Sex differences in Alzheimer disease — the gateway to precision medicine

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Abstract | Alzheimer disease (AD) is characterized by wide heterogeneity in cognitive and behavioural syndromes, risk factors and pathophysiological mechanisms. Addressing this phenotypic variation will be crucial for the development of precise and effective therapeutics in AD. Sex-related differences in neural anatomy and function are starting to emerge, and sex might constitute an important factor for AD patient stratification and personalized treatment. Although the effects of sex on AD epidemiology are currently the subject of intense investigation, the notion of sex-specific clinicopathological AD phenotypes is largely unexplored. In this Review, we critically discuss the evidence for sex-related differences in AD symptomatology, progression, biomarkers, risk factor profiles and treatment. The cumulative evidence reviewed indicates sex-specific patterns of disease manifestation as well as sex differences in the rates of cognitive decline and brain atrophy, suggesting that sex is a crucial variable in disease heterogeneity. We discuss critical challenges and knowledge gaps in our current understanding. Elucidating sex differences in disease phenotypes will be instrumental in the development of a 'precision medicine' approach in AD, encompassing individual, multimodal, biomarker-driven and sex-sensitive strategies for prevention, detection, drug development and treatment.

Although Alzheimer disease (AD) is recognized as a public health priority by the WHO[1] and is expected to affect 90 million people worldwide by 2050 (REF.[2]), the condition remains incurable and all clinical trials in AD conducted in the past decade have failed. Heterogeneity of disease manifestation and progression among patients has been identified as a critical issue in the current approach to developing new therapies for AD[3,4]. Therefore, characterization of genetic, demographic and phenotypic traits that predict disease onset, prognosis and treatment response (exemplified by work in the oncology field[5,6]) is of growing interest in AD research. Phenotypic[7,8] and genetic[9] factors have been proposed as characteristics that can guide patient selection, stratification and clustering for AD diagnosis and treatment. However, whether demographic variables such as sex should be considered in relation to AD phenotypic variability is unclear.

Differences in brain structure[10,11] and function[12] between men and women are emerging, as are effects of sex on the manifestation and progression of neurological conditions, such as ischaemic stroke[13], Parkinson disease[14] and migraine[15]. In a longitudinal study of >2,000 patients with Parkinson disease, sex accounted for 2.6% of the predictive information provided by a seven-factor clinical–genetic risk score for cognitive decline[16]. However, current discussion of sex differences in AD primarily focuses on epidemiological aspects (BOX 1), with very little attention given to the role of sex in the clinical and neuropathological manifestations.

To address this knowledge gap, this Review — written on behalf of the Women's Brain Project and the Alzheimer Precision Medicine Initiative (APMI; Supplementary Box 1) — provides the first comprehensive overview of sex-related differences in the phenotypes of sporadic AD. The aims of the Review are to raise awareness of published evidence, to propose measures to increase the number and quality of studies in this field, and to highlight the importance of considering sex in preclinical and clinical studies in the context of a multivariate, precision medicine approach for AD[17]. Detailed discussion of sex differences in AD epidemiology are available elsewhere[18–21]. In this Review, we focus on sex differences in clinical manifestations, biomarker profiles, risk factors and treatment of patients with AD.

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Key points

- Men and women with Alzheimer disease (AD) exhibit different cognitive and psychiatric symptoms, and women show faster cognitive decline after diagnosis of MCI, dementia or AD.
- Levels of amyloid-β peptide measured with PET-based brain imaging and biochemical analysis of cerebrospinal fluid do not differ between the sexes.
- Brain atrophy rates and patterns differ along the AD continuum between the sexes; in mild cognitive impairment, brain atrophy is faster in women than in men.
- The prevalence and effects of cerebrovascular, metabolic and socio-economic risk factors for AD are different between men and women.
- No data are available on sex differences in the efficacy and safety of drugs used in recently completed phase III clinical trials for mild to moderate AD.
- Systematic studying and reporting of sex differences in disease symptomatology, biomarkers, progression, risk factors and treatment responses will be crucial for the development and implementation of precision medicine in AD.

Clinical manifestations of AD

Sex differences in AD symptomatology have not been studied systematically. In the vast majority of reports of AD symptoms, data are not stratified by sex. The common practice of adjusting data by sex prevents the possibility of analysing the effects of sex in a given data set. However, over the past 20 years, numerous studies have identified differences between the sexes across the full spectrum of clinical manifestations of sporadic AD (BOX 2) and throughout the continuum of disease, from preclinical AD to severe dementia (Supplementary Table 1). In this section, we provide a critical overview of these studies in relation to known sex differences in the non-cognitively impaired (NCI) population.

AD-related cognitive impairment

Sex differences in neuropsychological performance among NCI people have been extensively documented: women score more highly than men in verbal tasks at all ages[12,22–24] and exhibit slower cognitive decline[12,25], even among the elderly population (average baseline age 64.1–69.7 years[24]). On the other hand, men score more highly in visuospatial and motor coordination tasks[12,24,25].

Two studies have demonstrated that the higher performance of women than men in the verbal memory domain among the NCI population is maintained in prodromal AD[26,27]. Both studies demonstrated that verbal memory is preserved in women with amnestic mild cognitive impairment (aMCI) relative to that in men with the same diagnosis, despite comparable hippocampal atrophy[26] and comparable temporal lobe glucose metabolic rates[27]. However, the sex difference in verbal memory tasks observed in NCI and at early stages of AD is not seen among patients with a diagnosis of dementia[25,28]. The majority of studies in which cognitive data were stratified by sex in AD dementia indicate that women score lower than men in verbal memory and fluency tasks, particularly confrontation naming tasks, even after controlling for possible demographic and psychological confounders, such as age, education and depression[22,29,30] (Supplementary Table 1). In early AD dementia, even a lack of sex differences in memory performance, as observed in one study[26], could indicate meaningful effects of sex, as this observation deviates from the findings in NCI people for that specific domain.

