



Investigating Sex Differences In Polygenic Risk For Sex-biased Brain Disorders: Impacts On Diagnosis And Brain Age Gap

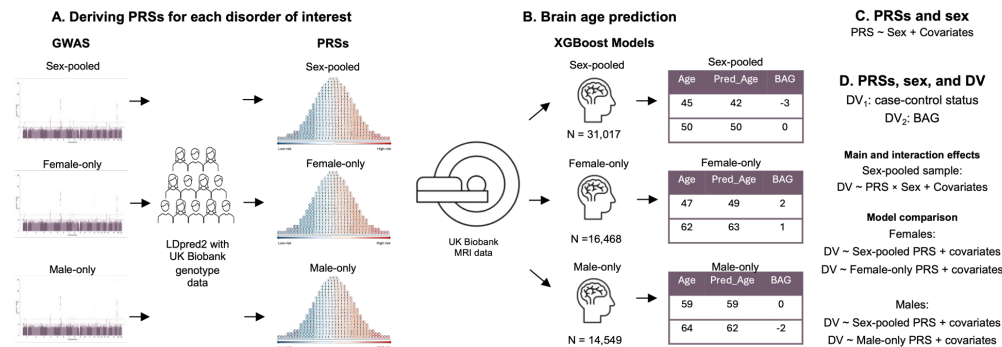
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WHAT WE KNOW

Sex differences are observed in the prevalence, manifestation, and disease burden of several mental and neurological disorders. However, it remains unclear whether genetic risk for these conditions interacts with sex in relation to case-control status or brain age gap (BAG) – a well-established proxy for brain health.

WHAT WE DID

In a sample of 220,836 females and 187,651 males from the UK Biobank (aged 39–81), we assessed how sex and polygenic risk scores (PRSs) for major depressive disorder (PRS_{MDD}), Alzheimer's disease (PRS_{AD}), schizophrenia (PRS_{SCZ}), and Parkinson's disease (PRS_{PD}) relate to case-control status and BAG.



WHAT WE FOUND

PRS_{SCZ} was higher in females, while no other PRSs differed by sex. A significant PRS_{AD}-by-sex interaction for case-control status revealed stronger PRS effects in females for AD status. Sex-pooled models outperformed same-sex models for case-control status, apart from PRS_{AD}. The female-only PRS_{AD} model outperformed the sex-pooled model, while male-only and sex-pooled PRS_{AD} models performed similarly. No sex-by-PRS interactions were significant with BAG. However, male sex, higher PRS_{MDD}, higher PRS_{AD}, and lower PRS_{PD} were associated with higher BAG. Finally, BAG model performance did not differ between sex-pooled and sex-specific PRS models.

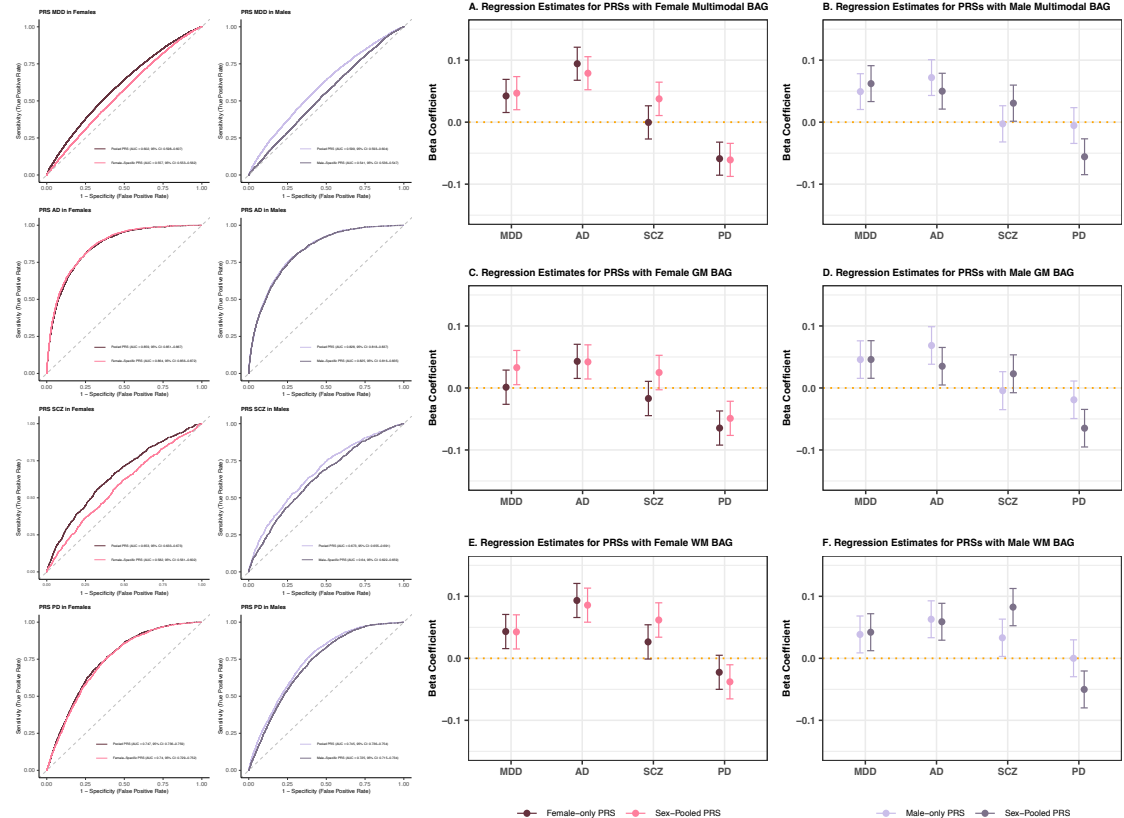


Figure 1. Comparing AUCs of sex-pooled and sex-specific models for case-control prediction.

Figure 2. Regression estimates for sex-pooled and sex-specific PRSs in association with female-only and male-only multimodal and tissue-specific BAG.

CONCLUSION

Our findings highlight an interaction between sex and PRS_{AD} for case-control status, as well as sex differences in PRSs and BAG, but suggest that sex-specific PRSs currently offer limited value over sex-pooled PRSs. However, sex-specific PRS models showed promise for PRS_{AD}, suggesting that the value of sex-specific PRSs will likely grow with increased statistical power.