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RESEARCH ARTICLE

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Sex differences in the confounders influencing the relationships linking socioeconomic factors and cognitive performance with family history of Alzheimer's disease and related dementias

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Abstract

INTRODUCTION: Limited information is available regarding sex differences in the relationship of socioeconomic status and cognitive performance with Alzheimer's disease and related dementias (ADRD) family history.

METHODS: Leveraging the UK Biobank ($N = 448{,}100$) and All of Us Research Program ($N = 240{,}319$), we conducted observational and genetically informed analyses to test the sex-specific associations of socioeconomic factors and cognitive performance with ADRD and its family history.

RESULTS: Observational and genetically informed analyses highlighted that higher socioeconomic status and cognitive performance were associated with reduced ADRD and sibling–ADRD family history. Conversely, these were associated with increased parent-ADRD family history. Sex differences in these relationships were also identified. Additionally, although their sample size was limited, population minorities showed different patterns with respect to ADRD versus parent–ADRD family history.

DISCUSSION: This study highlights sex differences in the misestimated associations of ADRD family history that appear to be related to socioeconomic factors and cognitive performance.

KEYWORDS
Alzheimer's disease and related dementias, cognitive performance, family history, Mendelian randomization, polygenic risk scores, socioeconomic factors

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Highlights

- Alzheimer's disease family history is differently linked to socioeconomic factors.
- Observational and genetic analyses highlighted sex differences in these dynamics.
- Cause–effect relationships could contribute to biases in Alzheimer's disease assessment.

1 | BACKGROUND

With the increase of the aging population worldwide, Alzheimer's disease and related dementias (ADRD) are one of the most challenging diseases of this century, because of its heavy medical and economic burden on individuals and society.[1] In 2021, an estimated 56.9 million people suffered from ADRD, indicating an age-standardized prevalence rate of 694.0 per 100,000 population.[2] It is estimated that ADRD cases in preclinical, prodromal, and dementia stages comprised 416 million individuals, accounting for 22% of the total population aged ≥ 50.[3] Annually, 1.95 million deaths were attributed to ADRD (25.2 per 100,000 population),[2] which was the eighth leading cause of death worldwide.[4] The estimated global economic burden of ADRD has reached $2.8 trillion in 2019.[5] This figure was predicted to increase to $16.9 trillion in 2050,[5] with the prevalence number expected to triple.[1]

ADRD is attributable to biological and environmental influences, including genetic, psychosocial, cardiometabolic, and lifestyle factors.[6–18] Among these, positive socioeconomic factors (e.g., higher income level and educational attainment) are demonstrated to be protective against ADRD.[6,9,11,16,17] As a prodromal symptom, cognitive decline is a good predictor of clinical ADRD onset among older adults, independent of education and intelligence.[19–22] However, in research on late-onset diseases such as ADRD, one difficulty is that even prospective studies with large sample sizes may not observe enough clinically diagnosed cases for robust analysis, due to the low incidence in the middle-aged population.[23] Therefore, researchers used ADRD family history as a proxy of ADRD to improve statistical power. For instance in genome-wide association studies (GWASs) conducted in participants younger than ADRD's expected age of onset.[24–26] Several analyses reported that ADRD family history is associated with reduced cognitive performance.[27–31] However, a genetically informed study recently highlighted that investigating ADRD family history as a proxy for ADRD can introduce biases due to uncorrected survival bias and non-random participation in parental illness surveys.[32] Moreover, in most studies, ADRD family history is based on self-reported information, which can introduce additional biases.[33,34] This raises important issues related to the dynamics linking socioeconomic factors and cognitive performance to ADRD family history. Additionally, because of the known sex differences in ADRD risk[35] and social determinants of health,[36] it is crucial to assess whether these relationships may be influenced by sex-specific effects, differentiating the assessment of ADRD family history in females and males.

This study examined sex-specific associations of socioeconomic factors and cognitive performance with ADRD and ADRD family history to understand possible confounders and biases affecting the latter differently in females and males. Specifically, we conducted observational and genetically informed analyses in two independent cohorts comprising a total of 688,419 participants and used multiple data sources to investigate sex-specific confounders contributing to the different association patterns observed between ADRD versus its family history.

2 | METHODS

2.1 | Study design

We investigated the associations of socioeconomic factors and cognitive performance with ADRD and its family history by leveraging multiple analytical approaches (Figure 1). First, we conducted an observational analysis using generalized linear regression models to estimate sex-specific socioeconomic factors, cognitive performance, and apolipoprotein E (*APOE*) ε4 allele associations with ADRD and its family history (sibling, mother, and father). To assess the effect of possible confounders in associations observed, we performed sensitivity analyses controlling for other factors such as parental death and parental age at death. Using genetic data, we further investigated the associations related to mother– and father–ADRD by performing polygenic risk score (PRS) and bidirectional one-sample Mendelian randomization (MR) analyses. Sensitivity analyses were also performed in the genetically informed investigations to assess the effect of possible confounders.

2.2 | Data source

Phenotypic and genetic data were obtained from the UK Biobank (UKB)[37] and the All of Us Research Program (AoU).[38] UKB is a large population-based cohort including information regarding health conditions and genetic variation from participants recruited in the United Kingdom.[37] AoU is a prospective, nationwide cohort study aiming to recruit > 1 million participants in the United States.[38] The sample investigated in the present study (Table 1) included 448,100 UKB participants (54% females; mean age at recruitment 56.7 years; median year of birth 1950) and 240,319 AoU participants (AoU Controlled Tier

Dataset of Curated Data Repository version 7;[39] 61% females, mean age at recruitment 54.5 years).

2.3 | ADRD

In UKB, ADRD was assessed with "first occurrence" information derived from combining primary care, hospital admission, death register, and self-reported data. Individuals with a first occurrence date of the ICD-10 (Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems) G30 (Field ID: 131036) and F00 (Field ID: 130836) codes were considered ADRD cases. Sibling–, mother–, and father–ADRD were assessed through the UKB touchscreen questionnaire considering the "Alzheimer's disease/dementia" reply to the following items, "Have any of your brothers or sisters suffered from any of the following illnesses?" (Field ID: 20111), "Has/did your mother ever suffer from?" (Field ID: 20110), and "Has/did your father ever suffer from?" (Field ID: 20107).

In AoU, using electronic health record data standardized by the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM), ADRD (Concept ID: 378419) was identified from the domain "conditions."[40] Information regarding ADRD family history was collected using two-level self-reported survey questions. In the first question, participants were asked: "Have you or anyone in your family ever been diagnosed with the following brain and nervous system conditions? Think only of the people you are related to by blood. Select all that apply" (Participant-provided information, Concept ID: 43529272). If "Dementia (includes Alzheimer's, vascular, etc.)" was selected from the optional diseases, then the second question was applied: "Including yourself, who in your family has had dementia (includes Alzheimer's, vascular, etc.)? Select all that apply" (Concept ID: 836807). Participants' choices of "sibling," "mother," and "father" were used to define sibling–, mother–, and father–ADRD, respectively.