Rates of cognitive decline

Marked sex differences in the rates of progression have been consistently reported among individuals with aMCI recruited to the Alzheimer's Disease Neuroimaging Initiative (ADNI) study: cognitive deterioration is faster in women than men over 1 year[31] and becomes twice as fast over 8 years[32] (even after normalization for apolipoprotein E (*APOE*) genotype; Supplementary Table 1). A study published in 2017, in which a multilayer clustering algorithm was used to analyse 5-year longitudinal data from the ADNI cohort, demonstrated that in a cluster of 'fast progressors', cognitive decline was faster in women[8]. Similarly, a study published in 2015 showed that annual progression rates from aMCI and non-amnestic MCI (naMCI) to AD dementia were 2–3% higher in women than in men in the French National Alzheimer Database[33], irrespective of age and education level.

The faster cognitive decline observed in women could result from later diagnosis of AD in women than men. Indeed, a study published in 2014 showed women to have lower Mini-Mental State Examination (MMSE) scores (indicating worse global cognitive status) than men at initial diagnosis of AD, even after adjustment for age and education level[34]. However, this possibility needs to be confirmed in further studies. Similarly, the biological underpinnings of the sex differences in cognitive status and deterioration remain to be elucidated. Comorbidities such as cardiovascular and cerebrovascular disease[35], synaptic biology[36], brain-derived neurotrophic factor levels[37], and systemic[38] and brain[39,40] immune responses are all affected by sex and could contribute to the observed effects, but no studies have investigated the role of these factors in the observed sex-related differences in cognitive function and decline.

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Box 1 | **Sex differences in Alzheimer disease epidemiology**

A substantially larger number of women than men have Alzheimer disease (AD) worldwide (2:1 women:men ratio[103,148]). However, whether epidemiological indicators of burden and risk (such as prevalence and incidence) are affected by sex is a subject of intense debate. Analysis of the prevalence of AD by sex (that is, the number of women affected divided by the total number of women in the population) reveals that the prevalence of AD among women is significantly greater than that among men in some but not all geographical regions[2]. Although the effect is significant, it is moderate and mostly driven by a higher prevalence of AD among older women than older men. Furthermore, the difference seems to be influenced by secular trends, and prevalence in older old women is lower in the most recent reports[21]. Sex differences in the incidence of AD are also affected by geographical region and historical time of analysis; evidence for a higher incidence of AD in women in the USA is limited[149], but the 10/66 Dementia Research Group study of dementia in low-income and middle-income countries did demonstrate higher incidence in women[101]. These results suggest that socio-economic factors, such as education and occupation, rather than biological mechanisms are at play in determining overall AD risk[20,21].

On the basis of these controversial results, a commonly held view is that the observed sex differences in AD frequency are largely explained by the longer life expectancy of women, even after diagnosis of AD, than of men, and by the selective survival of men with the best cardiovascular health into old age[92]. This view is supported by the fact that mild cognitive impairment, which occurs at younger ages than AD, is more prevalent among men[150]. However, this viewpoint remains controversial and is the subject of several high-quality reviews[18–21,151].

Behavioural symptoms of AD

Several sex differences in behavioural symptoms of AD have been reported, although many of these observations are based on single studies with limited sample sizes (Supplementary Table 2). The available evidence indicates that men who are diagnosed with AD are more likely than women to exhibit apathy[41], agitation[42] and abusive and socially inappropriate behaviour[41,43,44], whereas women more often present with depressive symptoms[45], reclusiveness[41], emotional lability[41], delusions[46], and affective and manic symptoms[47]. In a study of neuropsychiatric symptoms among 1,120 individuals with sporadic AD, behavioural dysfunction and mood component scores were worse in women than in men[48]. Nevertheless, women with AD seem to score equally to[49] or more highly than[30] men on functional independence scales. However, women with AD dementia experience a partial loss of independence earlier in the disease course than men[49], so spend a greater proportion of their remaining lives with dependence and extensive disabilities. Additional studies with larger cohorts are required to confirm the observed sex differences in behavioural symptoms.

Biomarker patterns in AD

Cognitive and behavioural impairments in AD are paralleled by specific and progressive neuropathological changes in the brain that precede the onset of detectable clinical symptoms by years to decades (BOX 3). Differences in AD biomarkers between the sexes are starting to be explored systematically thanks to large, international, collaborative initiatives, such as the ADNI, the Australian Imaging, Biomarkers & Lifestyle Flagship Study of Ageing (AIBL) and the Harvard Aging Brain Study (HABS). However, in many studies of biomarkers, results are adjusted for age and sex, thereby hindering examination of sex differences.

In this section, we review the available evidence for sex differences in the absolute levels of diagnostic biomarkers (amyloid-β (Aβ) and tau) and markers of disease progression (brain atrophy) and in the relationship between biomarker status and clinical manifestations of AD (Supplementary Tables 2,3).

Amyloid-β burden

Sex differences in Aβ burden in NCI elderly individuals are controversial. Some studies have indicated no sex differences at all[23,50]. One study has demonstrated slightly higher uptake of Pittsburgh compound B (PiB) in men than women[51], but two other reports have indicated higher PiB uptake in women than men[52,53]. The discrepancies between publications could be the result of differences in study designs, sample sizes and ages of individuals included in the study (Supplementary Table 2).

In mild cognitive impairment (MCI) and AD, no clear sex differences in Aβ burden have been reported. Post-mortem studies conducted in the past 15 years have indicated no clear sex differences in the occurrence or distribution of Aβ plaques in the hippocampi and neocortices of patients with AD[54]; one study indicated a higher degree of cerebral amyloid angiopathy in men than in women[55]. Similarly, sex seems to have no impact on cerebrospinal fluid (CSF) concentrations of $A\beta_{1-42}$ in living patients with AD dementia, people with prodromal AD or NCI individuals[31,56]. Furthermore, a meta-analysis of PET studies revealed no sex differences in amyloid positivity among individuals with subjective cognitive impairment, aMCI or naMCI[57]. A similar meta-analysis to investigate sex differences in Aβ burden in patients with AD is, to our knowledge, currently lacking.

