggest a tight association. In addition, measuring biomarkers can be invasive and expensive.

The examination of cognitive profiles in total populations across age groups reveals that there is a wide distribution, with some older individuals maintaining high performance and others experiencing marked impairment[52,53] (FIG. 3). To define which individual performance over time (trajectory) constitutes failure and which constitutes success is a challenge when there are continuous distributions. These findings cause us to reflect on what these measures mean. It has long been known that those who develop dementia in studies that follow individuals over at least a few years (longitudinal studies) have lower cognitive scores at the start of the studies than those who remain dementia free — with verbal memory identified most often as the best predictor. But the discrimination refers to groups, not individuals. No tests are yet sufficiently robust to identify individuals with dementia with certainty[54–56]. Misidentification of at-risk individuals would carry formidable consequences for individuals and their families as well as for health and social services. Existing strains on most health and social care systems dealing with large numbers of frail older people are considerable, and most could not cope with large numbers of false positives on screening tests that seemed promising in selected settings. So, this kind of performance test is not robust enough to be used as a diagnostic for the early detection of dementia.

Risk over a lifetime

If screening has yet to be proven efficacious, what is the evidence regarding early risk and dementia? In earlier generations, there was little merit in expending effort on personal and societal investment at younger ages to improve health in later life, but the revolution in life expectancy dictates a different approach. Increased understanding of risk for dementia has come from studies in which risk factors were measured many years earlier.

There are now pieces of evidence from all stages of life, including prenatal periods (for reviews, see REFS 57,58). Common themes of risk for chronic disease emerge across the age span. One example is the examination of blood pressure in childhood, mid-life and later life[59–62]. Tracking of blood pressure over time reveals that those with a higher blood pressure when young tend to be those who have higher blood pressures in mid-life. Health patterns over a lifetime therefore indicate that the risk observed in mid-life for raised blood pressure and in later life for dementia has an early life origin. Cognition has been measured in developmental cohorts whose members are now entering their seventh decade. High rates of heart disease in the last half of the twentieth century led to a number of large cohorts with extensive cardiovascular measures now being examined in relation to cognition. Such cohorts, linked to novel technologies such as functional imaging, are powerful resources for examining early life risk, intermediate phenotypes and disease outcome[63].

Evidence is growing for a relationship between physical activity, metabolic syndrome, diabetes and dementia throughout life. Diabetes (type II) doubles the risk for dementia[7,8]. This links closely with obesity and physical activity, which have also been reported as risks when measured well before dementia onset[64–66]. This is supported by meta-analysis of the effect of exercise on cognitive impairment and dementia[67], which reveals consistent evidence that exercise is associated with improved cognition and less likelihood of developing dementia. It has been suggested that "Fitness is serving a neuroprotective function for the ageing human"[68]. However, the link between risk factors and dementia is not always clear-cut; caution is sensible when evaluating risks[69]. Risk factors evolve over a lifetime in nonlinear ways. High blood pressure in mid-life is associated with increased risk, but this is not necessarily the case in later life[47]. Several observational studies have now reported that limited social contact in

later life is associated with increased risk for dementia[70,71]. The degree of social integration earlier in life is not associated with later dementia[70]. Further illustrations of the complexity of these potential risks include a report that early life socioeconomic status is linked to the level of cognition in later life, but not to decline[72], which contrasts with other studies[73]. Efforts to reduce dementia based on later life findings might be hampered by the need to understand the lifelong aspects of potential risk factors and their relation to changes in cognitive function[74].

Life risk and prevention

Given patterns of risk factors across the lifetime, what is the evidence that changes in these risks could alter brain ageing? Eradication of a risk closely associated with the disease outcome should lead to a measurable reduction in that disease. A great challenge is therefore to work out whether 'risks' identified by late-life dementia studies are merely a marker of risk or an actual cause of dementia. Homocysteine measured in the blood is an example of an identified risk factor for dementia that has been confirmed in many longitudinal studies, but it is not yet clear if homocysteine is associated with one of the causal pathways leading to dementia. Moreover, it is not proven that reducing homocysteine by treatment with folate and/or vitamin B12 will reduce the risk of dementia[75–77]. As mentioned in the introduction, the reviews that suggest that dementia is largely preventable[4] are based on observational studies. Such studies are all too often followed by trials that suggest a lack of effect[47], or even increased risk. This is perhaps predictable given the lack of attention paid to the ways by which evidence is generated[78], and is well illustrated by the apparently paradoxical findings of observational studies and trials for hormone replacement therapy[79,80], anti-inflammatory medication[81,82], vitamin supplementation[83,84] and statins[85,86]. Fish consumption has also been proposed to protect against dementia, but investigation of diet in early life shows that many of the protective features cluster together, making it hard to interpret the data[87]. Alcohol consumption is similarly fraught with difficulties of interpretation: although moderate alcohol intake has an apparent protective effect[88], it could be subject to unmeasured confounding, as this level of alcohol consumption is likely to be associated with existing good health and a healthy lifestyle in many cultures.

