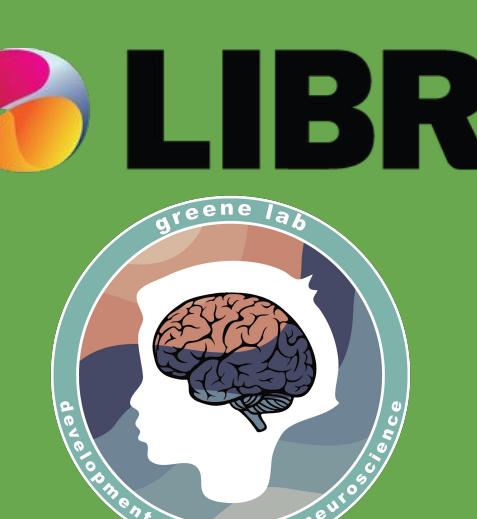


Multinational Comparison of the Impact of Polygenic Risk for Multiple Sclerosis on White Matter Integrity in the ABCD Study



Jonathan Ahern^{1,2}, Sana A. Ali¹, Abigail R. Baim¹, Sarah E. Chang¹, Damion V. Demeter¹, Emily M. Koithan¹, Sujin Park¹, Salma Zreik¹, Deanna J. Greene¹, Wesley K. Thompson², Chun Chieh Fan^{2,3}, Robert Loughnan^{1,2,4,5}

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BACKGROUND & SAMPLE

What is Multiple Sclerosis?

- Multiple Sclerosis (MS) is an autoimmune disease affecting the brain and spinal cord, impairing nerve signal transmission and leading to motor and sensory deficits¹.
- MS is associated with both genetic² and environmental risk factors³.

Previous work in Adolescents

- Previous work in a Dutch sample reported that adolescents with higher genetic risk of MS, measured using a Polygenic Risk Score (PRS), had detectable differences in measures of white matter integrity quantified using diffusion imaging⁴.
- They found increased global fractional anisotropy (FA) and tract-specific differences in FA and radial diffusivity (RD)⁴.

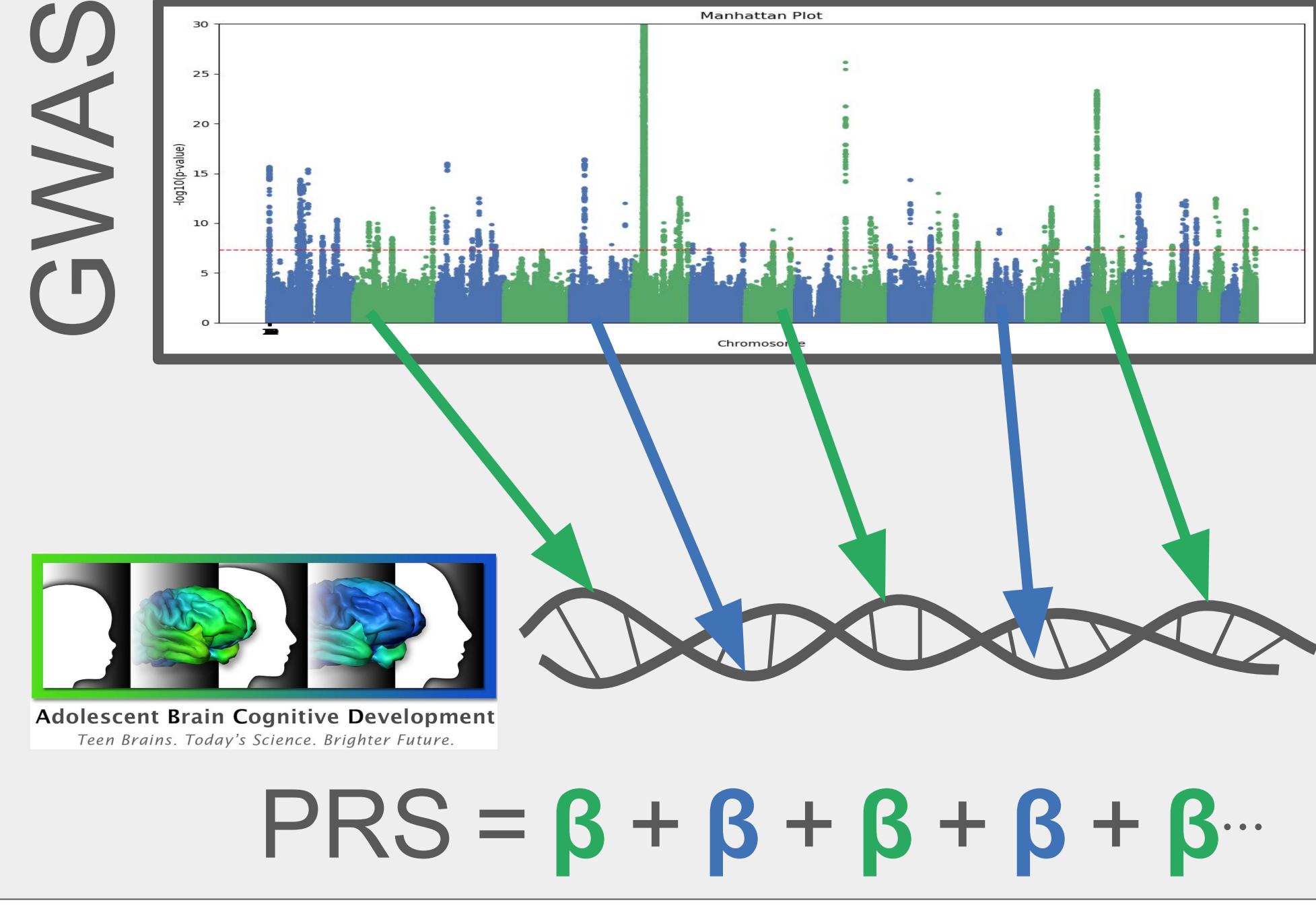
We examine if these results replicate in a similar adolescent sample in ABCD