2.4 | Socioeconomic factors and cognitive performance

In UKB, socioeconomic factors were assessed through self-reported information related to material deprivation, household income, and educational attainment. Specifically, material deprivation was assessed using the Townsend Deprivation Index (Field ID: 22189), which combines information regarding unemployment, non–car ownership, non-home ownership, and household overcrowding for any geographical area.[41] This was calculated for each UKB participant based on the preceding national census output areas in which their postcode was located. Average total household income before tax (Field ID: 738) was assessed in the touchscreen questionnaire item "What is the average total income before tax received by your HOUSEHOLD?" This question provided five answer options: less than £18,000, £18,000 to £30,999, £31,000 to £51,999, £52,000 to £100,000, and greater than £100,000. UKB educational attainment was derived from three touchscreen questionnaire items: "At what age did you complete your continuous full-time education?" (Field ID: 845), "In which year did you first finish full-time education (school, college, or university)?" (Field ID: 22501), and "Which of the following qualifications do you have?" (Field ID: 6138). With respect to cognitive performance, we leveraged information from the UKB cognitive function assessment considering two phenotypes with available GWAS data and single nucleotide polymorphism (SNP)-based heritability $Z > 4$ in both sexes (Table S1 in supporting information): maximum digits remembered correctly (Field ID: 4282) and fluid intelligence score (Field ID: 20016; a sum of the number of correct answers to 13 fluid intelligence questions).[22,42] A description of the questions and tasks used in the UKB assessment is available at https://biobank.ndph.ox.ac.uk/showcase/.

In AoU, household income (Concept ID: 1585375) was determined through the survey question "What is your annual household income from all sources?" with nine answer options: "Less than $10,000", "$10,000–$24,999", "$25,000–$34,999", "$35,000–$49,999", "$50,000–$74,999", "$75,000–$99,999", "$100,000–$149,999", "$150,000–$199,999", and "$200,000 or more." Educational attainment (Concept ID: 1585940) was assessed via the survey question "What is the highest grade or year of school you completed?" with eight options: "Never attended school or only attended kindergarten,"

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using PubMed to search studies investigating socioeconomic factors and cognitive performance with respect to Alzheimer's disease and related dementias (ADRD) and its family history. In most studies, higher socioeconomic status and cognitive performance have been inversely linked to ADRD, yet the relationship between cognitive performance and family history of ADRD remains unclear. We did not identify any previous analyses regarding sex differences in socioeconomic factors and cognitive performance relationships with ADRD and ADRD family history.
2. **Interpretation**: This study applied observational and genetically informed analyses, observing that higher socioeconomic status and cognitive performance were related to reduced ADRD and sibling–ADRD. This relationship appears to be inverse for parent ADRD. These associations also present differences when considering probands and parents' sex. Overall, these findings highlight how ADRD family history can be affected by dynamics related to reporting, recall, and survival confounders.
3. **Future directions**: Our results have substantial implications for ADRD studies that leverage ADRD family history as a disease proxy or as a characteristic to recruit informative participants. Further studies can build on these findings to develop analytical designs that control and correct for the confounders related to family history of ADRD-related.

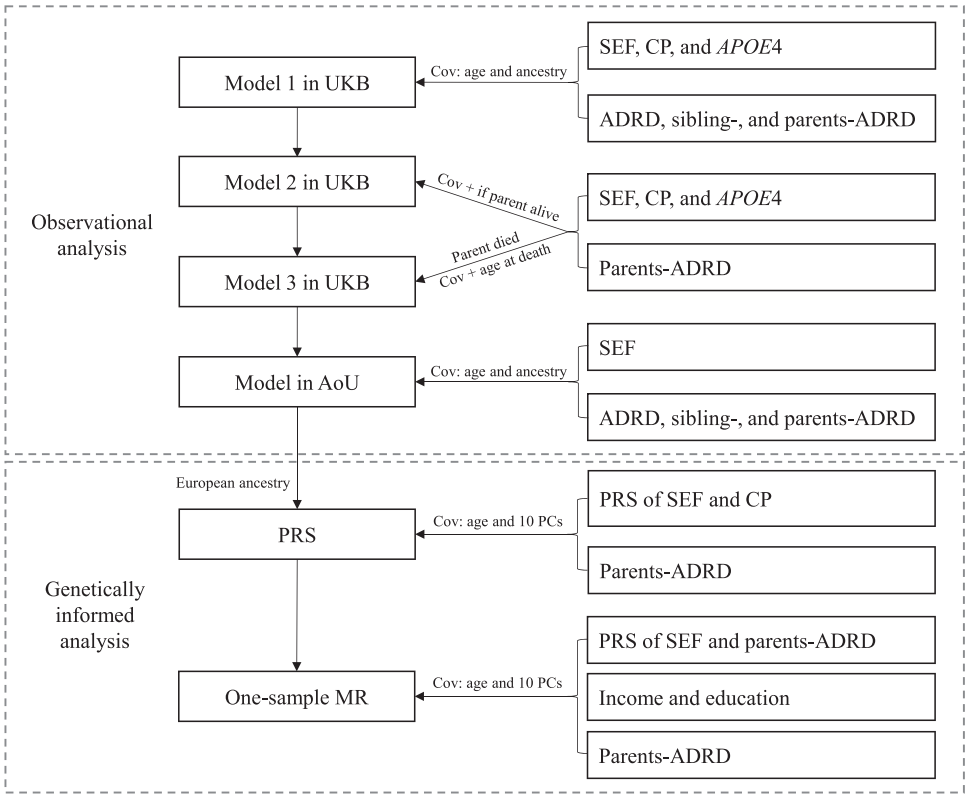

FIGURE 1 Flowchart of the analyses performed in the present study. ADRD, Alzheimer's disease and related dementias; AoU, All of Us Research Program; Cov, covariates; CP, cognitive performance; MR, Mendelian randomization; PC, principal component; PRS, polygenic risk score; SEF, socioeconomic factors; UKB, UK Biobank

"Grades 1 through 4 (Primary)," "Grades 5 through 8 (Middle school)," "Grades 9 through 11 (Some high school)," "Grade 12 or GED (High school graduate)," "1–3 years after high school (Some college, Associate's degree, or technical school)," "College 4 years or more (College graduate)," and "Advanced degree (Master's, Doctorate, etc.)." No cognitive assessment is currently available in AoU.

2.5 | Genetic data

We leveraged individual-level genetic data available from UKB and AoU. UKB genetic information has been described previously.[37] Briefly, UKB participants were genotyped using a custom Axiom array and imputed using the Haplotype Reference Consortium reference panel.[37] In our analysis, we used quality control criteria and ancestry assignments performed by the Pan-UKB initiative.[43] AoU genetic information was extracted from whole-genome sequencing data using the ACAF threshold callset.[44] Quality control criteria and ancestry inference have been described elsewhere.[45] Based on the dataset provided by AoU, we also removed variants with minor allele frequency (MAF) < 1%, call rate < 0.95, and Hardy–Weinberg equilibrium $P < 1 \times 10^{-6}$.

APOE genotypes were defined considering rs429358 and rs7412 SNPs as previously described.[46] In our analysis, individuals were stratified into *APOE* ε4 carriers and non-carriers based on their genotypes.