Tau burden

The vast majority of post-mortem pathological studies of brains from patients with AD have not indicated any effect of sex on the global burden of neurofibrillary tangles or tau hyperphosphorylation. Individual reports have indicated possible effects in specific brain regions: higher numbers of neurofibrillary tangles have been found in women with AD than in men in certain cortical areas, including the midfrontal, superior temporal, entorhinal and inferior parietal cortices[54] and the nucleus basalis of Meynert[58], but these results require replication.

Studies of tau accumulation via CSF analysis and PET imaging in living patients have produced similar findings. In a study published in 2017, sex had no impact on CSF tau concentrations in patients with AD dementia, people with prodromal AD or NCI individuals[56]. Another study indicated higher tau concentrations in women than in men with (undefined) MCI, but the trend was not significant ($P = 0.06$)[31]. PET studies have also indicated no sex differences in tau accumulation in ageing and early AD[50,59]. However, data from several other studies in patients were not stratified by sex, so knowledge of sex-dependent tau accumulation and spreading in patients with AD is limited.

Box 2 | **Definition of Alzheimer disease**

In this Review, the term 'Alzheimer disease' (AD) refers to the entire pathological continuum from initial, asymptomatic degenerative changes in the brain to frank, overt dementia, as proposed by the revised International Working Group (IWG-2) criteria[152]. In addition to cognitive deficits, neuropsychiatric and behavioural symptoms (including depression, psychosis, apathy, wandering and agitation) and loss of functional independence are also clinical manifestations of the AD continuum[153,154].

We refer to three stages of sporadic AD:

Preclinical AD
The asymptomatic stage that precedes the development of cognitive impairments (clinical stage) but is characterized by at least one in vivo biomarker of AD neuropathology.

Prodromal AD
The symptomatic phase of AD before dementia, in which amnestic syndrome of the hippocampal type is present, but instrumental activities of daily living are not affected and a diagnosis of dementia is not required. Although similar to the construct of amnestic mild cognitive impairment[155], diagnosis of prodromal AD requires in vivo biomarker evidence of AD pathological changes in the brain.

AD dementia
A dementia syndrome that comprises an amnestic syndrome of the hippocampal type in the presence of in vivo biomarkers indicative of AD neuropathology.

In the absence of a positive biomarker-based diagnosis of AD, we refer to AD dementia or mild cognitive impairment (MCI), following the nomenclature used by the authors. Amnestic MCI is characterized by memory dysfunction, and non-amnestic MCI (naMCI) refers to conditions characterized by deficits in other cognitive domains[155]. If the MCI subtype is not indicated in the study, we refer to it as 'undefined'. The diagnostic criteria used in each paper are indicated in Supplementary Tables 1–3.

Brain atrophy and atrophic rates

Among the NCI population, elderly men exhibit greater age-related atrophy in frontal, parietal and temporal regions[23], and lower cortical thickness in AD signature areas[53], particularly temporal areas[50]. However, studies of absolute brain volume in patients with AD dementia (Supplementary Table 3) have produced inconsistent findings: lower hippocampal volume has been reported in men[26] and in women[60]. These inconsistencies could be due to the method used for brain volume normalization: intracranial volume is larger in men than women, so volumetric measurements that are normalized to intracranial volumes can be skewed[61]. In future studies, quantification of cortical thickness, which is independent of intracranial volume, could help to clarify the role of sex in AD-related atrophy.

In contrast to the volumetric findings, sex differences in atrophy rates in several brain regions have been demonstrated at all clinical stages (NCI, undefined MCI and AD dementia)[31,62]. The ADNI study[63] and the Minimal Interval Resonance Imaging in Alzheimer Disease (MIRIAD) study[64] determined that atrophy rates were faster by 1–1.5% per year in women with aMCI and AD dementia than in men (FIG. 1; Supplementary Table 3).

Relationship between neuropathology and clinical symptoms

In a seminal paper, Barnes et al.[54] reported in 2005 that each additional unit of AD pathology (calculated as a global measure of the burden of neuritic plaques, diffuse plaques and neurofibrillary tangles across four brain regions) was associated with a >20-fold increase in the odds of dementia in women but only a 3-fold increase in men. Importantly, the difference was unlikely to be due to unequal occurrence of cerebrovascular events between the sexes because normalization of data to the number of cerebral infarcts did not affect the results[54].

In concurrence with these findings, analysis of longitudinal data from the ADNI cohort found a significant interaction of sex with CSF levels of AD biomarkers in relation to the development of neurodegeneration and dementia at follow-up (0–9 years)[65]. In this study, female sex was associated with greater hippocampal atrophy and faster cognitive decline in the presence of AD biomarkers (CSF levels of $A\beta_{42}$ and total tau) than was male sex, particularly among patients with (undefined) MCI[65]. Similarly, a study published in 2017 showed that, among patients with aMCI who were classified as fast progressors (identified with a multilayer clustering algorithm), progression rates were higher in women than in men, even when levels of diagnostic biomarkers were similar[8]. Whether the prognostic values of specific biomarkers are modulated by sex[66] deserves further investigation.

Risk factors for AD

Prevalence of risk factors

Research conducted in the past decade indicates that, although the prevalence of cardiovascular risk factors and cerebrovascular events (such as hypertension, hyperlipidaemia, diabetes, stroke and microinfarcts) is higher overall in men than in women under the age of 60 years, this prevalence is equal or even higher among women after menopause or older than 60 years[13,67–69]. Depression and sleep disorders — both risk factors for AD — are also known to be more prevalent in women[70,71].

Modulation of individual risk factors

Studies indicate that sex can modulate not only the prevalence of risk factors for AD but also the susceptibility to AD conferred by a given risk factor. Below, we discuss the evidence for three of these risk factors for which the evidence of sex differences is most robust: *APOE* genotype, vascular risk factors and depression.