ABCD Samples

Ancestry	Session	Total Sample Size	Age (±std)	# Female
European -like Ancestry	Baseline	5,472	9.91 (±0.62)	2,554
	Year 2 Follow Up	5,164	11.94 (±0.65)	2,391
African -like Ancestry	Baseline	712	9.90 (±0.59)	352
	Year 2 Follow Up	615	11.98 (±0.62)	303
Admixed Ancestry	Baseline	3,161	9.89 (±0.62)	1,502
	Year 2 Follow Up	2,809	11.91 (±0.66)	1,337

METHODS

Generating Polygenic Risk Scores



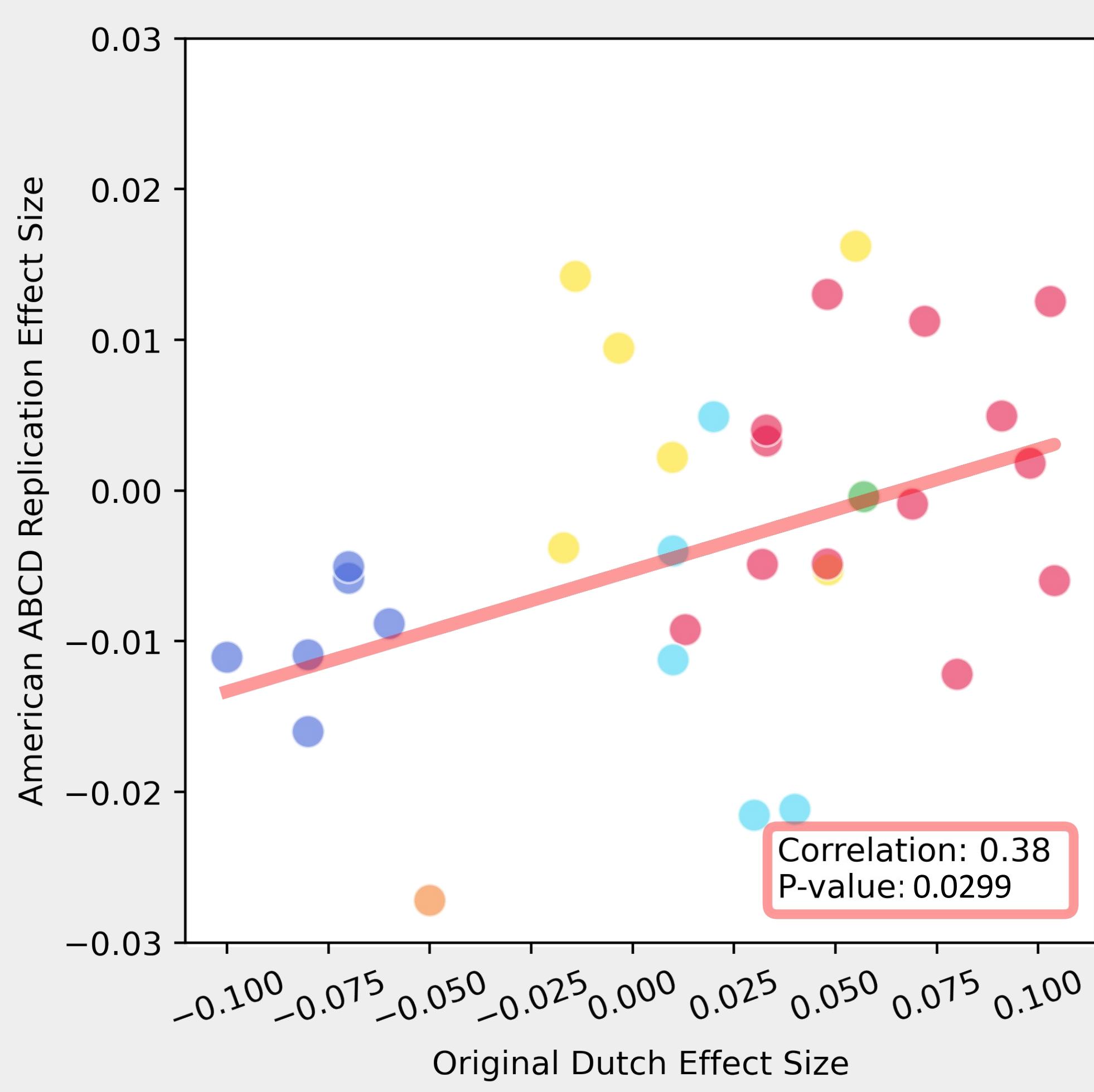
- Genome Wide Association Study data was obtained from the International Multiple Sclerosis Genetics Consortium (IMSGC)³ and the Million Veterans Program (MVP)⁵
- Summary statistics were cleaned and aligned to genome build GRCh38 with cleansumstats⁶
- The adolescent sample comes from the Adolescent Brain Cognitive Development® (ABCD) study (5.1 Release)⁷
- The Polygenic Risk Score (PRS) was calculated using PRScs⁸ and aligned to ABCD using PLINK 2.0⁹
- Genetic ancestry is imputed using SNPweights¹⁰ and genetic principal components (PCs) are generated with PC-Air¹¹
- White matter phenotypes from the ABCD study (5.1)¹² were associated with PRS in each ancestry using generalized linear regression with the formula below