To further investigate relationships among ADRD family history, socioeconomic factors, and cognitive performance, we also used sex-stratified genome-wide association statistics previously calculated using the UKB cohort. Details regarding the quality control and the association analysis are available at https://github.com/Nealelab/UK_Biobank_GWAS. Briefly, the genome-wide association analysis was conducted using regression models available in Hail (available at https://hail.is/) and including the top-20 within-ancestry principal components (PCs), age, and age^2 as covariates. Because of the limited sample size available for other ancestry groups, we used genome-wide data generated from the analysis of 361,194 unrelated individuals of European descent.

2.6 | Observational analysis

We applied logistic regression models to UKB and AoU phenotypic data to investigate socioeconomic factors and cognitive performance associations with ADRD and its family history (sibling, father, and mother) in females and males. In UKB, three models were considered. In Model 1, we estimated sex-specific associations of socioeconomic factors, cognitive performance, and *APOE* ε4 status with ADRD and its family history, adjusting for age and genetically inferred ancestry. In Model 2, we assessed the same sex-specific relationships with father– and mother–ADRD, adjusting for age, genetically inferred ancestry,

TABLE 1 Characteristics of female and male participants available from UKB and AoU.

Characteristics	Overall	Female	Male
UKB	***n* = 448,100**	***n* = 242,199**	***n* = 205,901**
Age at recruitment, mean (SD), year	56.7 (8.1)	56.5 (8.0)	56.9 (8.2)
Ancestry, *n* (%)			
European	426,884 (95)	230,871 (95)	196,013 (95)
African	6751 (2)	3980 (2)	2771 (1)
Admixed-American	996 (< 1)	645 (< 1)	351 (< 1)
CSA	9064 (2)	4176 (2)	4888 (2)
East Asian	2783 (< 1)	1836 (< 1)	947 (< 1)
Middle Eastern	1622 (< 1)	691 (< 1)	931 (< 1)
Father–ADRD, *n* (%)	20,880 (5)	11,696 (5)	9184 (5)
Mother–ADRD, *n* (%)	39,624 (9)	22,466 (10)	17,158 (9)
Sibling–ADRD, *n* (%)	2662 (< 1)	1528 (< 1)	1134 (< 1)
ADRD, *n* (%)	4045 (< 1)	2111 (< 1)	1934 (< 1)
*APOE ε*4 carriers, *n* (%)	128,296 (29)	69,370 (29)	58,926 (29)
Household income, *n* (%)			
Less than £18,000	87,039 (23)	49,398 (25)	37,641 (21)
£18,000 to £30,999	98,218 (26)	53,005 (27)	45,213 (25)
£31,000 to £51,999	100,163 (26)	50,794 (25)	49,369 (27)
£52,000 to £100,000	77,322 (20)	36,975 (19)	40,347 (22)
Greater than £100,000	20,123 (5)	9378 (5)	10,745 (6)
Age completed full time education, mean (SD), year	16.7 (2.3)	16.7 (2.1)	16.7 (2.5)
Fluid intelligence score, mean (SD)	6.0 (2.2)	5.9 (2.1)	6.1 (2.2)
AoU	***n* = 240,319**	***n* = 145,563**	***n* = 94,756**
Age at recruitment, mean (SD), year	54.5 (17.0)	53.2 (16.9)	56.5 (16.9)
Ancestry, n (%)			
European	130,813 (54)	78,248 (54)	52,565 (55)
African	55,500 (23)	31,977 (22)	23,523 (25)
Admixed-American	44,273 (18)	29,567 (20)	14,706 (16)
CSA	3177 (1)	1691 (1)	1486 (2)
East Asian	5641 (2)	3590 (2)	2051 (2)
Middle Eastern	915 (< 1)	490 (< 1)	425 (< 1)
Father–ADRD, *n* (%)	5449 (5)	3612 (5)	1837 (5)
Mother–ADRD, *n* (%)	8782 (8)	5706 (8)	3076 (9)
Sibling–ADRD, *n* (%)	1126 (1)	742 (1)	384 (1)
ADRD, *n* (%)	574 (< 1)	313 (< 1)	261 (< 1)
Household income, *n* (%)			
Less than $10,000	35,339 (19)	19,606 (17)	15,733 (21)
$10,000 to $24,999	28,138 (15)	17,439 (15)	10,699 (14)
$25,000 to $34,999	16,908 (9)	11,001 (10)	5907 (8)
$35,000 to $49,999	18,445 (10)	11,974 (10)	6471 (9)
$50,000 to $74,999	24,454 (13)	15,556 (14)	8898 (12)
$75,000 to $99,999	18,828 (10)	11,603 (10)	7225 (10)
$100,000 to $149,999	23,144 (12)	13,657 (12)	9487 (12)
$150,000 to $199,999	10,798 (6)	6261 (5)	4537 (6)
$200,000 or more	14,891 (8)	7917 (7)	6974 (9)

(Continues)

TABLE 1 (Continued)

AoU	*n* = 240,319	*n* = 145,563	*n* = 94,756
Education attainment, *n* (%)			
None or kindergarten	367 (< 1)	232 (< 1)	135 (< 1)
Grades 1 through 4	2226 (< 1)	1532 (1)	694 (< 1)
Grades 5 through 8	5840 (2)	3701 (3)	2139 (2)
Grades 9 through 11	15,506 (7)	8492 (6)	7014 (8)
Grade 12 or General Educational Development	48,483 (21)	27,150 (19)	21,333 (23)
1–3 years after high school	60,537 (26)	39,055 (27)	21,482 (23)
College 4 years or more	52,976 (23)	33,707 (24)	19,269 (21)
Advanced degree	49,139 (21)	29,019 (20)	20,120 (22)

Abbreviations: ADRD, Alzheimer's disease and related dementias; AoU, All of Us Research Program; *APOE*, apolipoprotein E; CSA, Central/South Asian; UKB, UK Biobank; SD, standard deviation.

and parental death (father's death [Field ID: 1797] for father–ADRD and mother's death [Field ID: 1835] for mother–ADRD). In Model 3, the sex-specific association analysis was restricted to participants whose parent died (participants whose father died in father–ADRD analysis and participants whose mother died in mother–ADRD analysis) and included age, genetically inferred ancestry, and parental age at death (father's age at death (Field ID: 1807) for father–ADRD and mother's age at death (Field ID: 3526) for mother–ADRD). Bonferroni correction was applied to account for the number of tests performed ($P < 8.93 \ \varepsilon \ 10^{-4}$ in Model 1 and $P < 1.79 \ \varepsilon \ 10^{-3}$ in Models 2 and 3). Variables surviving multiple testing correction were then entered into a multivariable model to estimate whether their sex-specific effects were independent of each other. Additionally, we estimated sex differences by comparing sex-specific association statistics using the *Z* test.

In AoU, we tested the sex-specific association of household income and educational attainment with ADRD and sibling–, father–, and mother–ADRD including age and genetically inferred ancestry as covariates. Because no information regarding parental death and parental age at death is available in AoU, we could not consider other models. However, because AoU is an ancestrally diverse cohort, we conducted an ancestry-stratified analysis to examine whether ADRD and family-history association patterns were consistent across populations. In both cross-ancestry and ancestry-stratified analyses, Bonferroni correction was applied to account for the number of tests performed. All variables were subsequently entered into a multivariable regression model to assess their independent effects.

