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Sex Differences in the Genetic Architecture of Alzheimer's Disease

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Abstract

Purpose of Review.—Summarize sex-specific contributors to the genetic architecture of Alzheimer's disease (AD).

Recent Findings.—There are sex differences in the effects of Apolipoprotein E (*APOE*), genes along the *APOE* pathway, and genes along the neurotrophic signaling pathway in predicting AD. Reported sex differences are largely driven by stronger associations among females. Evidence also suggests that genetic predictors of amyloidosis are largely shared across sexes, while sex-specific genetic effects emerge downstream of amyloidosis and drive the clinical manifestation of AD.

Summary.—There is a lack of comprehensive assessments of sex differences in genome-wide analyses of AD and a need for more systematic reporting a sex-stratified genetic effects. The emerging emphasis on sex as a biological variable provides an opportunity for transdisciplinary collaborations aimed at addressing major analytical challenges that have hampered advancements in the field. Ultimately, sex-specific genetic association studies represent a logical first step towards precision medicine.

Keywords

Alzheimer disease; Sex difference; Genetics

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Conflict of Interest

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Human and Animal Rights and Informed Consent

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Introduction

There is a growing emphasis on evaluating sex as a biological variable within models of clinical Alzheimer's disease (AD), including recent charges from both the *Lancet Neurology* Commission and the Society for Women's Health Research Interdisciplinary Network that highlight sex as an essential consideration in theoretical models aimed at moving the field towards more effective prevention and treatment strategies.^{1,2} There are striking sex differences in the clinical manifestation and neuropathological presentation of AD^{3,4} and other neurodegenerative diseases,⁵ including notable differences in the downstream neurodegenerative cascade in response to AD neuropathology.^{4,6} For example, females show a 22-fold increase odds of clinical AD for each additional unit of AD neuropathology observed at autopsy compared to a 3-fold increase in males.^{3,4} Similarly, females show a stronger association between biomarkers of AD neuropathology and cognitive decline when compared to males,⁴ which likely contributes to faster rate of cognitive decline among females with mild cognitive impairment (MCI) compared to males with MCI.^{7,8} Despite these sex differences, the epidemiology of AD is quite complex. Females make up two-thirds of clinical AD patients,⁹ yet as highlighted in a recent commentary¹⁰ and multiple review papers,^{2,11} sex differences in incident AD are small to non-existent depending on the age, time period, and region of the world that is being evaluated. Given the complexities and growing interest, recent review papers have provided detailed overviews on sex differences in the biomarkers, clinical manifestation, and risk factors of AD.^{2,11-13} The goal of this review is to highlight well-established and emerging evidence of sex-specific genetic contributors to clinical AD. While there is a rich history of sex-specific explorations into candidate genes of clinical AD,^{14,15} including large meta-analyses focusing on Apolipoprotein E (*APOE*),^{16,17} only recently has there been an emphasis on exploring sex differences at the genome-wide level. We will highlight sex-specific genetic associations with clinical AD, discuss how the emerging picture of sex-specific genetic contributors shapes our theoretical understanding of AD, and suggest how transdisciplinary collaboration can strengthen the analytical models that are leveraged in large-scale genetic studies of AD to move the field towards more effective interventions.

Apolipoprotein E and a Theoretical Model of the Emergence of Sex-Specific Genetic Contributors to AD

APOE is the strongest genetic risk factor for sporadic AD with the $\epsilon 4$ allele conferring increased risk and the $\epsilon 2$ allele conferring protection. Sex differences in the association between *APOE* $\epsilon 4$ and clinical AD are well established,^{14,17} with female $\epsilon 4$ carriers showing stronger risk for clinical AD than male $\epsilon 4$ carriers, particularly between 55 years and 70 years of age (female-OR=1.43, male-OR=1.07).¹⁷ Similarly, female $\epsilon 2$ carriers are more protected against clinical AD than male $\epsilon 2$ carriers (female-OR=0.51, male-OR=0.71).¹⁷ A recent review paper has provided a comprehensive overview of the complex interactions among *APOE*, sex, and age on clinical AD, and we would refer readers to that review for a thorough analysis of sex differences in *APOE*.¹⁸ Here, we will focus on sex differences in the association between *APOE* and biomarkers of AD neuropathology.