<phenotype> ~ PGS + age + sex + PC1..PC10 + MRI_Scanner + MRI_Software + Intracranial_Volume

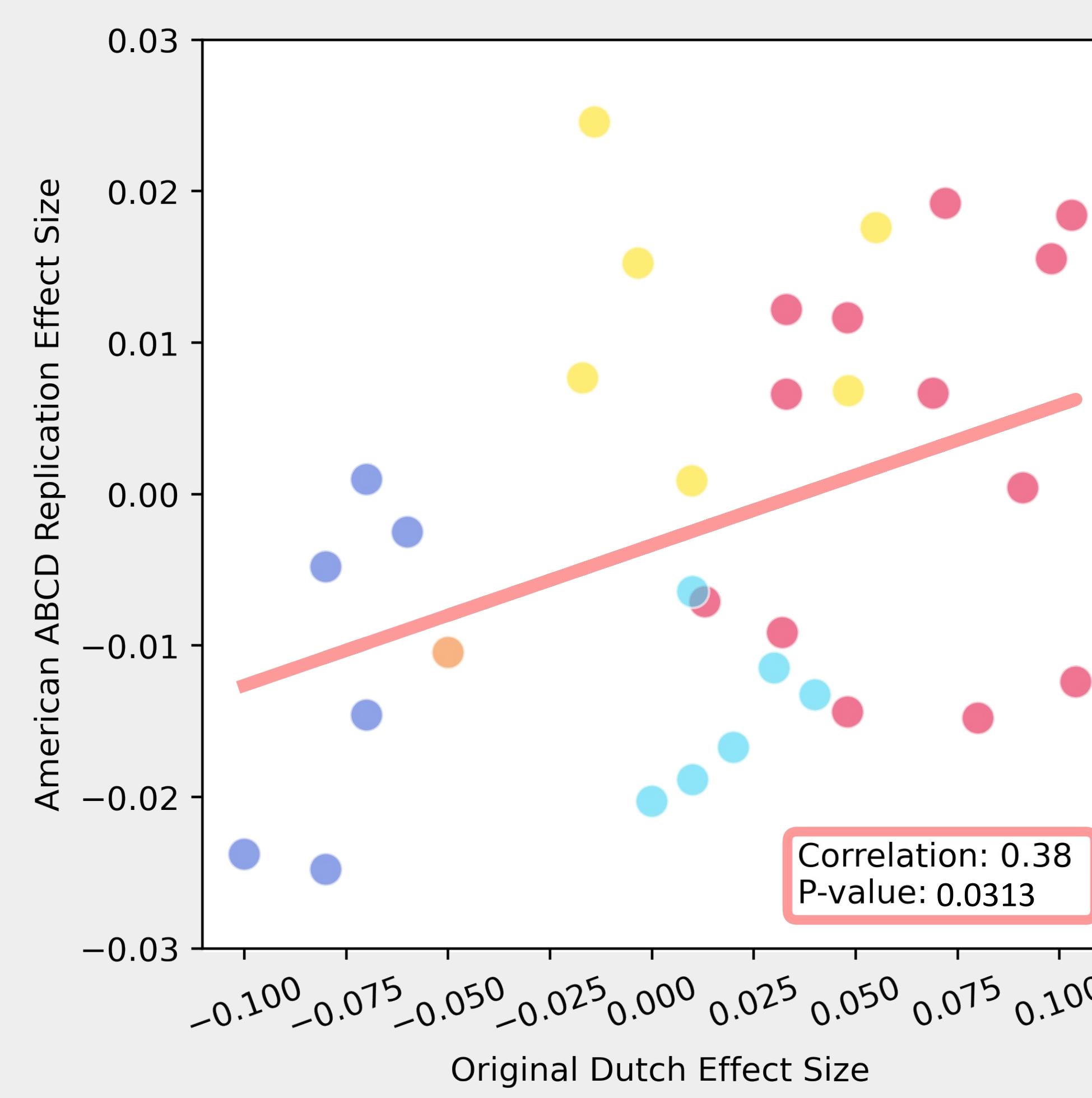
RESULTS

We were Unable to Replicate Dutch Findings in a European-like sample in ABCD, but the Effect Sizes of MS PGS on Brain Phenotypes are Correlated Across Samples

European-like Ancestry Baseline n = 5,472



European-like Ancestry Year 2 Follow Up n = 5,164



Legend
● Fractional Anisotropy (FA)
● Mean Diffusivity (MD)
● Volume
● Nonverbal IQ
● Longitudinal Diffusivity (LD)
● Transverse Diffusivity (TD)

- We were unable to replicate the associations between MS PGS and global and tract-specific FA
- Effect sizes were correlated with the original study at baseline and year 2
- There were trending associations between the MS PRS and lower global average MD and decreased LD in specific tracts at baseline and increased thalamic volume at 2 year
- Results did not remain significant after multiple comparisons correction
- Results were not significantly changed when accounting for socioeconomic status

MS PRSs Show Varied Performance Across Diverse Subpopulations

- MS PRSs were dependent on the chosen GWAS.
- MS PRSs show varied performance in diverse ancestries reflecting the need for greater representation in all levels of genetics and methods.

