MS polygenic risk is not associated with white matter integrity in UK Biobank

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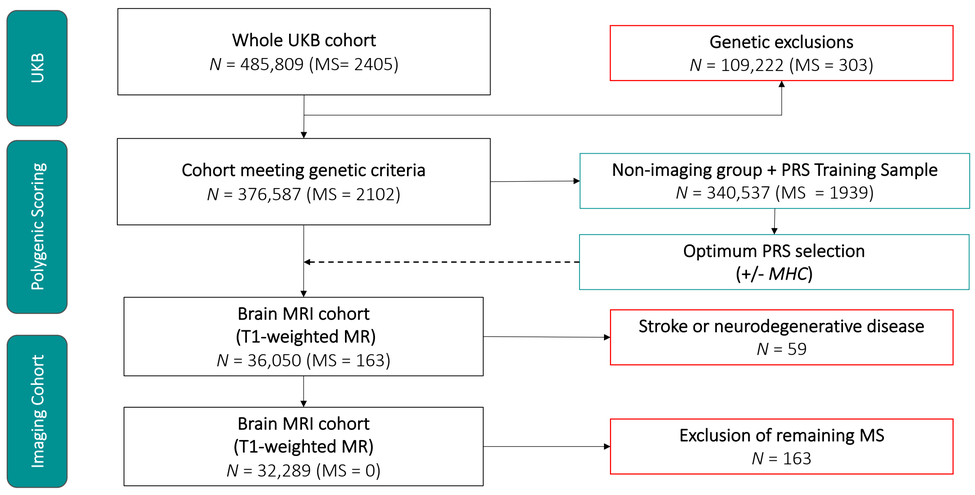
Background

- Multiple Sclerosis (MS) is a chronic autoimmune disorder with a range of genetic and environmental risk factors.
- Recent studies[1,2] have reported associations between genetic risk of MS and Magnetic Resonance Imaging (MRI) metrics of white matter tract integrity in healthy children.
- We sought to replicate these findings, assessing whether MS polygenic risk (MS-PRS) is associated with white matter integrity in a large cohort of healthy UK Biobank (UKB) participants.

? Is MS polygenic risk associated with white matter integrity in healthy participants of the UK Biobank?