Because of the sample size differences between UKB and AoU cohorts and among the ancestry groups investigated, we conducted a statistical power analysis, using the Demidenko procedure with variance correction.[47]

We performed additional analyses to assess further the dynamics contributing to the differential association patterns observed with respect to ADRD and its family history in females and males. Because educational attainment and household income can reflect only part of the complexity related to socioeconomic factors, we investigated sex-specific relationships of ADRD and family history of ADRD with additional dimensions, which included occupational status (UKB Field ID: 6142; AoU Concept ID: 1585952), deprivation index (UKB Field ID: 22189; AoU reference[48]), psychosocial stress (UKB Field ID: 130910; AoU Concept ID: 440083), and traumatic experiences (UKB Field IDs: 20488 and 20523; AoU Concept ID: 4297375). Because of the impact of blood pressure on ADRD risk, we also included essential hypertension (UKB Field ID: 131286; AoU Concept ID: 320128) in our follow-up analyses.

To investigate whether the results observed in the observational and genetically informed analyses were driven by other factors, we re-calculated the effect of household income, educational attainment, fluid intelligence score, and Townsend Deprivation Index on ADRD family history controlling for private health-care use (Field ID: 4674), fluid intelligence scores (UKB Field ID: 20016), and parental age (mother's age, UKB Field ID: 1845; father's age, UKB Field ID: 2946). Additionally, we estimated the proportion of participants with only younger siblings (UKB Field ID: 5057) across income subgroups, cognitive levels, and deprivation index brackets. These analyses were limited to the UKB cohort, because of the larger sample size available.

2.7 | Polygenic risk scoring

PRS analysis was used to investigate sex-specific associations of socioeconomic factors and cognitive performance with parent–ADRD. Specifically, we derived PRSs from previously calculated UKB genome-wide association statistics (see section 2.5) and then tested them with respect to parent–ADRD in AoU. As mentioned above, this analysis was limited to European-descent individuals, because of the limited sample size available for other population groups. PRSs were estimated using Polygenic Risk Score–Continuous Shrinkage (PRS-CS)[49] and UKB European-ancestry participants as the linkage disequilibrium reference panel.[50] Then, PRS-CS weights were used to estimate individual PRSs for AoU participants of European descent via PLINK 1.9–score command.[51] PRS associations were estimated via logistic regression with the PRS as the independent variable, mother– or father–ADRD as the dependent variable, and age and the top 10 within-ancestry PCs as

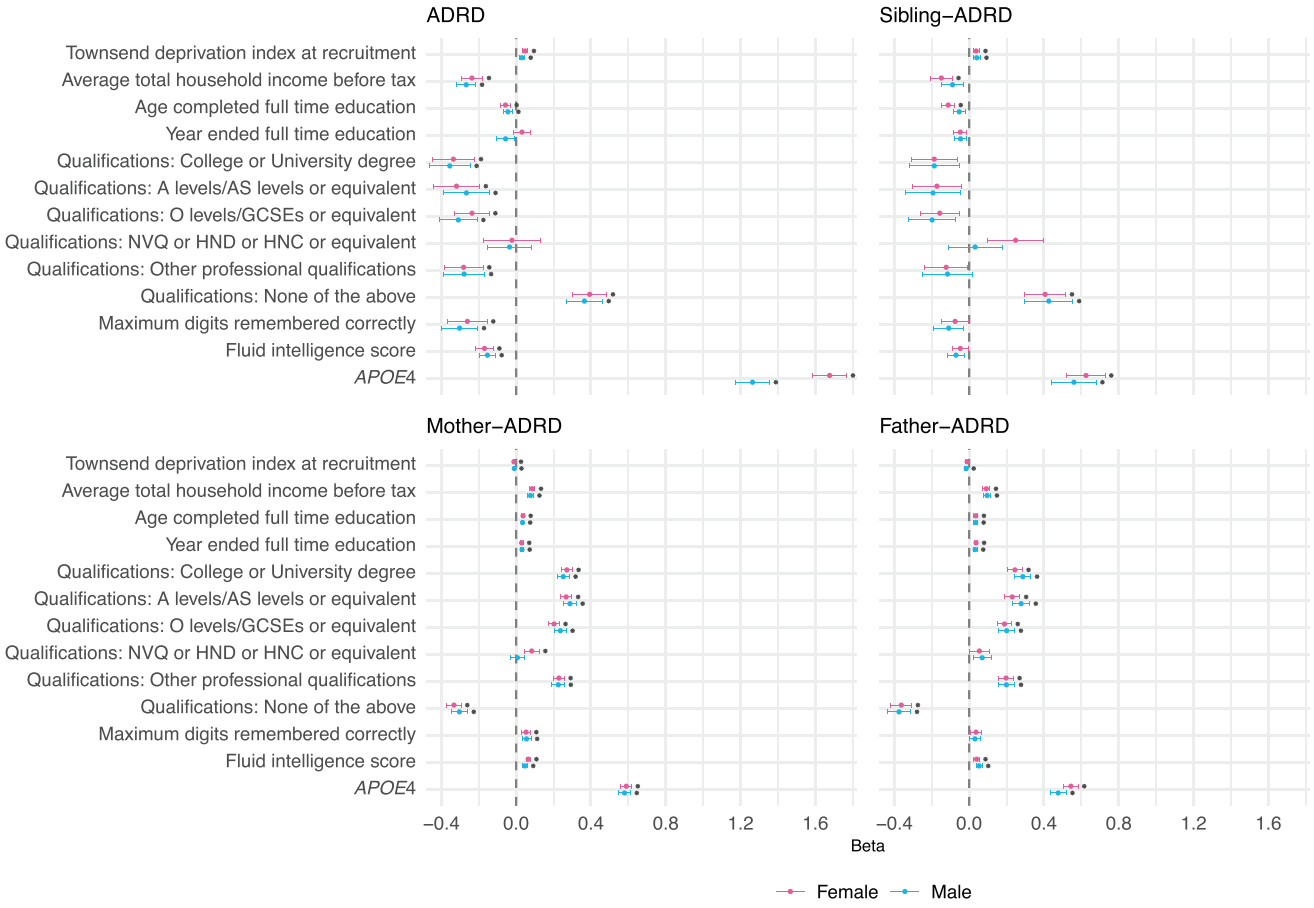

FIGURE 2 Associations of socioeconomic factors, cognitive performance, and *APOE ε4* status with ADRD family history in the UKB. Full results are available in Table S2. Star symbols indicate associations surviving Bonferroni multiple testing correction. ADRD, Alzheimer's disease and related dementias; *APOE*, apolipoprotein E; UKB, UK Biobank

covariates. With respect to socioeconomic factors and cognitive performance, we tested PRSs related to the Townsend Deprivation Index, household income, age completed full-time education, education qualification, year ended full-time education, maximum digits remembered correctly, and fluid intelligence score. To account for the number of PRS tests performed, we applied a Bonferroni correction ($P < 1.67 \varepsilon 10^{-3}$). Socioeconomic factors and cognitive performance PRSs surviving multiple testing were then entered into a multivariable regression model to assess their independent effects.