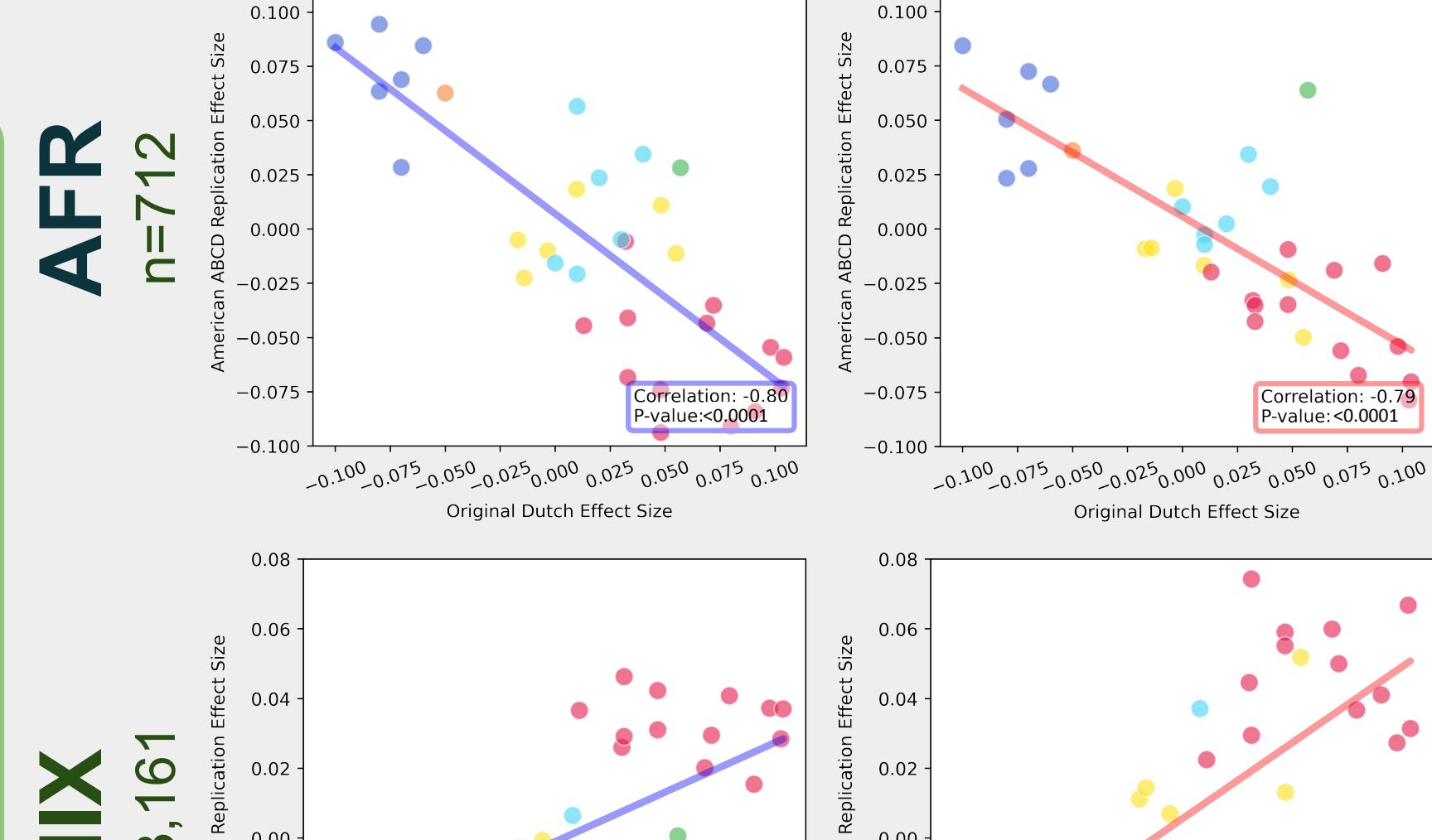
AFR: Continental African-like Ancestry

MIX: Admixed Ancestry (Two or More Continental Ancestries)