As we have highlighted previously,¹⁶ *APOE* is involved in a large number of signaling cascades relevant to AD pathophysiology, including notable associations with amyloid,^{19,20} tau,²¹ cerebral glucose metabolism,^{22,23} and neurodegeneration.²⁴ Given *APOE*'s established role in A β production²⁵ and clearance²⁶, amyloidosis is thought to be the primary pathway underlying the strong association between *APOE* and clinical AD. However, it is notable that the preponderance of evidence to date suggests there is not a sex difference in the association between *APOE* and amyloid deposition.^{16,19,27-29} In contrast to amyloidosis, work from our group¹⁶ and others³⁰ has highlighted a sex-specific association between *APOE*- ϵ 4 and CSF tau levels, such that the association is stronger among females (standardized- β =0.37) than males (standardized- β =0.20), particularly among amyloid-positive individuals.¹⁶ Further, a recent multi-cohort study of preclinical AD suggests that female *APOE* ϵ 4 carriers who are amyloid positive show more rapid cognitive decline than their male counterparts (stratified coefficients not reported), despite the fact that there was no observed sex difference in the association between ϵ 4 and amyloidosis in this study.³¹ Together, these results suggest that sex differences in the effects of *APOE* may emerge downstream of amyloidosis and drive the clinical manifestation of disease. In support of such a model, there is evidence in the literature of a stronger association between *APOE* ϵ 4 and both glucose hypometabolism and cortical thinning among females compared to males,³² although these sex differences have not been observed consistently depending on the age and disease stage of the included participants.^{4,33,34} Given the large sample sizes needed to explore sex $\times$ *APOE* interactions, there is a pressing need in the field for studies that focus on molecular biomarkers of AD to report *APOE* ϵ 4 and ϵ 2 associations stratified by sex to enable large-scale meta-analyses on the topic.

Although amyloid and tau are central components of AD neuropathology, they are not the only disease processes in which sex differences in *APOE* are observed. Recent evidence has also highlighted sex differences in the association between *APOE* and concomitant disease processes, including neuropsychiatric symptoms^{35,36} and cerebrovascular disease³⁷ among AD patients. Two studies have reported on sex differences in the association between *APOE* ϵ 4 and neuropsychiatric symptoms among individuals with AD,^{35,36} with the most recent work suggesting that the stronger ϵ 4 association with psychotic symptoms among females is driven by Lewy body pathology.³⁵ Previous work has also highlighted a female-specific interaction between *APOE* ϵ 4 and hormone levels on a range of neuropsychiatric symptoms.³⁶ In contrast to the majority of female-predominant *APOE* associations with disease, the *APOE* ϵ 4 association with cerebral microbleeds is actually stronger among males compared to females,³⁷ although the sex $\times$ *APOE* ϵ 4 interaction for cerebral microbleeds has not been observed consistently in the literature.³⁸ A more thorough analysis of *APOE* effects on AD and concomitant disease pathologies, and how those associations differ by sex, would substantially improve our understanding of the molecular pathways that contribute to disease. To summarize the current knowledge, it appears that females show a stronger association between *APOE* and clinical AD, that this association is driven by a difference in a neurodegenerative rather than amyloid process, and that *APOE* effects on cerebrovascular pathways of disease may be stronger among males.

The complex interactions between *APOE* and sex highlight the pressing need to better characterize sex differences across the genome, as similar sex-dependent, age-dependent,

and disease-pathway-dependent genetic effects likely contribute to multiple facets of the neuropathological cascade in AD. Based on the current evidence, we suggest the following hypothetical model of sex-specific genetic contributors to AD pathogenesis (Figure 1) that will guide the rest of this review. Under the proposed framework, the genetic predictors of amyloidosis are largely shared across sexes (signified by the larger middle arrow and smaller top and bottom arrows to the left of amyloid), with *APOE* driving most of the genetic signal. However, among those who are amyloid positive, a sex-specific genetic architecture begins to emerge (signified by the larger top and bottom arrows after amyloid) led by a stronger contribution of *APOE* to clinical AD among females compared to males. In the following sections, we highlight the most recent sex-specific genetic associations with clinical AD and endophenotypes of AD (see Table 1 for summary), suggest where the observed effects may fall within the AD pathological cascade, and recommend some ways that modern statistical approaches can be leveraged to improve sex-specific genetic models of disease.