APOE genotype. Some evidence has suggested that sex can change the risk conferred by the *APOE**ε4 allele: the risk of AD onset or conversion from MCI was reported to be higher among women carriers than among men carriers[72–74]. A highly powered, global meta-analysis published in 2017 that included >50,000 individuals has refined these observations[75]. An increased incidence of MCI or AD in female *APOE**ε4 carriers was found only in younger age brackets (55–70 years for MCI and 65–75 years for AD), suggesting an early susceptibility of women carriers. Hormonal and metabolic alterations that occur early in menopause[76], which immediately precedes the risk age, could explain this age-specific effect, although this hypothesis has not been investigated. Additional studies are needed to elucidate whether perimenopausal changes interact with *APOE* genotype to affect AD risk.

Interactions between sex and *APOE* genotype have been observed in NCI individuals: impaired episodic

Box 3 | **Biomarkers of Alzheimer disease**

In vivo measurements of amyloid-β (Aβ) load (via PET using the tracers Pittsburgh compound B, florbetapir, florbetaben or flutemetamol) and cerebrospinal fluid biochemical analysis (measurements of Aβ, total tau and phosphorylated tau concentrations) are considered to be core diagnostic biomarkers of Alzheimer disease (AD) pathology according to the revised International Working Group (IWG-2) criteria[152]. Emerging tau PET tracers are being developed in clinical research[156]. By contrast, downstream topographical biomarkers such as hippocampal and basal forebrain nuclei atrophy (measured with structural MRI) and cortical hypometabolism (measured using FDG–PET) are categorized as markers of disease progression[152] as they closely correlate with worsening of cognitive performance but lack pathological specificity for AD. In 2018, both the FDA[157] and the European Medicines Agency[158] endorsed the use of biomarkers for the diagnosis of AD and the monitoring of drug effects in clinical trials.

memory[77], decreased default-mode network activity[78], decreased hippocampal connectivity[79] and increased hypometabolism and atrophy have been observed in women carriers of *APOE**ε4 compared with age-matched men carriers[80]. In addition, greater hippocampal atrophy has been observed in female *APOE**ε4 carriers with MCI than in male carriers with MCI[77]. Given that no sex differences in Aβ load have been established[23], the increased risk of AD in female *APOE**ε4 carriers could be explained by an increased sensitivity to Aβ or it could be the result of Aβ-independent mechanisms; these possibilities need to be tested.

Vascular risk factors. Whether cognitive decline and the risk of AD are affected by an interaction of sex with cerebrovascular pathology (such as subcortical leukoencephalopathy, lacunar infarcts, ischaemic and haemorrhagic strokes and leukoaraiosis) and cardiovascular risk factors (including hypertension, metabolic syndrome, insulin resistance, hyperhomocysteinaemia, hyperlipidaemia, chronic inflammatory diseases, vitamin D deficiency, alcohol consumption and smoking) has not been systematically investigated, but several studies on the topic have been published. As an example, a landmark study showed that brain infarcts lowered the threshold for dementia in elderly women with AD pathology compared with age-matched women with no AD pathology[81], but whether the interaction between brain infarcts and dementia is seen to the same extent in men and women is unclear. Further examination of the effect of cerebrovascular pathology (white matter hyperintensities and brain infarcts) and amyloid pathology (assessed with PiB–PET) on the risk of cognitive decline in a population of elderly NCI individuals showed that vascular and amyloid pathologies have an additive effect on cognitive decline[82]. Stratification of data by sex revealed similar patterns of decline in men and women with both pathologies; sex differences in the risk of MCI or dementia progression were not examined. Given the small subset of subjects with both vascular and amyloid pathology stratified by sex (19 women and 26 men), a firm conclusion cannot be drawn about sex differences in the impact of cerebrovascular and amyloid pathologies on cognition and dementia, warranting future studies[82]. For cardiovascular factors, in mixed cohorts, a greater risk of aMCI and multiple-domain aMCI was found among men with type 2 diabetes mellitus than among women with the same condition[83]. In a study published in 2017, onset of or established hypertension in midlife was estimated to increase the risk of dementia among women only, although midlife hypertension was more prevalent among men[84].

One study has shown that the first manifestation of cardiovascular disease differs between men and women[35], which could differentially influence the risk of AD. This study showed that men were more likely than women to develop coronary heart disease as their first cardiovascular event over a follow-up period of 20 years, whereas women were more likely to develop cerebrovascular diseases (stroke, transient ischaemic attack or carotid revascularization) and heart failure as their first manifestation[35]. Given the evidence that vascular disease contributes to cognitive impairment and the risk of AD[85,86], sex differences in the burden and manifestations of cardiovascular and cerebrovascular risk factors, and their impact on AD, deserve further investigation. Several aspects remain particularly unclear: whether the occurrence of vascular risk factors and vascular brain pathology throughout the AD continuum differs between men and women; whether the additive effects of vascular and AD pathologies have different impacts on the risk of AD between the sexes; and whether sex differences in the effects of vascular factors on the risk of AD are due to higher mortality among males than females with these risk factors or whether genetic and/or hormonal differences could play a role.

Depression. Studies have demonstrated that the risk of MCI[87] or conversion from (undefined) MCI to AD is higher among women with depression than among men with depression[74,87]. In a study published in 2017, mild depressive symptoms were associated with a twofold greater risk of aMCI in men but no increase in risk in women, whereas moderate or severe symptoms were associated with a twofold greater risk of aMCI in women but no increased risk in men[88]. Given that depression is more prevalent and severe among women[70], careful consideration must be given to these results. In particular, the smaller size of patient groups of men with depression than that of groups of women with depression might reduce the chances of identifying correlations between depression and AD in men because of insufficient statistical power.