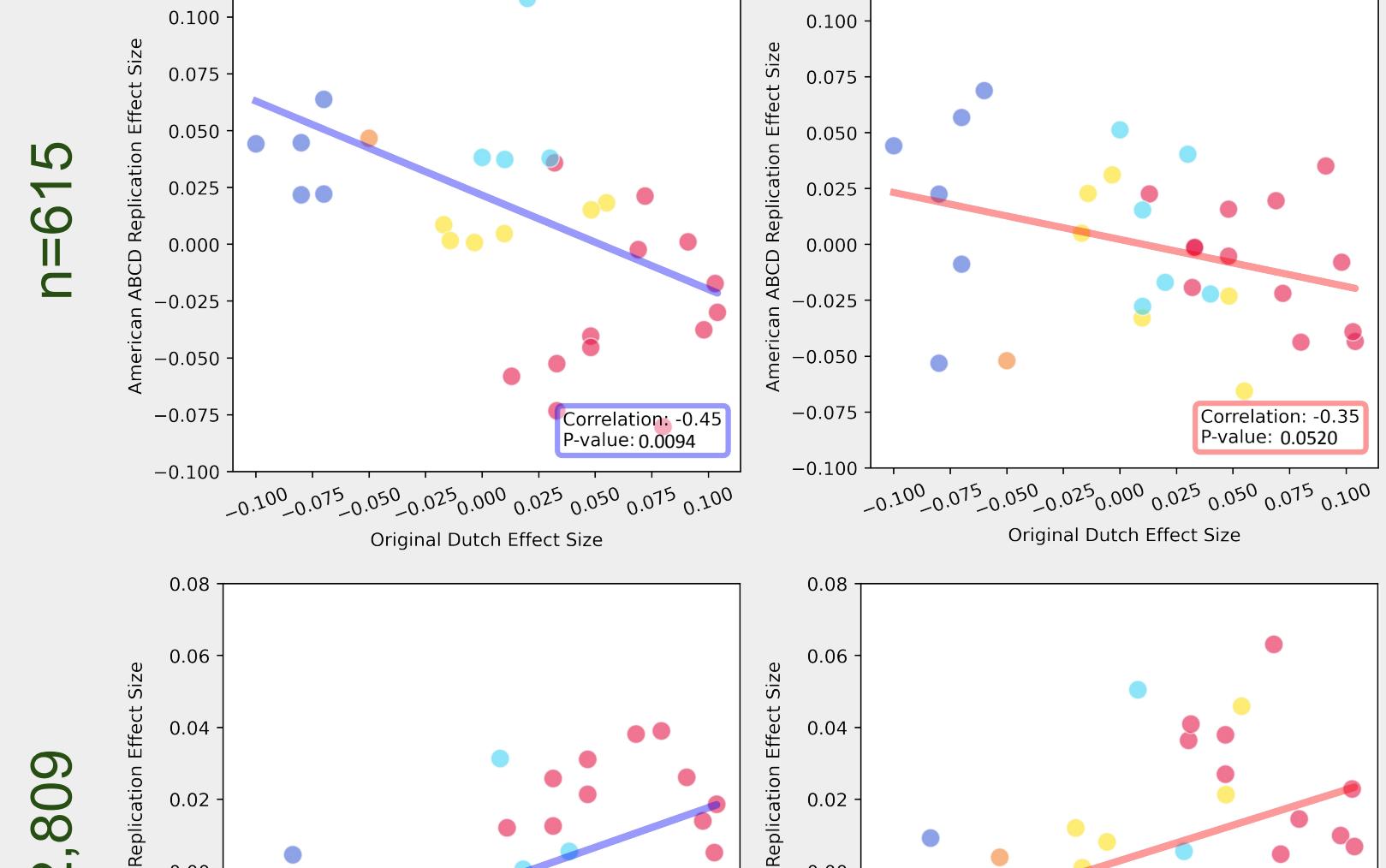
GWAS Training Sample: IMSGC (European)³

MVP (African American or Afro-Caribbean)⁵

Baseline



Year 2



* Please note that the range of the y-axis is consistent within subpopulations, but varies between subpopulations

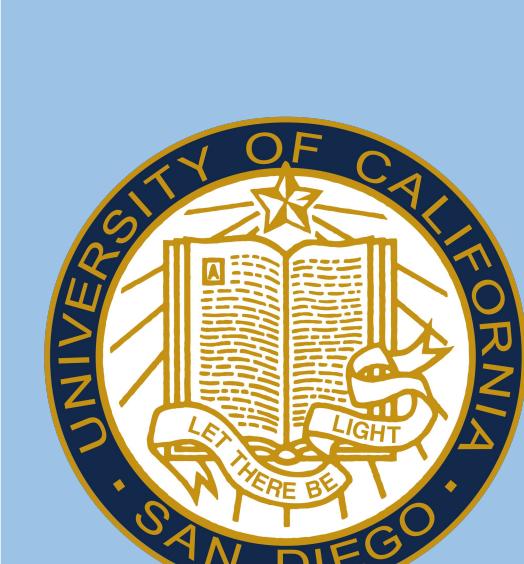
CONCLUSIONS

- We were unable to replicate the findings of the original paper and failed to identify any significant associations between MS PGSs and white matter integrity in a similar sample from ABCD.
- More research is needed to understand potential differences in environmental factors or gene environment interactions between the Netherlands and the United States that may have led to an inability to replicate the original findings.
- MS PGSs tested across ancestries in ABCD showed differential performance. This underscores the limitations of polygenic translation across ancestries and highlights the need to include more diverse populations at all levels of genetic research.

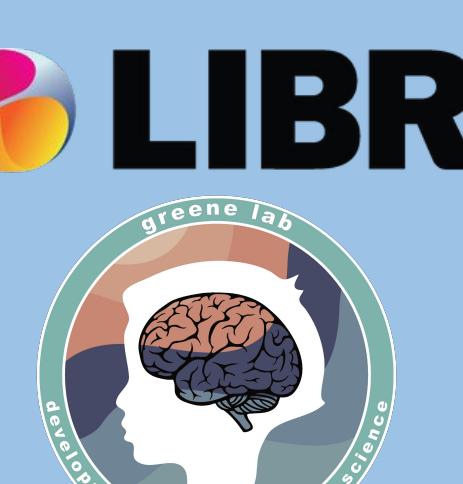
Corresponding Author: Jonathan Ahern - jahern@ucsd.edu

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OUT OF DATE

What is Multiple Sclerosis?