2.8 | One-sample MR

To investigate further the sex-specific dynamics linking socioeconomic factors (i.e., educational attainment and household income) to parent–ADRD, we performed a bidirectional one-sample MR analysis in females and males separately.[52,53] Using PRSs as instrumental variables, we performed an MR analysis in AoU European-ancestry participants by applying the two-stage predictor substitution (TSPS) estimator available in the OneSampleMR package in R.[54] Age and the top 10 within-ancestry PCs were included as covariates. When the outcome in the model was a binary variable, logistic regression was used in the second stage; when the outcome was a quantitative variable, linear regression was used. Bonferroni correction ($P < 0.005$) was applied to account for the number of MR tests performed. To ensure the reliability of our findings, we also recalculated MR estimates using the two-stage least squares (2SLS) estimator available in the ivreg package in R. Finally, we conducted weak-instrument and Wu–Hausman tests to examine whether the instrumental PRS was weakly correlated with the exposure variables and whether the 2SLS estimator was consistent with the ordinary least squares (OLS) estimator.

3 | RESULTS

3.1 | Observational analysis

After adjusting for age and genetically inferred ancestry, increased socioeconomic status and cognitive performance were associated with reduced ADRD and sibling–ADRD, while their relationship with father– and mother–ADRD was reversed (i.e., increased socioeconomic status and cognitive performance were associated with increased parent–ADRD; Figure 2, Table S2 in supporting information). For instance, with respect to socioeconomic factors, high house-

hold income was associated with reduced ADRD (β_{female} = −0.236, P = 1.54 ε 10^{-15}; β_{male} = −0.267, P = 3.05 ε 10^{-24}) and sibling–ADRD (β_{female} = −0.148, P = 7.20 ε 10^{-7}; β_{male} = −0.089, P = 0.003) but increased mother–ADRD (β_{female} = 0.086, P = 2.98 ε 10^{-33}; β_{male} = 0.077, P = 3.59 ε 10^{-24}) and father–ADRD (β_{female} = 0.092, p = 1.29 ε 10^{-22}; β_{male} = 0.096, P = 5.51 ε 10^{-22}). This dynamic was consistent also when considering negative socioeconomic factors such as not having any education qualifications, which was associated with increased ADRD (β_{female} = 0.393, P = 4.05 ε 10^{-17}; β_{male} = 0.365, P = 1.57 ε 10^{-13}) and sibling–ADRD (β_{female} = 0.406, P = 5.09 ε 10^{-13}; β_{male} = 0.426, P = 9.60 ε 10^{-11}), but reduced mother–ADRD (β_{female} = −0.333, P = 9.10 ε 10^{-65}; β_{male} = −0.303, P = 8.08 ε 10^{-42}) and father–ADRD (β_{female} = −0.363, P = 2.65 ε 10^{-37}; β_{male} = −0.375, P = 1.84 ε 10^{-31}). Cognitive performance measurements showed the same association pattern. For example, high fluid intelligence was associated with reduced ADRD (β_{female} = −0.169, P = 1.03 ε 10^{-12}; β_{male} = −0.153, P = 3.62 ε 10^{-12}) and sibling–ADRD (β_{female} = −0.047, P = 0.030; β_{male} = −0.070, P = 0.003) but increased mother–ADRD (β_{female} = 0.065, P = 9.09 ε 10^{-31}; β_{male} = 0.047, P = 1.31 ε 10^{-15}) and father–ADRD (β_{female} = 0.040, P = 6.59 ε 10^{-8}; β_{male} = 0.054, P = 2.31 ε 10^{-12}). Different from socioeconomic factors and cognitive performance, *APOE* ε4 carrier status showed increasing effects on ADRD, sibling–ADRD, mother–ADRD, and father–ADRD (Figure 2, Table S2). Comparing female and male effects, we observed a sex difference only for *APOE* ε4 carrier status on ADRD (β_{female} = 1.676 vs. β_{male} = 1.264, sex difference P = 4.95 ε 10^{-10}). When we entered Bonferroni-significant variables from the univariable analyses into multivariable models, socioeconomic factors and cognitive performance associations were strongly attenuated due to their overlap, but their effect directions were consistent with what was observed in the univariable analyses (Table S3 in supporting information).

To further investigate socioeconomic factors and cognitive performance relationships with parent–ADRD, we tested two additional models. In Model 2, controlling for parental death (father's death for father–ADRD and mother's death for mother–ADRD) in addition to age and genetically inferred ancestry, we observed no substantial difference with respect to the Model 1 effects (Figure S1, Tables S4 and S5 in supporting information). In Model 3, restricting the analysis to participants whose parent died (father died in father–ADRD analysis and mother died in mother–ADRD analysis) and including age, genetically inferred ancestry, and parental age at death as covariates, we observed a reduction in the effect size observed with several results becoming null. However, for those surviving Bonferroni multiple testing correction, the effect direction was consistent with Model 1 (Figure S1, Tables S6 and S7 in supporting information).

In the AoU cohort, high educational attainment and income were also associated with reduced ADRD and increased parent–ADRD in both sexes (Figure S2, Tables S8 and S9 in supporting information). Null effects were observed with respect to sibling–ADRD (P > 0.05). Leveraging AoU population diversity, we also investigated ancestry-specific associations (Figure 3; Table S10 in supporting information). Controlling for educational attainment and income and applying a Bonferroni correction accounting for the number of tests performed ($P < 2.5$ ε 10^{-3}), genetically inferred African descent (AFR) was associated with increased sibling–ADRD in females (β = 0.412, P = 0.002), while an inverse relationship was present with respect to father–ADRD in both females (β = −0.444, P = 8.2 ε 10^{-9}) and males (β = −0.539, P = 2.72 ε 10^{-4}). AFR descent was also inversely associated with mother–ADRD in males (β = −0.517, P = 8 ε 10^{-6}), but the effect was statistically smaller in females (β = −0.113, P = 0.043; sex difference P = 0.002). In males, mother–ADRD was also inversely associated with genetically inferred Central/South Asian (CSA; β = −0.953, P = 3.19 ε 10^{-4}) descent. Conversely, mother–ADRD was inversely associated with genetically inferred East Asian (EAS) descent in females (β = −0.477, P = 8.02 ε 10^{-4}) but not in males (P = 0.627). We also conducted an ancestry-stratified analysis, testing income and educational attainment associations with ADRD and family history of ADRD. In line with the results obtained in the whole AoU cohort, these factors were associated with reduced ADRD and increased parent–ADRD (Tables S11 and S12 in supporting information).

Our statistical power analysis highlighted that our observational analysis in the overall UKB and AoU cohorts was generally well powered (Tables S2 and S8). Because of the limited sample sizes available, our ancestry-stratified analyses were underpowered in multiple instances (Table S11). Nevertheless, there were several instances in which our analyses reached adequate statistical power also in minority groups. For example, we had > 90% of statistical power to test the association of educational attainment on ADRD, mother–ADRD, and father–ADRD in AoU participants of Admixed American descent.