Risk factor profiles and predictors

Sex differences in the prevalence of and susceptibility to AD that result from individual risk factors might result in sex-specific risk factor profiles and predictors. Indeed, the Mayo Clinic Study of Ageing (MCSA) has revealed sex-specific predictors of short-term conversion (median 5 years) from normal cognition to (undefined) MCI: smoking, midlife dyslipidaemia,

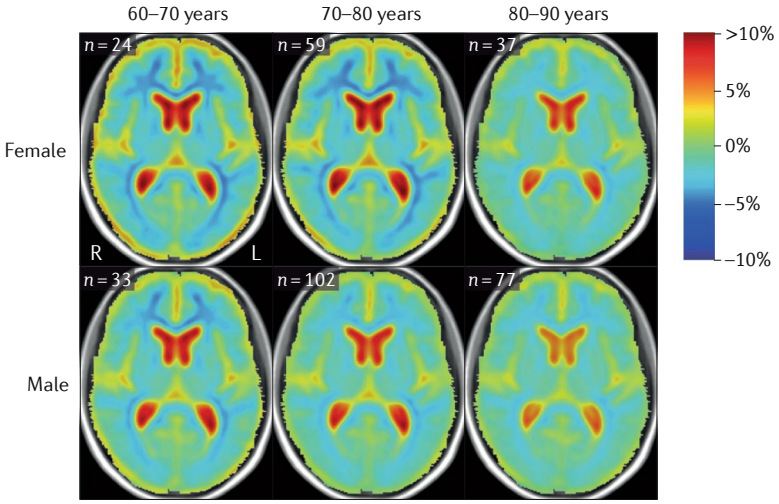

Fig. 1 | **Brain atrophy in women and men with amnestic mild cognitive impairment.** The maps represent average atrophy rates in individuals with amnestic mild cognitive impairment (aMCI) over a 1-year period. MRI data were collected from the Alzheimer's Disease Neuroimaging Initiative cohort and analysed with tensor-based morphometry. Results are stratified by age ranges and sex. Faster atrophy (darker blue) was observed in women than in men. Biomarker-based evidence of prodromal Alzheimer disease was not available in this study. Modified with permission from REF.[63], Elsevier.

diabetes mellitus and hypertension were specific predictors for women, whereas obesity and marital status were specific predictors for men[89]. Stroke, atrial fibrillation, a history of alcohol abuse, a low level of education and self-reported memory concerns were confirmed as equal predictors of AD in both men and women[89]. Similarly, in the Clinical Research Center for Dementia of South Korea (CREDOS) cohort, depression in combination with older age and the *APOE**ε4 allele was a risk factor for conversion from MCI to AD dementia specific to women; severe periventricular white matter hyperintensities and poorer global cognitive function were risk factors for conversion of (undefined) MCI to AD dementia specific to men[74]. In a multicentre prospective study of brain ageing conducted in France, men with (undefined) MCI were more likely than women to have a higher BMI, diabetes mellitus and stroke; women with MCI were more likely than men to have poor subjective health, disability and insomnia[90]. For men, the principal adjusted risk factors for progression to dementia were *APOE**ε4 allele, followed by a low level of education and loss of instrumental activities of daily living. For women, progression was best predicted by loss of instrumental activities of daily living, followed by the *APOE**ε4 allele, a low level of education, subclinical depression and the use of anticholinergic drugs[90]. In the Cache County Study, cardiovascular risk factors for vascular and AD dementia were found to significantly interact with sex; in particular, obesity was a female-specific risk factor for incident AD dementia at a 3-year follow-up[91]. On the basis of these published reports, AD risk factors seem to interact with sex differently according to the stage of the AD continuum examined (for example, conversion from NCI to MCI or AD, and conversion from MCI to AD); however, more data from larger data sets of fully characterized patients will be needed to confirm this possibility.

Sex-specific risk factor profiles could arise as a result of selective survival, whereby men are more likely than women to die from cardiovascular disease in midlife; therefore, those who survive to an older age are likely to have a healthier vascular system than women[92]. As a result, aged men and aged women might represent separate subgroups of patients with specific risk factor profiles that necessitate differential prevention strategies and treatment.

Female-specific risk factors

Some evidence suggests that conditions related to pregnancy and menopause are female-specific risk factors for AD. Pre-eclampsia has been associated with higher risks of cardiovascular disease[93], cognitive impairment later in life[94] and protein misfolding with defective amyloid processing[95], although the link between pre-eclampsia and AD has not been thoroughly investigated. Higher risks of cognitive decline[96,97] and dementia[96] and higher levels of AD neuropathology[97] have been associated with early, surgically induced menopause, indicating that menopause before the age of 40–45 (as a result of ovarian removal, chemotherapy, aromatase inhibitor treatment or premature ovarian insufficiency) represents a female-specific risk factor for AD dementia. Whether additional pregnancy-related hypertensive disorders, such as HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count), are female-specific risk factors for AD remains to be elucidated.

Gender-related risk factors

Socio-economic risk factors for dementia and AD are known to vary according to gender[98] (which differs from sex; BOX 4); for example, in most cultures, a low income and a low level of education are more common among women than men[29,53,99,100]. Another risk factor more commonly associated with women than men is being a primary informal caregiver; 75% of unpaid caregivers for people with chronic debilitating diseases such as dementia are women[101]. The caregiving burden is associated with lower rates of employment[99] and an increased prevalence of psychological AD risk factors, such as sleep disorders and depression, in women caregivers compared with men caregivers[102,103]. Furthermore, compared with men who are caregivers, women caregivers tend to report a higher caregiver burden, and greater caregiver-related role conflict, strain and psychological morbidity[102,104].

Another gender-related factor is that older women are more likely than older men to live alone[105], often because of their longer lifespan. This difference might make enrolment and retention of women in trials more difficult, as they might lack a representative who can provide informed consent on their behalf, a problem that has been identified in the field of stroke[13]. Indeed, in the recently completed phase III trials of the γ-secretase inhibitor semagacestat[106], the β-secretase inhibitor verubecestat[107] and the anti-Aβ monoclonal antibodies solanezumab[108] and bapineuzumab[109], ~50% of participants were women, which does not reflect the

Box 4 | **Definitions of sex and gender**

In this Review, we apply the following definitions to the terms 'sex' and 'gender'. Important to note is that sex and gender, although distinct terms that do not necessarily overlap, strongly interact to shape an individual's body and predisposition to disease.