Female-Specific Genetic Associations

The APOE Signaling Pathway

In addition to sex differences in *APOE* associations, sex interactions have also been observed among genes along the *APOE* signaling pathway including the sortilin related receptor 1 (*SORL1*)^{39,40} which is a receptor for *APOE*, the ATP-binding cassette transporter 1 (*ABCA1*)⁴¹ which is known to interact with *APOE* directly,⁴² and the translocase of outer mitochondrial membrane 40 (*TOMM40*) gene which is located next to *APOE* and has not been disentangled from *APOE* effects (due to linkage disequilibrium) within a sex-specific context.⁴³ In all these cases, genetic variation was more robustly associated with clinical AD among females compared to males, reinforcing the importance of *APOE* signaling among females. Unfortunately, the evidence supporting sex interactions among these *APOE*-related genes is sparse and requires further validation. In particular, efforts to disentangle the sex-specific effects of *TOMM40* from *APOE* would be important given the growing evidence of sex-specific effects of mitochondria in AD pathogenesis.^{44,45} Pathway analysis of *APOE* may also clarify where sex differences begin to emerge along the diverse set of *APOE* signaling molecules. Given evidence that sex differences in *APOE* emerge downstream of amyloidosis, our hypothesis is that these sex-specific effects are also in response to the presence of amyloid rather than drivers of amyloidosis, but additional evidence is needed to confirm this theory.

The Neurotrophic Signaling Pathway

Several genes along the neurotrophic signaling pathway also appear to show female-specific associations with clinical AD. Most notably, polymorphisms within the brain-derived neurotrophic factor (*BDNF*) gene have been shown to be associated with clinical AD among females, but not males,^{15,46,47} which may in part explain the inconsistent reports of *BDNF* associations in the literature. Interestingly, a female-specific association is also observed between *BDNF* polymorphisms and perceptual speed among individuals with normal cognition,⁴⁸ suggesting the sex difference in *BDNF* may not be specific to the AD cascade. In addition to *BDNF*, other genes in the neurotrophic signaling pathway show evidence of sex effects in the pathogenesis of AD, including reelin⁴⁹ (*RELN*, which is regulated by

BDNF)⁵⁰, neurotrophic receptor tyrosine kinase 1⁵¹ (*NRTK1*, which codes the TrkA neurotrophic receptor), and butyrylcholinesterase⁵² (*BCHE*, which is neurotrophically regulated and metabolizes acetylcholine).

Neurotrophic signaling is an interesting candidate pathway for female-specific effects in AD because estrogen directly modulates neurotrophic signaling,⁵³ likely through a direct effect on *BDNF*^{53,54} which includes an estrogen response element. Notably, both *BDNF* and neurotrophic receptor tyrosine kinases co-localize with estrogen receptor β in the brain.⁵⁵ It is possible that the change in estrogen levels in the post-menopausal female brain results in substantial changes in cholinergic signaling, ultimately conferring increased susceptibility to the downstream clinical consequences of AD neuropathology among females. A second possibility is that the neurotrophic pathway acts directly on AD neuropathology in a sex-dependent manner. For example, a number of neurotrophic molecules, including *BDNF*, directly modulate glycogen synthase kinase 3 (*GSK-3*),⁵⁶ and *GSK-3* has direct effects on tangle pathology through the phosphorylation of tau.^{57,58} Evidence also suggests *BDNF* is regulated by *APOE* $\epsilon 4$,⁵⁹ leaving open the possibility that the sex differences in *APOE* and *BDNF* have a common etiology. A better understanding of the neurobiology underlying the sex differences along the *BDNF* and neurotrophic signaling pathway may clarify the mechanism of action and lead to more actionable sex-specific targets for intervention. Ultimately, large-scale sex-stratified genomic analyses are needed to replicate and extend these associations and clarify the role of sex differences in genetic effects along the neurotrophic signaling pathway.