With respect to other socioeconomic dimensions, occupational status and essential hypertension showed association patterns differentiating ADRD from its family history similar to the ones observed for educational attainment, income, and cognitive performance (Table S13 in supporting information). With respect to sex difference, the inverse relationship between mother–ADRD and employment status was stronger in females than males (β_{female} = −0.119, P = 9.60 ε 10^{-12}; β_{male} = −0.059, P = 0.002; sex difference P = 0.023) in UKB cohort.

The additional sensitivity analyses in UKB permitted us to assess the effect of fluid intelligence score, parental age, and private health-care use on the relationship between socioeconomic factors and cognitive performance with parent–ADRD (Table S14 in supporting information). Overall, we observed that controlling for these factors reduced the inverse relationships in both females and males (Figure S3 in supporting information). Additionally, we observed that the proportion of participants with younger siblings increased among individuals with high income and fluid intelligence scores and low material deprivation (Table S15 in supporting information).

3.2 | Polygenic risk scoring

To further investigate parent–ADRD, we leveraged UKB GWAS to derive socioeconomic factors, cognitive performance, and family history of ADRD PRSs and tested them in the AoU cohort. In both males and females, the strongest parent–ADRD associations were related to

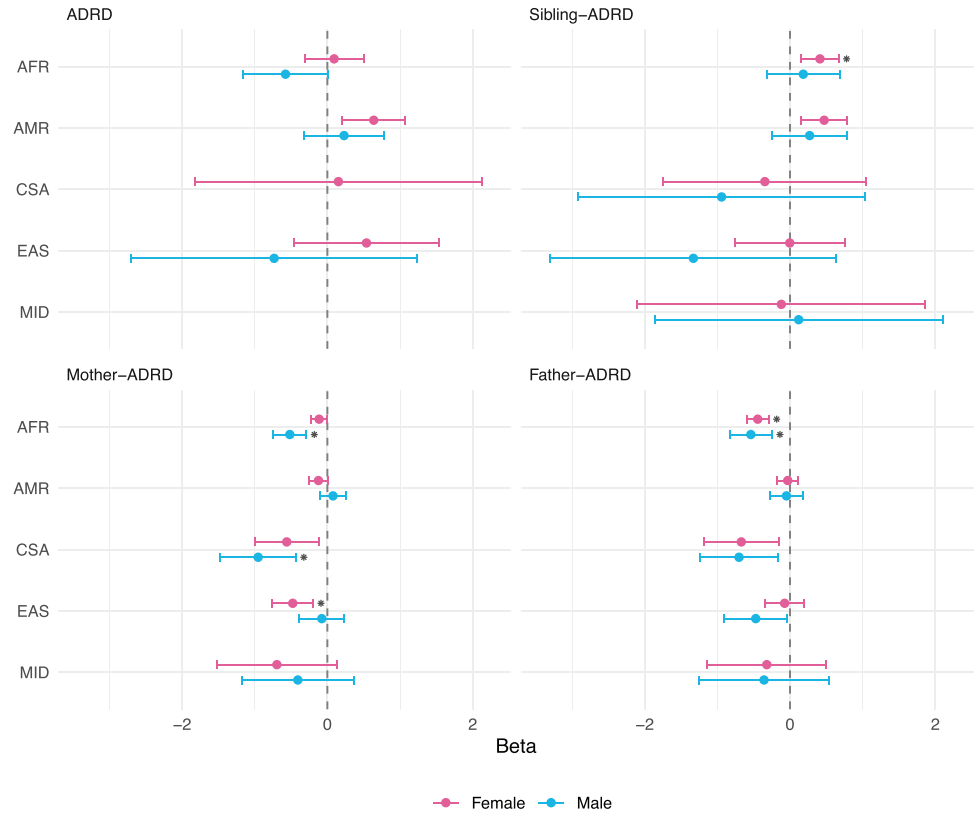

FIGURE 3 Associations between genetically inferred ancestry and ADRD family history in the AoU. ADRD betas in CSA (males) and MID (both sexes) are not shown due to extremely small sample sizes. Full results are available in Table S10. ADRD, Alzheimer's disease and related dementias; AFR, African ancestry; AMR, Admixed American ancestry; AoU, All of Us Research Program; CSA, Central/South Asian ancestry; EAS, East Asian ancestry; EUR, European ancestry; MID, Middle Eastern ancestry

PRSs derived from "Illnesses of mother: Alzheimer's disease/dementia" and "Illnesses of father: Alzheimer's disease/dementia" (Figure 4, Table S16 in supporting information). The direction of the association was in line with the expectation that high parent–ADRD PRS would be associated with increased parent–ADRD. Interestingly, in both sexes, we observed cross-parent PRS associations with mother–ADRD PRS associated with father–ADRD and vice versa (Figure 4, Table S16). However, there was a sex difference in the association of mother–ADRD PRS with father–ADRD, which was stronger in males ($\beta = 2.028$, $P = 1.08\ \varepsilon\ 10^{-11}$) than in females ($\beta = 1.004$, $P = 1.07\ \varepsilon\ 10^{-5}$; sex difference $P = 0.006$). Considering Bonferroni-significant socioeconomic factor PRS associations ($P < 1.67\ \varepsilon\ 10^{-3}$), we observed the same pattern of the observational analyses described above, where PRSs related to positive socioeconomic factors were associated with increased parent–ADRD (Figure 4, Table S16). For instance, having a college or university degree was associated with increased father–ADRD in both females ($\beta = 0.687$, $P = 2.12\ \varepsilon\ 10^{-6}$) and males ($\beta = 0.677$, $P = 3.69\varepsilon 10^{-4}$). While several socioeconomic factors' PRSs were Bonferroni significant only in one sex but only nominally replicated or null in the other (Figure 4, Table S16), we observed only one statistically significant sex difference. Townsend Deprivation Index PRS was associated with reduced mother–ADRD in males ($\beta = -0.784$, $P = 0.001$), but not in females ($\beta = 0.034$, $P = 0.868$; sex difference $P = 0.009$). None of the cognitive performance PRSs survived Bonferroni multiple testing correction, but the effect direction of the nominally significant results was consistent with the observational findings described above (Table S16). Finally, we conducted a multivariate analysis of socioeconomic factors and ADRD family history PRS, which confirmed the independence and the direction of the effects detected in the initial PRS analyses (Table S17 in supporting information).