Sex

Sex refers to the biological characteristics (primary and secondary) that differentiate female from male. Primary sex characteristics are genetically determined morphological traits (such as external genitalia) arising from the expression of sex chromosomes (XX for female and XY for male). Sex also encompasses phenotypic traits that are typical of males and females (such as breast development in women), which are driven by the effects of genetically determined or exogenous gonadal hormones[159].

Gender

Gender refers to the socially determined meaning of being a man or a woman, which shapes the definition of feminine and masculine behaviours, products, technologies, environments and knowledge in a particular society. The social and cultural dimension of gender contains the construction of culturally imposed behavioural and temperamental traits considered appropriate for males and females[160], including gender norms, roles, stereotypes and inequalities, which influence factors such as education, occupation and income[161].

epidemiology of the disease: 60–70% of people affected are women. A gender difference in enrolment and retention in clinical trials might signal a more widespread gender inequality in the care offered; indeed, in the Swedish Dementia Registry, women were less likely than men to receive lumbar punctures and MRI, an effect that was mostly driven by their higher age[110]. Such gender differences in the management of AD deserve careful consideration.

Treatment

Safety and efficacy data from randomized clinical trials of cholinesterase inhibitors and other interventions for dementia have not been systematically analysed by sex. Therefore, whether sex has specific roles in drug responses, the occurrence of adverse events or the modulation of genetic influences on treatment outcomes remains to be elucidated. Furthermore, sex is rarely considered during preclinical drug development, although several sex differences have been observed in animal models of AD (BOX 5). In this section, we discuss the limited evidence for potential sex differences in AD treatment.

Cholinesterase inhibitors

In one study, rivastigmine treatment in the prodromal stages of AD delayed progression from MCI to AD only in women[111], suggesting a specific benefit of early treatment in women. However, in advanced dementia, preclinical studies and clinical studies of treatment with cholinesterase inhibitors have indicated a stronger and more selective benefit for males[112–116]; only one study demonstrated greater efficacy in women[117]. Nevertheless, in another study, survival times after treatment were longer for women than men, suggesting that the sex differences associated with the anti-dementia effects of cholinesterase inhibitors are distinct from those associated with their effects on survival[118]. The observed sex differences might be due to sexual dimorphism of the cholinergic system[119] or to a greater susceptibility of female cholinergic neurons to AD pathology[58,120]. Furthermore, specific interactions of cholinesterase inhibitors with sex hormones[121,122], limbic and/or hypothalamic activity and steroid regulation[123] might affect the overall pharmacokinetics of the drugs between the sexes[124]. Supporting this hypothesis, one study has shown that the effects of donepezil and rivastigmine are modulated by oestrogen receptor 1 (*ESR1*) genotype[117].

In a 2017 systematic review of sex and gender differences in 48 randomized clinical trials of three cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and memantine, including a total of 20,688 patients[113], only two studies investigated sex differences in safety and efficacy; these studies found no effects for donepezil[113]. Similarly, a second systematic study found an almost complete lack of data on sex differences in the adverse effects of cholinesterase inhibitors in clinical trials[125]. As an example, none of 16 clinical trials of donepezil reported sex-stratified analysis of adverse events[125]. The small proportion of studies that examined sex differences shows that a thorough examination of sex differences seen with currently used, second-generation cholinesterase inhibitor treatment remains to be performed[114].

Treatment of neuropsychiatric symptoms

In the National Alzheimer's Coordinating Center (NACC) cohort in the USA and the Medication use and Alzheimer's disease (MEDALZ) cohort in Finland[126], women with AD were more likely than men to be users of antidepressants and anxiolytics. This result has been replicated in a UK-based study in which primary care records of 68,061 community-dwelling dementia patients were analysed[127]. Such differences in pharmacological regimens, which probably stem from the sex-specific psychiatric symptoms described above, might be an additional factor contributing to the clinical heterogeneity between men and women with AD in the context of polytherapy (the use of multiple medications at the same time, which is very common among elderly patients[128]). In fact, different combinations of drugs might result in sex-specific profiles of drug interactions and drug metabolism. The need for sex-dependent dose adjustment due to different safety profiles between men and women could be relevant in clinical practice and in ongoing clinical trials, and this area deserves further investigation.

Interventions under investigation

Few data are available on sex differences in recently completed phase III clinical trials of pharmacological compounds against mild-to-moderate AD. In the case of the γ-secretase inhibitor semagacestat, sex-specific analysis was performed in phase I tolerability studies (in which

Box 5 | **Sex differences in animal models of AD — similarities to clinical data and limitations**

Poorer cognitive performance and earlier onset of deficits in female transgenic (Tg) mice than in male Tg mice have been extensively characterized in the 3xTg line and reported in other models, including the APP–PS1, the APP–PS1–dE9 and the Tg2576 models (REF.[162]).

In contrast to clinical observations, in these models higher amyloid load is observed in aged-matched female APP-Tg mice than in male mice[162–164]. In mice with equal amyloid burden, females had lower cognitive scores and increased neurodegeneration compared with males[165,166]. The greater susceptibility to amyloid pathology in females might be mediated by tau; in fact, double Tg female mice expressing mutated amyloid precursor protein and human tau were found to be more vulnerable to $A\beta^-$ and injury-induced tangle degeneration[167,168]. However, studies of the effect of sex on tau hyperphosphorylation in single tau-Tg models have produced contradictory results, with some reports indicating higher levels of pathology in male Tg mice[169], and others indicating higher levels in females[167,170]. The possibility that sex modulates tau phenotype differently across various tau-Tg models, according to the mutation expressed (P301S[169] and P301L[167,170]), remains to be tested.