Many variables that seem to be socially or educationally related have been linked to dementia[73]. The cohort studies with measures taken early in life and those which measure these features at the end of life tend to show that individuals who have higher levels of education, higher social class, better social integration or lower chronic disease are those who age better on the whole[89,90], and that they might compensate to some extent for age-related changes in the brain by employing different strategies. This is illustrated by functional imaging studies that show more diffuse activation for a given cognitive task in such individuals[91] — this is referred to as cognitive reserve[92,93]. There is some positive evidence for trials of intellectual stimulation such as memory training leading to an improved cognitive performance in the short term[92], but not as yet for dementia outcomes.

Risk variation for populations

Many risk factor patterns in populations are mirrored in differences in major chronic diseases. Many of the chronic diseases in midlife are markedly higher in the United States than in the United Kingdom[94], and even less common in southern Europe — however, dementia has not been shown to vary accordingly[10]. Nor have differences been found within a country (the United Kingdom) with differing chronic disease risk levels[95,96]. Some of the lack of variation might be due to the strong association of dementia with death, in that those who become demented die much faster than those who do not[97–99], an observation that is further complicated by the fact that risk and protective factors are also related to mortality. Therefore, it seems that many risk factors for dementia relate to lifelong complex causal pathways.

Public health

What does this mean for public health and policy? This depends on a wider set of questions. How large is the effect found in a study, how representative of normal older people who get dementia is the population studied, what is the pattern of the risk or protective factor in our older population, is there any evidence that changing a risk factor at a given age will change outcomes, and if so, by how much? Single, small studies at the forefront of risk investigation tend to report higher risk estimates than later, larger studies, as illustrated in a systematic review of the link between paraoxinase polymorphisms and heart disease[100]. There is undoubtedly publishing and fashion bias — researchers are much less likely to bother to write a paper on a null finding. Even clear risks such as diabetes need further research; for example, would preventing diabetes reduce dementia in the population? Possibly not, because of complex survival issues. A recent review for the Policy Workforce on social care in the United Kingdom has reported on a model that attempts to investigate the impact of reduction of chronic disease risk for cognitive impairment, taking into account differences in mortality and survival in different health states. It predicts that much of the estimated and assumed prevention of dementia through improvement of the risk factor profile would be attenuated by the increased survival of the population, with little change in overall dementia[101]. The chance of developing cognitive decline has to include the likelihood of surviving to the age of risk in a given society. This will already be linked to a combination of life experience, lifestyle, chronic disorders including mental health and healthy ageing. The West and Japan have the longest-living societies in the world, and the highest proportions of the population with dementia. Average life expectancy is going up inexorably[102]. We do not know whether this is accompanied by an equivalent shift in the average age of onset of dementia, because there are not sufficiently robust true population cohort studies. If longer life results from interventions that allow us to live longer with chronic diseases which are themselves risks for dementia, then the average age of onset of dementia might not increase[103].

If effective treatments for specific dementias become available, the disparity between the West and the less developed regions of the world (and the inequalities in provision within individual countries) will increase, particularly if such drugs are recommended for early stage disease. Those individuals and countries that can afford medication will benefit from them; most others will not. Health services already struggle to fund the costs for some medication for the treatment of dementia, and this problem will worsen with increased numbers of patients.

The elephant in the room

At present we do not have to confront many of the issues raised in this article, because no single treatment or preventive action for dementia or cognitive decline has accrued the necessary evidence to support it. But if such evidence becomes available, it is essential that it is population-based, to enable us to contextualize findings and to assess their public health impact. Changes in societal attitudes such as the expectation

of pharmaceutical intervention at biologically detectable early stages of particular dementias, extending beyond very high risk groups, might cause a marked increase of demand on health services and of consequent costs. It is also essential to be able to estimate the potential benefits and costs of such attitudinal change. It could be that new preventative or therapeutic approaches will lead to a marked amelioration in populations of the devastating effect of dementia. However, there is no existing evidence of benefit at the population level. Much hype has come from the assumption that results in one setting are transferable to another and that the size of risk is the same as the size of potential benefit. Age remains the elephant in the room whose large effects dwarf other risk estimates. Despite much discussion about the possibility of avoiding ageing[104] or arguing that ageing as a single process does not exist[105], the fact remains that individuals aged 90 or over have more than 25 times the risk of developing dementia than those aged 65 to 69 (REF. 106). A balanced view is required, taking into account the full complexity of dementia from biology to policy across age groups and populations and across diverse sociocultural, economic and historical backgrounds.

Conclusion

Although there has been enormous progress in our understanding of the natural history of dementia and associated disorders at the biological, clinical and population levels, this progress has not yet been translated into any effective prevention at the population level. Interpretations from research studies must take into account different populations and public health contexts to form strategies for the assessment of the potential positive and negative aspects of scientific advances.

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Competing interests statement
The author declares no competing financial interests.

DATABASES
The following terms in this article are linked online to:
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Alzheimer's disease | frontotemporal dementia | Lewy body dementia | Parkinson's disease

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CORRIGENDUM

Regulation of cell fate in the sensory epithelia of the inner ear

Matthew W. Kelley

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On page 843, in the section on *Sox2* it was stated that the *Ysb* and *Lcc* mutations were generated by ENU treatment, which is incorrect. In fact, *Ysb* was generated through transgene insertion, whereas *Lcc* was caused by X-ray irradiation.

On page 849, the highlighted statement starting "A seminal study…" should be attributed to reference 86, rather than reference 85.