3.3 | One-sample MR

Using the TSPS approach to perform a one-sample MR analysis, we investigated the bidirectional relationship between socioeconomic factors and parent–ADRD. In both sexes, we observed that genetic liability to mother–ADRD affected father–ADRD and vice versa (Figure 5, Table S18 in supporting information). The results derived using the TSPS method were highly consistent with the analyses obtained from the 2SLS approach (Table S19 in supporting information). With both methods, female genetic liability to father–ADRD affected mother–ADRD more strongly than female genetic liability to mother–ADRD affected father–ADRD (TSPS difference $P = 0.038$, Table S18; 2SLS difference $P = 0.008$, Table S19). We observed Bonferroni-significant effects of educational attainment and household income on father–

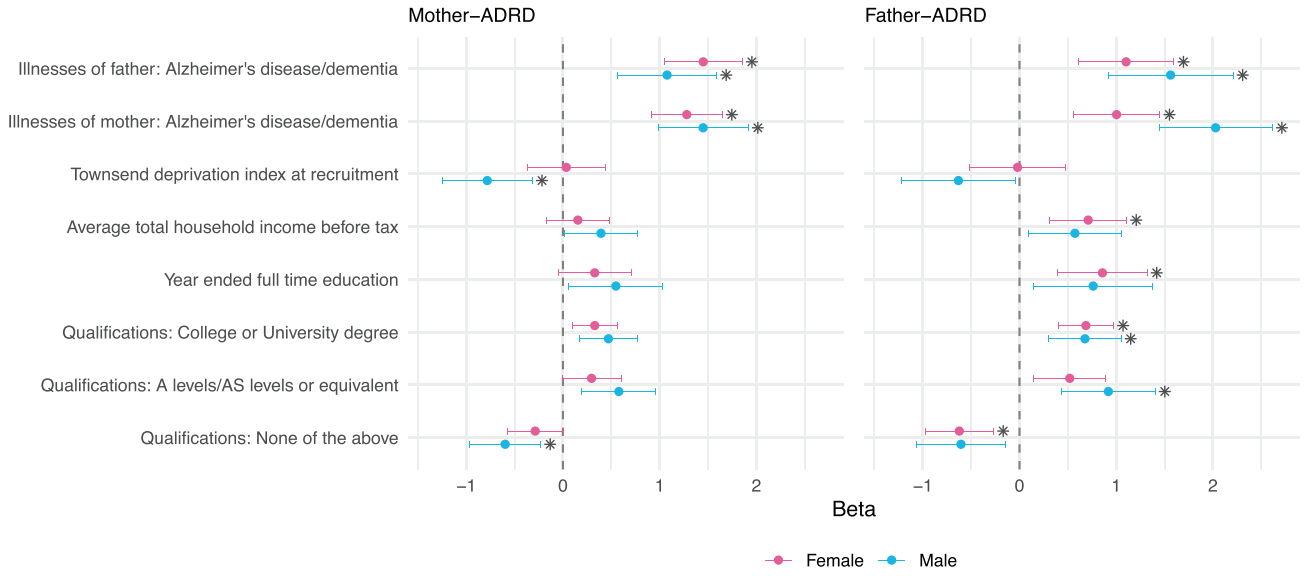

FIGURE 4 Associations of polygenic risk scores related to socioeconomic factors and cognitive performance with ADRD family history. Full results are available in Table S16. Star symbols indicate associations surviving Bonferroni multiple testing correction. ADRD, Alzheimer's disease and related dementias.

(A)

Direction	Beta (95% CI)	Female	Beta (95% CI)	Male
Education→father	0.39 (0.14, 0.64)*		0.33 (-0.07, 0.73)	
Education→mother	0.20 (-0.01, 0.41)		0.52 (0.20, 0.84)*	
Income→father	0.26 (0.10, 0.42)*		0.25 (0.03, 0.47)	
Income→mother	0.07 (-0.07, 0.20)		0.18 (0.00, 0.36)	

0 0.2 0.4 0.6 0.8 0 0.2 0.4 0.6 0.8

(B)

Direction	Beta (95% CI)	Female	Beta (95% CI)	Male
Mother→father	9.56 (4.40, 14.73)*		16.51 (9.36, 23.67)*	
Father→mother	23.74 (11.35, 36.12)*		12.72 (4.83, 20.61)*	
Father→education	3.03 (0.77, 5.29)		2.10 (0.17, 4.02)	
Mother→education	1.32 (0.24, 2.40)		1.39 (0.20, 2.59)	
Father→income	3.22 (-1.34, 7.77)		4.17 (-0.39, 8.73)	
Mother→income	2.61 (0.12, 5.10)		1.70 (-0.68, 4.08)	

0 5 10 15 20 25 0 5 10 15 20 25

FIGURE 5 Bidirectional relationships between socioeconomic factors and ADRD family history. A, Causal effects of household income and educational attainment on parent–ADRD. B, Causal effects of parent–ADRD. The TSPS estimator was used to assess the causal relationships. Full results are available in Table S18. Star symbols indicate associations surviving Bonferroni multiple testing correction. ADRD, Alzheimer's disease and related dementias; CI, confidence interval; TSPS, two-stage predictor substitution

ADRD in females and of educational attainment on mother–ADRD in males (Figure 5; Table S18). The sensitivity analyses confirmed the reliability of the one-sample MR results, highlighting the lack of weak instrument bias and indicating that the outcomes tested are associated with the variables in our models (Table S19).

4 | DISCUSSION

The prevalence of ADRD has been rising in the twenty-first century due to increased life expectancy and an aging population, resulting in an enormous disease and economic burden.[5,55] Family history has been used to investigate ADRD genetic basis in cohorts including participants younger than the disease expected age of onset.[23–26] Recently, concerns have been raised about potential confounders affecting ADRD self-reported parental information.[32] In the present study, we used phenotypic and genetic data from two large cohorts to identify sex-specific confounders affecting ADRD family history, also exploring differences across population groups. In line with previous evidence,[6,11,22] we found that high socioeconomic status and cognitive performance were associated with reduced ADRD. However, while the effect was consistent for sibling–ADRD, we observed an

inverse relationship with respect to parent–ADRD: participants with better socioeconomic status and/or cognitive performance reported increased father– and mother–ADRD. Similar ADRD versus parental–ADRD effect-direction differences were also observed for the association with employment status and cardiovascular risk factors, such as essential hypertension. Several dynamics could explain parental–ADRD results. One is reporting bias, which is prevalent in studies related to self-reported information and varies across different population groups, for example, individuals of lower socioeconomic status and cognitive performance may be less likely to report accurate information.[56] Regarding family history, the bias varies among family members; for example, the number of self-reported paternal family histories of cancer was reported to be significantly lower than that of maternal family histories.[57] The second potential bias is misclassification.[58] As material deprivation and socioeconomic factors are important determinants of health-care service accessibility and are intergenerationally transmissible, low-income individuals are more likely to have economic insurance or be uninsured.[59,60] Consequently, the limited access to medical services and the low frequency of visits lead to underestimates of ADRD diagnosis of parents, while high socioeconomic status could lead to more aggressive follow-up of cognitive symptoms and earlier detection of ADRD in their parents. Third, there may be recall bias: self-reported records could suffer more from recall bias in a population with cognitive decline.[61] Therefore, those with poor cognitive performance may report a lower proportion of true ADRD family.[62] Fourth, survival bias may play an important role in these associations. It has been recognized that socioeconomic factors are associated with all-cause mortality.[63] Under this scenario, parents of individuals of lower socioeconomic status would die early due to competing risks before they had a chance to develop ADRD.[64] This is consistent with our finding that the associations substantially attenuated when we restricted the analysis to participants whose father or mother was deceased. Parental age could also be a confounder. Typically, the age at birth of individuals is correlated with socioeconomic status.[65] Thus, those parents in families with lower socioeconomic status will be younger, resulting in a relatively lower prevalence rate of ADRD family history.