A clear effect of sex has been demonstrated in *Apoe**ε4 mice, in which only female mice exhibit cognitive impairments and present with faster rates of decline than males[171,172], possibly owing to a lower density of presynaptic elements[77,173]. However, mice produced by crossing APP-Tg mice with *Apoe**ε4 knock-in mice do not fully reproduce the sex differences seen in human studies, especially with regards to cerebral microbleeds, which are more common among men than women with Alzheimer disease (AD) but more common among female Tg mice[174].

At least two caveats exist when modelling AD-like sex differences with Tg mice. First, the longitudinal effects of sex on brain atrophy might be hard to reproduce in mice that live up to 2–3 years, especially in pure APP models, which lack overt neurodegeneration. Second, menopause, with its gradual progression, altered pattern of production of steroid hormones and complex compensatory changes, does not occur in the normal lifespan of mice. Thus, the choice of animal models for studying AD-like sex differences has to be carefully considered.

no differences in pharmacokinetics and dynamics were observed[129]). However, stratification of efficacy and safety data by sex is absent from the report of phase III results[106]. Similarly, sex differences in pharmacodynamics were studied in the phase II trial of the anti-Aβ monoclonal antibody solanezumab, which indicated slight differences in peripheral volume of distribution between men and women[130]; however, effects of sex were not analysed in the phase III trial[108]. Likewise, to the best of our knowledge, no sex-specific data were reported for phase III clinical trials of the anti-Aβ monoclonal antibody bapineuzumab[109] or the β-secretase 1 inhibitor verubecestat[107].

In all of these studies, men and women were represented equally and balanced across placebo and verum groups. The published data of these trials were sex-adjusted, and the protocols for trials of solanezumab, semagacestat and verubecestat (which were published as supplementary material in the original reports) included subgroup analysis by 'gender'. However, stratification of data by sex and the interaction of sex with the main outcomes have not yet been presented to our knowledge. Adjusting the groups by sex without studying interactions of sex with efficacy and safety can obscure important differences in treatment outcomes between men and women. After careful stratification of data by sex, differences in the efficacy and safety between the sexes became evident for several drugs (including propranolol, zolpidem, digoxin, tissue plasminogen activator, warfarin and aspirin[131]), with high impact in clinical practice[13,132].

Sex differences in efficacy were assessed in a secondary analysis of a phase II clinical trial of intranasal insulin in individuals with aMCI[133]. The analysis revealed a significant overall modulation of treatment outcome by sex: the effects of treatment on delayed story recall were greater for men than for women, and the effects on activities of daily living were greater for women than for men[133].

Several interventional studies of the effects of lifestyle modification on AD prevention have been completed in the past few years, such as the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)[134] and Multidomain Alzheimer Preventive Trial (MAPT)[135] studies. However, as for many studies of pharmacological treatments, no data stratification by sex or analysis of interactions between sex and outcomes are available for these studies to our knowledge.

Sex–genotype interactions in drug response

The treatment effects of some cholinesterase inhibitors are modulated by *APOE* genotype in a sex-dependent manner[112,136]. Among women treated with tacrine, those who carried the *APOE**ε4 allele had a lesser response to treatment than women with other *APOE* genotypes and exhibited minimal difference from the corresponding placebo control group[136]. By contrast, treatment outcome was not affected by *APOE* genotype in men[136].

Sex–*APOE* interactions were also reported in observational and prospective studies that examined the effect of hormone replacement therapy (HRT) on long-term cognitive status and AD risk in postmenopausal women[137]. In studies in which HRT prevented cognitive decline and AD incidence overall, subgroup analysis revealed that *APOE**ε4 women carriers benefited the least from treatment[138–140]. In one study in which HRT was not protective against cognitive decline, cognitive status worsened in *APOE* *ε4 carriers upon HRT[141]. However, no interaction between *APOE* genotype and HRT was found in the Cache County prospective study[142] or in a randomized controlled trial that was specifically designed to test the efficacy of HRT for prevention of cognitive decline in postmenopausal women over the course of 4 years[143], so the available evidence is inconclusive. An incomplete understanding of the interactions between drugs and genotype

Box 6 | **Recommendations for future studies**

Reporting

- Development of best-practice guidelines for analysis and reporting of sex differences.
- Routine stratification of data by sex and analysis of sex interactions (instead of statistically controlling for sex) in preclinical and clinical studies.
- Meta-analysis of sex differences across multiple clinical studies to confirm or refute the sex differences identified in single studies.
- Publication of sex and gender studies with negative results to avoid publication bias.
- Adjust data for cardiovascular, cerebrovascular and pregnancy-related comorbidities.
- Stratify data by menopausal state of women, if possible.

Biomarkers

- Examine the sensitivity of neuropsychological tests for detecting sex-specific cognitive impairments in preclinical Alzheimer disease (AD).
- Perform secondary analysis of existing longitudinal data sets of biomarkers (including tau accumulation via PET tracers and hypometabolism via FDG–PET) and their relationship with clinical symptoms and progression.
- Re-examine cut-off values for diagnostic biomarkers according to sex.

Risk factor profiles

- Study sex-specific predictors in large, longitudinal data sets.
- Design risk scores for AD that take into consideration sex, sex differences in vascular risk factors, sex-specific risk factors and genetic predisposition.
- Consider gender differences in the analysis of possible psychosocial risk factors and moderators.
- Consider sex-specific guidelines for AD prevention.

Clinical trials

- Analysis and publication of safety and efficacy data (outcome and responder analyses) stratified by sex in clinical trial protocols (at all stages).
- Stratification by menopausal state if data are available.
- Sex-specific pharmacogenomic studies.
- Ensure enrolment of women in clinical trials.

Preclinical and drug-development research

- Use male and female experimental animals and ensure studies have sufficient power to report sex-specific differences.
- Use models that mimic AD-like neurodegeneration and menopause if the research question is focused on sex differences.

might explain some of the controversial results of HRT trials (Supplementary Box 2). Future studies are needed to investigate the interaction of *APOE* genotype with AD onset (rather than generic cognitive decline) after treatment with HRT; these studies should involve long-term follow-up and earlier administration of HRT after menopause.

