Sex differences in Alzheimer's disease and other dementias

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The *Lancet Neurology* Commission[1] draws attention to the dramatically increasing personal, societal, and economic costs of Alzheimer's disease (AD) and associated dementias, and provides a call to action for an innovative research response to develop prevention and treatment strategies. The Commission also emphasises that the symptoms and course of dementias necessitate long-term care, thus requiring outcome assessments that include both patients' health status and the viability of health-care systems. We assert that, integrated within the portfolio of research proposed by the Commission, a focus on the effect of sex on AD and other dementias is essential to ensure progress in understanding, treatment, and prevention of these disorders.

AD and other dementias disproportionately affect women. The Commission affirms that, for most regions of the world, the occurrence of AD and other dementias is higher in women than in men, particularly in the most elderly, and that women provide most caregiving for people with dementia.[1] However, beyond statistics showing the greater burden of dementias for women, empirical data about sex differences and emerging sex-specific findings in dementias can guide and inform the scientific approach to these illnesses for the benefit of both women and men.

Brain development and adult brain structure, function, and biochemistry differ by sex.[2] These sex differences in the brain are initiated through sex-determining genes and fetal hormonal programming. Such differences have important implications for brain-based disease risk and for clinical and investigational approaches. For example, with regard to genetic findings, the results of a large prospective cohort study published in 2015 confirmed previous case–control reports that women who are positive for the ε4 allele of the apolipoprotein E gene (*APOE* ε4) are at greater risk of developing AD than are men with this allele,[3] and they demonstrate more severe behavioural disinhibition.[4] As pointed out in these investigations, the inconsistency of past findings about this allele could be attributable specifically to investigators overlooking the *APOE*-ε4-by-sex interaction, resulting in missed opportunities to enhance understanding of the genetic underpinnings of AD.[3] Testing for the effects of numerous other genes implicated in dementias by sex, rather than pooling data for both sexes, would likewise speed efforts to discern new directions for personalised treatment and management.[5]

In terms of localised brain changes and brain function, reports suggest that women diagnosed with AD experience a faster progression of hippocampal atrophy than do men,[6] whereas men might be more likely to progress to AD in the presence of severe periventricular white matter hyperintensities and reduced global cognitive performance.[7] Women and men also have different clinical presentations, in that men show more aggressive behaviours, more comorbidity, and higher mortality than women; women tend to have more affective symptoms and disability but longer survival times.[8] These presentations might indicate different neuropathologies and certainly necessitate different management strategies to serve men and women with dementia.

From the perspective of treatment, emerging evidence also points to the possibility that sex-specific genetic and hormonal factors contribute to variance in clinical efficacy. For example, the improved response to acetylcholinesterase inhibitor treatment in women with AD was attributed to variants of the oestrogen receptor α gene (*ESR1*).[9] In addition to differences in genetic or brain-based vulnerabilities, broader societal factors also have roles in the risk, course, and outcome of dementias. Perhaps the most salient examples are education and occupation levels, both of which have repeatedly been

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shown to affect the risk of dementia and for which substantial inequalities have existed between the sexes in previous generations.[5] A host of behavioural and lifestyle choices, including diet, exercise, and tobacco and alcohol use, also affect vascular risk factors and the degree of disability in individuals with dementia. In brief, an individual's behaviours and experiences over the lifespan affect the brain, and many of these factors vary by sex.

Sex differences, extending from genetic to psychosocial domains, are relevant to productive and reproducible research, and they signal urgent priorities for public health planning. For example, almost all countries are facing the same demographic evolution in which women are diversifying their roles while carrying the heavier burden of caregiving. The availability of resources differs substantially across countries, yet the needs of a growing population of people with dementias cannot be met by public and social-care sectors alone, prompting important questions about the role of women in future caregiving.[1]

Advances have been made in various fields, from cardiology to addiction medicine, by analysing the effects of sex on outcomes.[10] The *Lancet Neurology* Commission provides a timely opportunity to embrace this approach in the research agenda for AD and other dementias.

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Fighting dementia in Europe: the time to act is now

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European policy makers don't seem to be fully aware of the huge burden that Alzheimer's disease (AD) and other dementias pose for the citizens of the European Union (EU). Although data about disease burden have been available for some time, this evidence is now comprehensibly explained by *The Lancet Neurology* Commission on defeating AD and other dementias.[1] Roughly 1·5–2% of the EU population is affected by dementia. AD is not a normal part of ageing, but old age is the primary risk factor for the disorder; without action, the prevalence of AD and other age-related dementias will increase substantially in the EU, and the cost of medical care and the societal burden of dementia will soon become unsustainable.

However, numbers alone are insufficient to push an issue to the top of policy makers' list of priorities. The translation of scientific evidence for dementia and other major public health issues into EU policy remains a challenge because, for politicians, evidence from research is thought of as one of several knowledge sources. Policy makers also take into account other factors, including financial concerns, commonplace knowledge, ideology, constituency input, political expediency, and social interactions, among others.[2]

There is a tendency for policy makers to take small steps—ie, to build on existing policies rather than attempting to establish wide reforms. There are several reasons for this approach. First, policy makers often have limited time and insufficient information. Second, the organisation of the European political system disperses responsibility among EU institutions and member states. Finally, most public health policy is formulated within a small network of elected officials, interest groups, researchers, and related stakeholders,