While it is difficult to fully demonstrate the impact of the aforementioned biases using the data from the present study, we performed multiple variable controls in the sensitivity analysis in an attempt to show their potential influence. Due to the lack of information regarding parental medical service use, we controlled for participants' access to private health care and observed that the inverse association between household income and parent–ADRD was attenuated. We also controlled for fluid intelligence score (to reduce recall bias) and parental age (a potential confounder bias), which migrated the implausible associations between all evaluated socioeconomic traits and parent–ADRD. Although the role of these biases still requires further verification, our findings indicate that multiple adjustments may be a potential approach for bias correction in future family history research. In addition, a study has demonstrated that higher income, education, and intelligence significantly reduce reporting bias in UKB, emphasizing the importance of using comprehensive methods to enhance phenotype accuracy and sample representativeness, including repeat measurements, regression calibration, imputation, weighted regression, and probability sampling or weighting.[33,66] In GWAS, additional methods have been introduced to reduce biases, such as constructing continuous phenotypes based on parental ADRD, parental age, and ADRD prevalence, which has proven effective in reducing survival bias.[32]

We did not observe inverse associations in sibling–ADRD analysis, possibly because their age gap is generally small as also observed in other sibling-based analyses.[67,68] The close age gap between participants and siblings may account for reduced survival bias and recall bias. Another possible reason is that the age of siblings correlates with socioeconomic factors. In the sensitivity analysis, we found that participants with higher income and cognitive levels were more likely to have younger siblings. In the observational analysis in the UKB cohort, *APOE* ε4 carrier status was consistently a risk factor for both ADRD and its family history, as expected.[46] Because this is a biological risk factor, it is less likely to be affected by biases related to self-reported family history. However, we still observed that *APOE* ε4's effect on ADRD was larger than that on ADRD family history.

Importantly, we found sex differences in ADRD versus its family history association patterns. In the UKB observational analysis, *APOE* ε4 was more strongly associated with ADRD in females than in males, consistent with the finding that females with this allele have a greater risk of developing ADRD than male *APOE* ε4 carriers.[69] In AoU, we identified multiple sex differences when investigating ADRD family history among population groups. After controlling for educational attainment and income, AFR and CSA male participants were less likely to report mother–ADRD than females. This sex-specific association was reversed in EAS with females were less likely to report mother–ADRD than males. This suggests that the sex-specific interplay of the biases discussed above with disparities in health-care access, life expectancy, and ADRD prevalence observed in population minorities.[70,71]

Genetically informed analyses suggested that father–ADRD and mother–ADRD may have a causal relationship. This could be due to caregiver distress, shared environmental exposures, and positive assortative mating.[72] Importantly, the presence of ADRD in one parent may also increase participants' recognition of ADRD symptoms in the other parent. Sex differences were also present in the PRS and one-sample MR analyses. Specifically, mother–ADRD PRS was more strongly associated with father–ADRD in males than in females. Additionally, one-sample MR analysis highlighted that female genetic liability to father–ADRD affected mother–ADRD more strongly than female genetic liability to mother–ADRD affected father–ADRD. These differences could be related to parental differences in the perception of family history. For example, females reported more obligation to care for their mother than their father, and mother–daughter dyads engaged in more mutually open conversations with less conflict.[73] Moreover, females might know more about their mother's health than their father's, and maternal family history was more strongly associated with ADRD risk factors than paternal family history.[74] Another possible aspect contributing to the sex differences in ADRD family history genetics is assortative mating (mate choice driven by pheno-

typic similarity). Recently, assortative mating, socioeconomic factors, and participation bias have been reported in the context of the polygenic risk of neuropsychiatric and behavioral traits.[75] Based on this previous evidence and our current results, we hypothesize that the interplay between ADRD family history and socioeconomic factors could contribute to sex-specific assortative mating.

Strengths of the present study include the use of phenotypic and genetic data from two large cohorts to investigate the sex-specific associations of socioeconomic factors and cognitive performance with ADRD and family history. This permitted us to triangulate robust evidence by integrating multiple approaches and data types. However, we need to acknowledge several limitations. First, we could not distinguish family history of Alzheimer's disease from the family history of other dementias (e.g., vascular dementias) in our analysis, because of the questionnaires used to assess UKB and AoU participants. This may have affected some of our results. For instance, it may have contributed to the reduced *APOE* ε4 effect on parent–ADRD compared to ADRD although this allele has been also associated with non-AD dementias.[76–78] Second, the limited sample size available limited the ancestry-stratified analyses in the AoU cohort. While in some cases we achieved adequate statistical power also in minority populations, our findings confirm the need to increase diversity of ADRD research. Third, although our analyses accounted for covariates such as sex, age, genetically inferred ancestry, parental death, and parental age at death, we could not conduct competing risk analyses or control for other factors due to limited information available for parents. For example, ADRD age of onset, psychosocial factors, lifestyle, and healthcare accessibility of first-degree relatives were not available in the datasets investigated. Another important limitation is related to the characteristics of UKB and AoU cohorts. While the consistency we observed between them supports the generalizability of our findings, the differences in sample size, participant's demographics, assessment strategies, data collection procedures, and questionnaire settings may have influenced some of our results. Finally, UKB and AoU are not cohorts with randomly selected participants and they are not representative of the general population, which may introduce volunteer bias as an additional source of confounding, thus affecting the estimated associations.[79]

In conclusion, the present study contributes to expanding the understanding of how sex-specific confounders can affect the associations of socioeconomic factors and cognitive performance with parent–ADRD. This can have substantial implications in the context of the potential dynamics affecting the recruitment and participation of females and males in ADRD research.

AUTHOR CONTRIBUTIONS

Jun He and Renato Polimanti designed the study. Eleni Friligkou and Jun He extracted and preprocessed the data. Brenda Cabrera-Mendoza and Gita A. Pathak provided statistical methodological support. Jun He conducted the formal analysis and wrote the manuscript. Jun He, Brenda Cabrera-Mendoza, Eleni Friligkou, Adam P. Mecca, Christopher H. van Dyck, Gita A. Pathak, and Renato Polimanti contributed to the data interpretation. All the authors participated in the critical revision of the manuscript for important intellectual content. Renato Polimanti obtained the primary funding and supervised the study. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The UKB individual data could be obtained by applying on the website (http://www.ukbiobank.ac.uk/). The UKB GWAS data could be downloaded from the Neale Lab (http://www.nealelab.is/uk-biobank). The AoU data in this article were accessed from the All of Us Curated Data Repository version 7 (https://www.researchallofus.org). PRSs were calculated using PRScs (https://github.com/getian107/PRScs) and PLINK 1.9 (https://www.cog-genomics.org/plink/1.9/). One-sample MR analyses were performed using OneSampleMR (https://github.com/remlapmot/OneSampleMR) and ivreg (https://github.com/zeileis/ivreg/).

CONSENT STATEMENT

The UK Biobank has approval from the North-West multi-center research ethics committee as a Research Tissue Bank approval. The All of Us Research Program was approved by the All of Us Institutional Review Board. All participants in the two studies provided informed consent at recruitment. The data used in this study were obtained through an application reference No. 58146 for the UK Biobank and through an approved data use agreement for the All of Us Research Program.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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