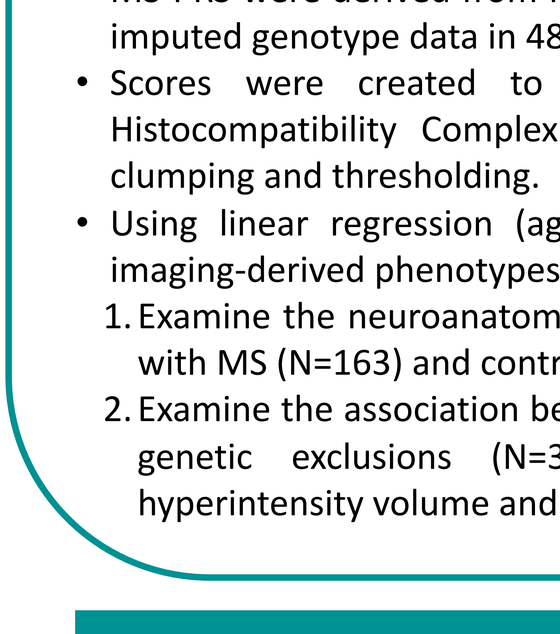
Methods



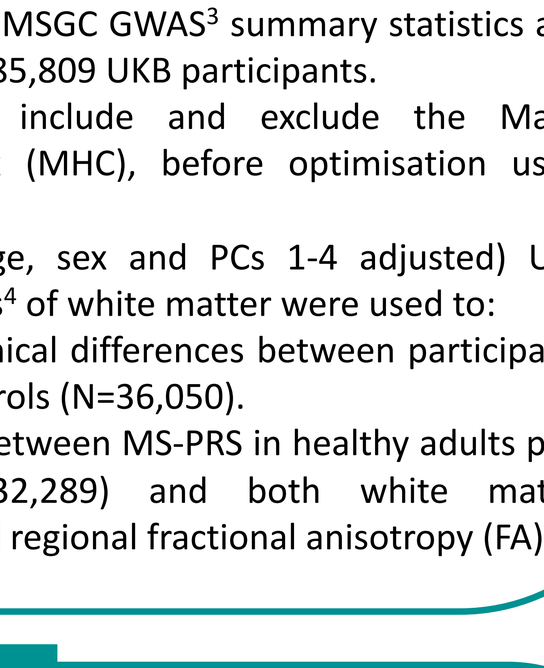
- MS-PRS were derived from IMSGC GWAS[3] summary statistics and imputed genotype data in 485,809 UKB participants.
- Scores were created to include and exclude the Major Histocompatibility Complex (MHC), before optimisation using clumping and thresholding.
- Using linear regression (age, sex and PCs 1-4 adjusted) UKB imaging-derived phenotypes[4] of white matter were used to:
  1. Examine the neuroanatomical differences between participants with MS (N=163) and controls (N=36,050).
  2. Examine the association between MS-PRS in healthy adults post genetic exclusions (N=32,289) and both white matter hyperintensity volume and regional fractional anisotropy (FA).

Results: MS-PRS

MS-PRS distribution



ROC Curves



- Optimised MS-PRS explained 3.3% (MHC) and 1.3% (non-MHC) of MS susceptibility (Nagelkerke's Pseudo-R^2).

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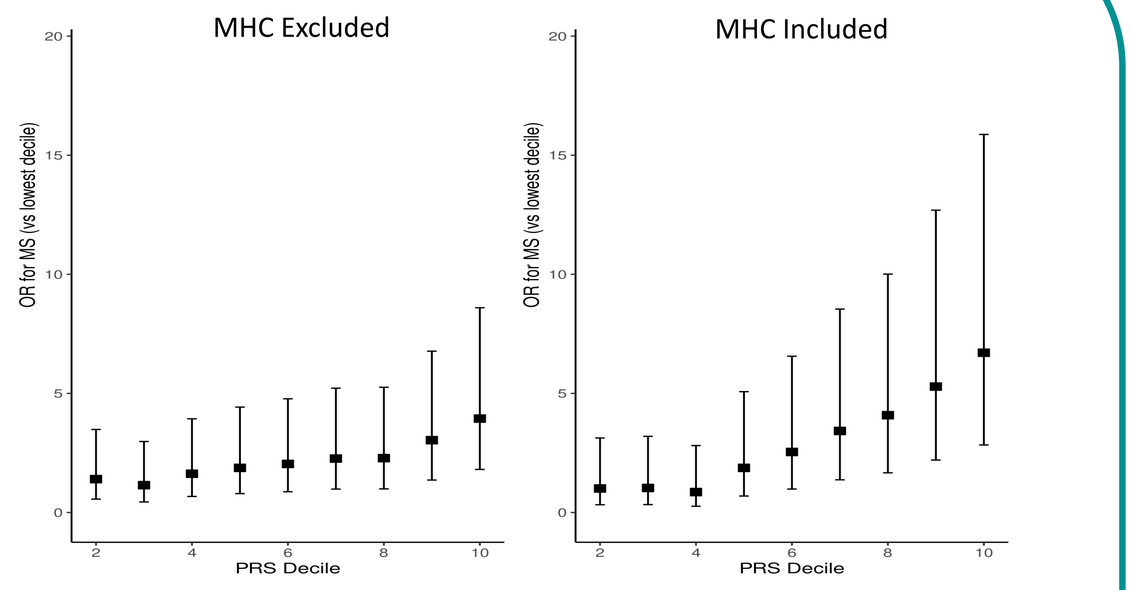
Results: MS Risk