Genetic Predictors of AD Biomarkers

As highlighted above, there are notable sex differences in the association between *APOE* and biomarkers of AD neuropathology, particularly CSF tau. There is also evidence in the literature of other female-specific genetic associations with AD biomarkers. A recent meta-analysis of 3,036 individuals with CSF biomarkers of AD neuropathology identified multiple loci that showed female-specific associations with CSF A β 42 and CSF tau.⁶⁰ In amyloid analyses, polymorphisms in the serpin family B member 1 (*SERPINB1*) gene were associated with CSF A β 42 levels among females, but not among males. Notably, mRNA levels of serpin family B genes measured in postmortem brain tissue also showed a female-specific association with amyloid burden, further validating *SERPINB1* as a sex-specific genetic risk factor. In the same study,⁶⁰ a polymorphism on chromosome 3, proximal to the osteonin gene (*OSTN*), showed a female-specific association with CSF tau levels, which was then validated in an independent sample in relation to an autopsy measure of neurofibrillary tangles.⁶⁰ Most interestingly, when looking at the genes within the cis-region of this variant, two genes showed female-specific associations between mRNA expression levels and tangle pathology, including *OSTN* and claudin 16.

In addition to identifying new genetic loci for AD biomarkers, this sex-stratified meta-analysis demonstrated the value of explicitly testing for sex differences. The chromosome 3 locus had been identified previously when sex was only modeled as a covariate.⁶¹ However, when sex differences were explicitly modeled the magnitude of the association was actually stronger among females (and absent among males), providing an increase in statistical

power. Further, the sex-specific associations provided plausible biological hypotheses of sex-specificity to help narrow the search for functional genes within the loci. The investigation and reporting of sex-stratified genetic effects in large-scale genomic studies of AD may similarly increase statistical power when true sex-specific genetic effects contribute, and provide clues as to which gene candidates in a region are functionally driving associations with AD.

Male-Specific Associations

Although the majority of sex-specific signals identified to date have been among females, a few genes have shown stronger associations with clinical AD in males compared to females including polymorphisms in neurexin 3 (*NRXN3*)⁶² and granulin (*GRN*)⁶³. It is notable that mutations in *GRN* are known to cause frontotemporal dementia (FTD)⁶⁴ and that these granulin forms of FTD are more common among females than males (in contrast to the male-specific association with clinical AD).⁶⁵ Granulin has known roles in sex differentiation,⁶⁶ and is hormonally regulated by both estrogen and androgen,⁶⁷ making it a fascinating candidate gene for further explorations in to sex differences in AD. In addition to genetic effects, male-specific associations have also been observed in proteomic analyses for a number of proteins coded by AD risk genes including TREM2,⁶⁸ insulin-like growth factor-II (IGF-II),⁶⁹ and proteins in the renin-angiotensin system (RAS).⁷⁰ Overall, the evidence for male-specific associations remains weak, perhaps because studies have not systematically evaluated effects in a sex-stratified manner. Further work may clarify whether genetic drivers of concomitant pathologies, like cerebrovascular disease and TDP-43, have a sex-specific role in disease, but current autopsy studies do not support such a conclusion.⁵

Epidemiological Considerations in Sex-Specific Genetic Associations

Work on sex differences in the genetic architecture of AD is relatively underdeveloped, and this topical area is ripe for transdisciplinary collaborations to help improve statistical models. As we have highlighted previously,¹⁶ a major challenge in understanding sex differences in AD and other age-related phenotypes is the known differences in life expectancy between males and females. Specifically, females are more likely than males to survive to older adulthood⁷¹ when most AD cases occur, and many of the risk factors for mortality are also risk factors for clinical AD. Research on AD is commonly restricted to individuals who survive to late life, and this selection process has the potential to induce a special case collider-stratification bias called survival bias.^{72,73} Collider-stratification bias refers to non-causal associations between two variables induced by conditioning on a factor influenced by both variables (called a “collider”). In survival bias, survival to late-life is the collider, and conditioning on survival to old age has the potential to induce associations between genetic factors and AD, even if the genetic factors have no causal effects on AD.