Finally, a study of intranasal insulin in individuals with aMCI has identified a significant sex–genotype interaction that affects treatment response. Among women who received a dose of 40 international units, cognitive performance worsened in *APOE**ε4 carriers, whereas performance in men carriers who received the same dose improved[133].

Conclusions

Sex differences in the clinical phenotype and progression of AD have been reported, indicating that women are protected relative to men at the prodromal phases but later exhibit steeper cognitive decline and higher rates of brain atrophy. Evidence for sex-specific susceptibility to the effects of the *APOE**ε4 allele and to cardiovascular risk factors is mounting, and effects of sex–genotype interactions on responses to HRT and cholinesterase inhibitors have been reported.

Taken together, the cumulative evidence indicates that sex is an important factor in phenotypic variability in AD and should not be neglected in clinical practice or in preclinical studies. The analysis and reporting of sex differences in clinical and preclinical studies need to be substantially improved to generate evidence that is robust enough to inform clinical practice and policy changes (BOX 6).

Although sex differences in any given variable might be small to moderate, the intricate network of sex interactions should be taken into account when designing predictive models for disease prevention, diagnosis and treatment response. We propose that large-scale, population-based screenings — including comprehensive AD risk assessment, biomarker collection and genetic stratification — should be performed. This screening would enable disease models to be generated on the basis of big data analysis that takes into account individual variability, including sex as well as genetic, epigenetic, biomarker, phenotypic, lifestyle and psychosocial characteristics, leading to the identification of subgroups of individuals at risk and patients[144,145] (FIG. 2). In 2017, the APMI and the APMI cohort programme were launched to stimulate such a paradigm shift towards precision medicine and precision pharmacology

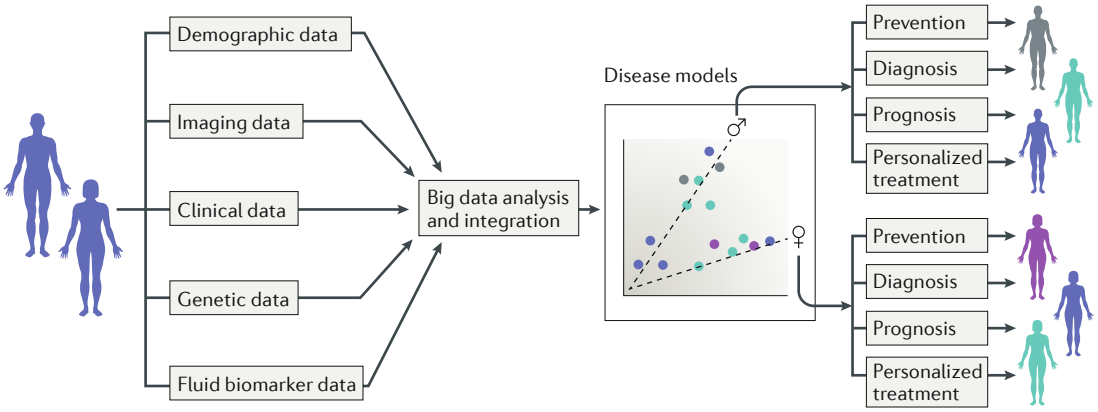

Fig. 2 | **Implications of AD sex differences for clinical practice.** We propose that large-scale population-based screening for the early diagnosis of Alzheimer disease (AD) should be performed, including comprehensive assessment of AD risk factors. Analysis of the big data produced, including neuroimaging, biological, clinical and genetic data, will enable disease models to be generated for the stratification of subsets of individuals at risk. This generation of models will be a crucial step for the implementation of customized, genetically stratified, biomarker-guided precision medicine approaches. Sex will be a crucial factor in the generation of comprehensive and predictive disease models as well as on the roadmap to pave disease-modifying therapies through the precision pharmacology approach for drug research and development[17,175]. Thus, sex-sensitive strategies for prevention, diagnosis, prognosis and treatment of AD are likely to be required in the design of clinical trials and in clinical practice. Colours indicate distinct disease models and the patients that fit these models.

in AD, highlighting the need for tailored interventions that take into consideration the individual's specific biological make-up, including sex[17,146,147].

In the face of high phenotypic variability and a high failure rate of clinical trials, such precision medicine in AD has the potential to improve the power of clinical trials while reducing their sample sizes and associated costs, and the potential to increase diagnostic accuracy.

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Author contributions
M.T.F., E.G. and H.H. conceived the paper. All authors contributed to the literature search and to the writing. M.T.F., E.C. and P.A.C. designed the figures. E.G., H.H., H.D., H.G. and S.M. provided guidance for specific areas of competence and overall paper design. A.C.S. contributed to the paper with her own expertise and points of view; the views and opinions expressed herein are those of the author and do not reflect the view of the Swiss Agency for Therapeutic Products (Swissmedic).

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Review criteria
We searched PubMed and Google Scholar for articles published in English without time limitations with the search terms "Alzheimer AND gender (or sex or women or female)", "Amyloid AND gender (or sex or women or female)", "plaques AND gender (or sex or women or female)", "tau AND gender (or sex or women or female)", "atrophy AND Alzheimer AND gender (or sex or women or female)", "cognitive decline AND gender (or sex or women or female)", "risk AND Alzheimer AND gender (or sex or women or female)", "stroke AND Alzheimer AND gender (or sex or women or female)", "cardiovascular AND Alzheimer AND gender (or sex or women or female)", "cerebrovascular AND gender (or sex or women or female)", "diabetes AND Alzheimer AND gender (or sex or women or female)", "depression AND Alzheimer AND gender (or sex or women or female)" and "APOE AND Alzheimer AND gender (or sex or women or female)". We also searched in the reference lists of identified articles for additional relevant publications. The final reference list was generated by choosing only papers published since 2012. Papers preceding 2012 were included only if considered by the authors to be landmark studies. Papers were selected on the basis of their perceived relevance to the topics covered in this Review.

Supplementary information
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