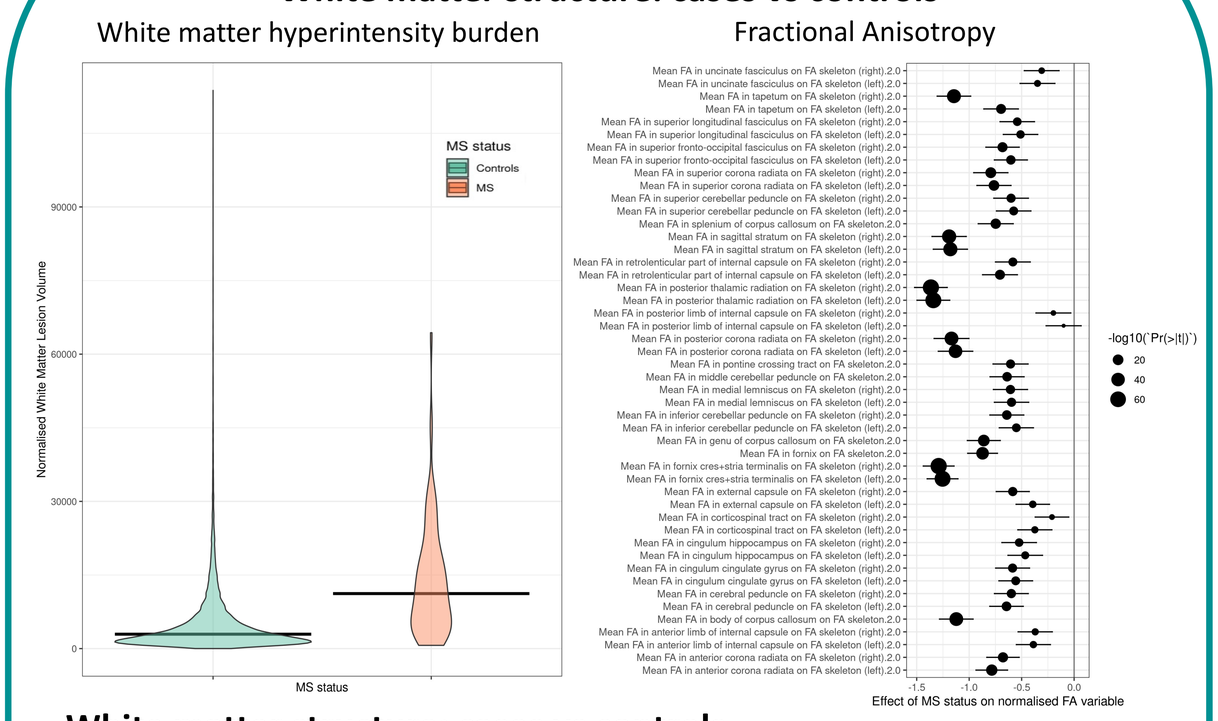


- MS-PRS was strongly associated with MS susceptibility after logistic regression (age, sex PCs 1-4 adjusted):
  - MHC $p=9.98\times10^{-19}$, OR 6.71, 95% CI 2.8-15.9
  - non-MHC: $p=2.5\times10^{-7}$, OR 3.94, 95% CI 1.8-8.6

Neuroimaging analyses were thresholded at $p_{FWE}<0.05$ over whole brain
Covariates: age, sex, scanner & total intracranial volume

Results: Neuroimaging

White matter structure: cases vs controls



White matter structure: cases vs controls

- Individuals with MS had higher total T2 hyperintensity volume and near global reduction in regional FA compared to controls.

White matter structure: MS-PRS

- Neither the MHC-PRS (p=0.23) nor the non-MHC-PRS (p=0.33) were associated with T2 hyperintensity volume in the healthy controls after linear regression (n=32,289).
- No association exceeded the multiple testing threshold (Bonferroni, alpha=0.05, number of tests=48) between either MHC-PRS or non-MHC PRS and regional FA.

Conclusions

MS polygenic risk does not correlate with white matter hyperintensity volume or regional fractional anisotropy in healthy adults.

Given our large sample size, our results argue against the concept of healthy adults with high MS genetic risk showing subclinical MRI evidence of disease.

References:

1. de Mol et al. White matter microstructural differences in children and genetic risk for multiple sclerosis: A population-based study. Mult. Scler. (2021).
2. IMSGC. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. Science 365. (2019).
3. de Mol et al. Polygenic Multiple Sclerosis Risk and Population-Based Childhood Brain Imaging. Ann. Neurol. (2020).
4. Alfaro-Almagro et al. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage. (2018).

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