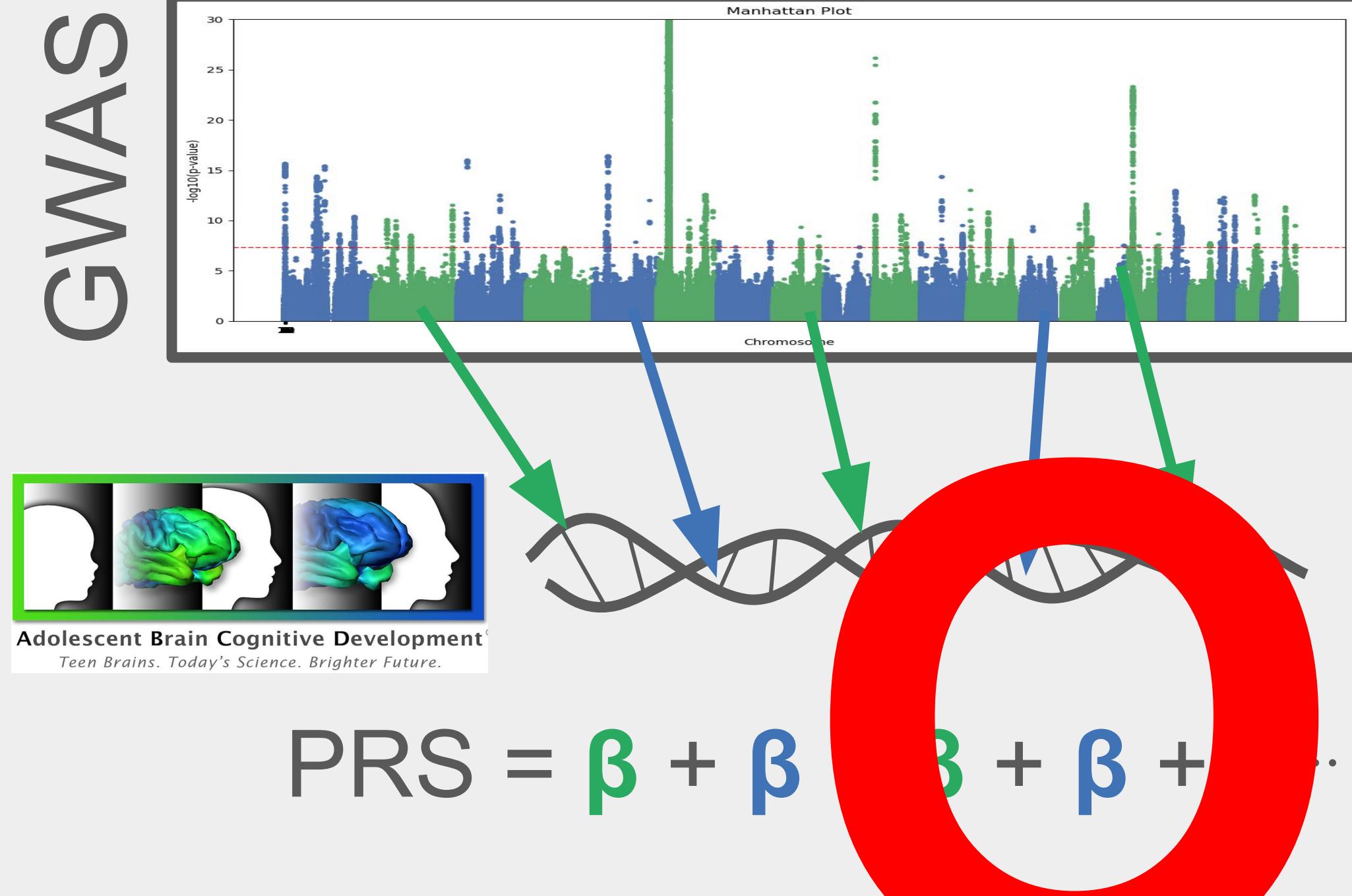
- Multiple Sclerosis (MS) is an autoimmune disease affecting the brain and spinal cord, impairing nerve signal transmission and leading to motor, sensory, cognitive, and visual problems.
- MS is associated with both genetic² and environmental risk factors³.

Previous work in Adolescents

- Previous work in a Dutch sample reported adolescents with higher genetic risk for MS had detectable differences in measures of white matter integrity quantified using diffusion imaging.
- They found increased global fractional anisotropy (FA) and tract-specific differences in FA and radial diffusivity (RD).