Survival bias is problematic in the study of genetic predictors of AD because spurious associations can be introduced when a gene has pleiotropic effects on risk for mortality and AD. Because of the differential survival distributions for males and females, this could result in different associations between genetic factors and AD-related outcomes in males and females, even if no true sex-differences in genetic effects on AD are present. *APOE* provides

an interesting example, although results in the literature are somewhat mixed.⁷⁴⁻⁷⁶ There are notable sex differences in the association between *APOE* $\epsilon 2$ and $\epsilon 4$ with mortality, with $\epsilon 4$ increasing the risk of mortality among men and $\epsilon 2$ decreasing the risk of mortality among women.⁷⁴ Similarly, the $\epsilon 2$ allele is associated with increased odds of age-adjusted prevalent cardiovascular disease (CVD) among males, while $\epsilon 2$ is associated with reduced odds of CVD among females.⁷⁷ Together, these findings leave open the possibility that *APOE* has an association with midlife vascular mortality in males that could contribute to the observed sex differences in associations between *APOE* and AD in late life. This example highlights the complicated interactions between sex, *APOE*, cardiovascular disease, AD, and mortality accentuating the need for studies and statistical approaches that can disentangle these important factors. Researchers have only recently begun estimating⁷² and accounting for⁷⁸ the potential magnitude of survival bias in studies of cognitive aging. Ultimately, similar sophisticated approaches will be needed to better distinguish sex differences in survival from sex differences in the genetic predictors of AD, and transdisciplinary collaborations will be key in ensuring statistical approaches are guided by the emerging knowledge about AD genetics.

Representation in research studies is also critical to ensure genetic findings and applications generalize to all populations. While there has been a growing emphasis on enrolling and analyzing genetic data from diverse populations in studies of AD,⁷⁹⁻⁸³ there has been no systematic integration of sex differences into those analyses. To date, non-European ancestry AD GWAS have simply covaried for sex without explicitly modeling sex interactions or performing sex-stratified analyses. There are notable differences in genetic associations with clinical AD across racial and ethnic groups, such as *APOE* which shows a weaker association with clinical AD among Caribbean-Hispanic and African American populations compared to European ancestry populations.⁸⁰ It is quite possible that there are also sex differences in clinical AD risk loci that vary across racial and ethnic groups. Larger studies that explicitly model sex differences will be needed to elucidate the extent to which sex differences in the genetic architecture of AD differ across racial and ethnic groups.

The Road Ahead: Moving from Sex Considerations to Personalized Interventions

Sex-specific genetic associations can provide new information about the molecular drivers of disease, but sex differences also have important implications for clinical intervention. As genomic technologies have become more clinically accessible, there has been a move towards integrating genetic information into treatments that are tailored toward the individual. While substantial progress has been made in individualized therapeutic approaches for cancer,⁸⁴ there is a growing emphasis on integrating genomic information into intervention strategies for common, complex traits like AD.⁸⁵ The interface of sex as a biological variable and large-scale genomics represents a unique nexus to take the first step towards precision interventions. As one example, there have been reports of sex differences in the effectiveness of cholinesterase inhibitors in treating the symptoms of AD,⁸⁶ and some reports of sex-by-*APOE* interactions on the efficacy of intranasal insulin treatments.⁸⁷ Yet, there is a striking lack of data from randomized controlled trials reporting sex stratified or

sex differences in clinical AD treatment efficacy, and very little work devoted to disentangling the therapy-modifying effects of these basic known contributors to the clinical manifestation of disease.⁸⁸ The analysis and reporting of sex by gene interactions in randomized clinical trials could be implemented immediately and could more rapidly move the field toward precision treatments.

In addition to the potential for pharmacogenomic applications of sex-specific genetic predictors of disease, there is also growing evidence of the potential clinical utility of polygenic risk scores (PRS).⁸⁹ While PRS for AD are not ready to be used in clinical decision making, they have been associated with numerous AD endophenotypes,⁹⁰ including statistical associations above and beyond the strong contribution of *APOE*.^{91,92} More sophisticated calculations of polygenic scores have increased their sensitivity and potential clinical utility,⁹³⁻⁹⁵ particularly in identifying cognitively normal individuals who are at heightened risk of future cognitive decline. Yet, sex-specific genetic risk factors have not been incorporated into polygenic scores to date, likely due to the lack of sex-stratified summary statistics available for analysis. Integrating sex into large scale genomic analyses of AD and calculating disease and endophenotype polygenic scores in a sex-specific manner is likely to increase PRS utility and move the field towards precision screening and intervention. While tremendous progress has been made in precision interventions, applications of sex as a fundamental contributor to individual variability in AD risk, progression, and treatment response has lagged behind. As a field, we need to actively prioritize sex considerations in our analytical models and report summary level data in a sex-stratified manner that will maximize their utility.

Conclusions

The genetic architecture of AD is complex, and the biological contribution of sex to genetic associations with AD appears to vary over the course of the neuropathological and clinical cascade. There is strong evidence of a sex difference in the association between *APOE* and clinical AD, and growing evidence that this sex difference is due to molecular drivers downstream of amyloidosis. Although there is some evidence of female-specific and male-specific genomic contributors to AD in the literature, there is a dearth of comprehensive genome-wide analyses that systematically evaluate sex differences. A major barrier towards the characterization and interpretation of sex differences is the known threat of survival bias, which presents an important opportunity for transdisciplinary collaborations that can provide the proper theoretical framework to analyze and interpret sex-specific genetic predictors of AD in older adulthood. Ultimately, a renewed focus on sex as a biological variable in genomic models, and an increased emphasis as investigators and reviewers on the inclusion of sex considerations in analytical models, will help the field move toward precision screening, prognosis, and treatment.

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*Important Recent Publication, **Very important Recent Publication

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Figure 1: Hypothesized Emergence of Sex-Specific Drivers of AD.

We posit that sex differences in the genetic drivers of AD largely emerge downstream of amyloidosis. Top Arrow: Female-specific genetic effects. Middle Arrow: Shared genetic effects; Bottom Arrow: Male-specific genetic effects. Width of Arrow: Effect size.

Table 1.**Summary of Sex-Specific Genetic Associations with AD**

Gene	Effects in Males	Effects in Females
<i>APOE</i>	$\epsilon 4$ allele is associated with cerebral microbleeds. ³⁷	$\epsilon 4$ allele carriers show stronger risk for sporadic AD, ^{7,10} higher CSF tau, ^{9,23} and faster cognitive decline in amyloid-positive carriers ²⁴ ; $\epsilon 2$ allele carriers show enhanced protection against AD ¹⁰
<i>SORL1</i>	Polymorphism associated with protected cognitive performance before the age of 75. ³⁵	Variants associated with late-onset AD. ^{35,36}
<i>ABCA1</i>		Variants associated with 1.75-fold higher risk for developing AD. ³⁷
<i>TOMM40</i>		Polymorphism associated with cognitive aging. ³⁹
<i>BDNF</i>		Polymorphisms associated with AD. ^{11,42,43}
<i>SERPINB1</i>		Polymorphisms negatively correlated with A β 42 levels. ⁵⁶
<i>OSTN</i>		Higher expression in brain is associated with decreased tau tangle pathology. ⁵⁶
<i>CLDN16</i>		Higher expression in brain is associated with decreased tau tangle pathology. ⁵⁶
<i>NRXN3</i>	Polymorphism associated with AD. ⁵⁸	
<i>GRN</i>	Polymorphisms associated with AD. ⁵⁹	
<i>TREM2</i>	Average higher levels of soluble TREM2 (sTREM2) in CSF; increased CSF sTREM2 is positively correlated with CSF tau and p-tau. ⁶⁴	
<i>IGF II</i>	IGF-II levels were elevated in CSF of AD patients compared to control subjects. ⁶⁵	