METHODS

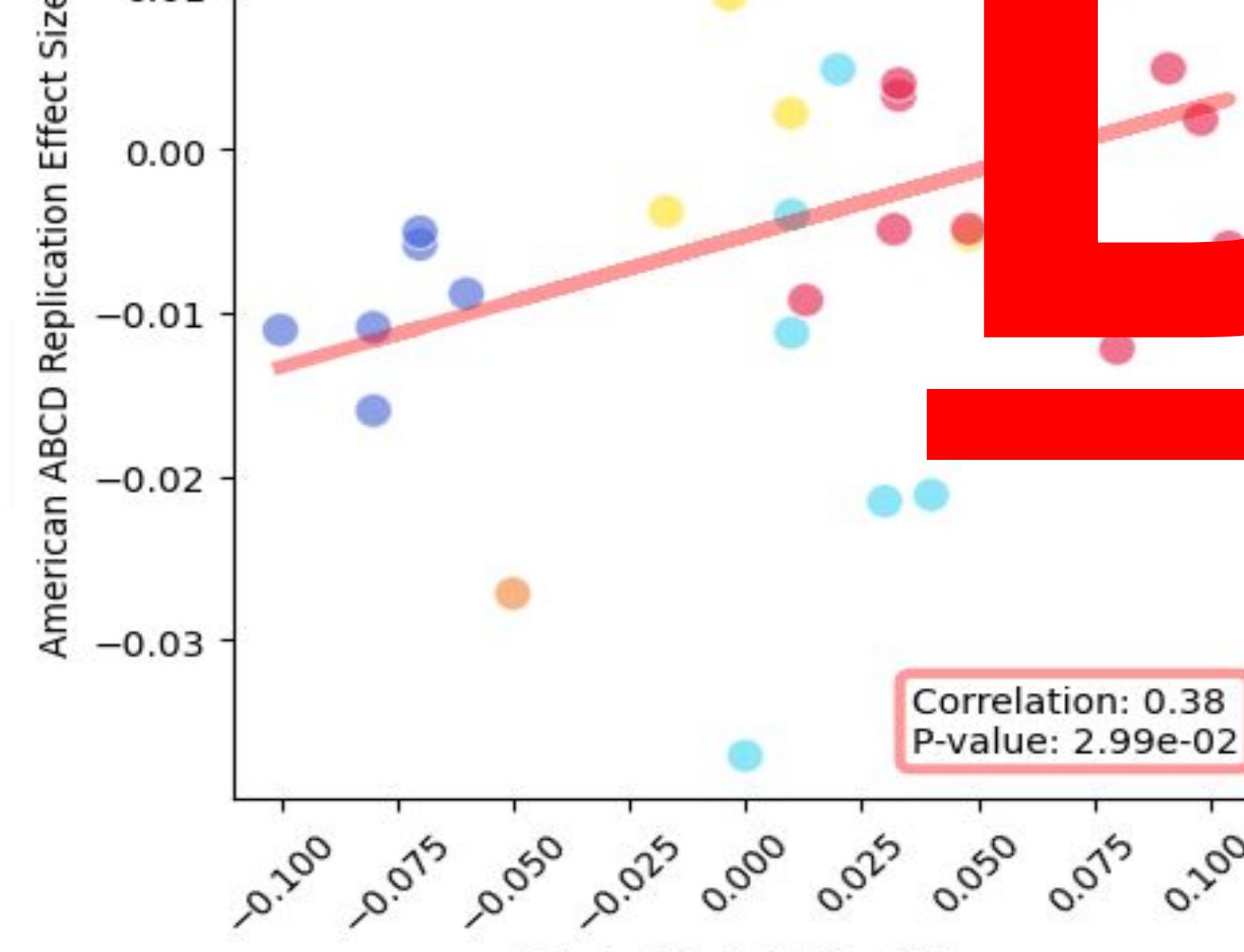
Generating Polygenic Risk Scores



- Genome Wide Association Study data was obtained from the International Multiple Sclerosis Genetics Consortium (IMSGC)³ and the Million Veterans Program (MVP)⁵.
- Summary statistics were cleaned and aligned to genome build GRCh38 with cleannumstats⁶.
- Our adolescent sample comes from the Adolescent Brain Cognitive Development® (ABCD) study (5.1 Release)⁷.
- The Polygenic Risk Score (PRS) was calculated using PRScs⁸ and aligned to ABCD using PLINK.
- Genetic ancestry was imputed using SNPweights⁹ and genetic principal components (PCs) were generated with PC-AiR.
- White matter phenotypes are from the ABCD study¹⁰ and are associated with PRS in each ancestry using generalized linear regression with MR_Solver and GICA_craniacal_Volume.

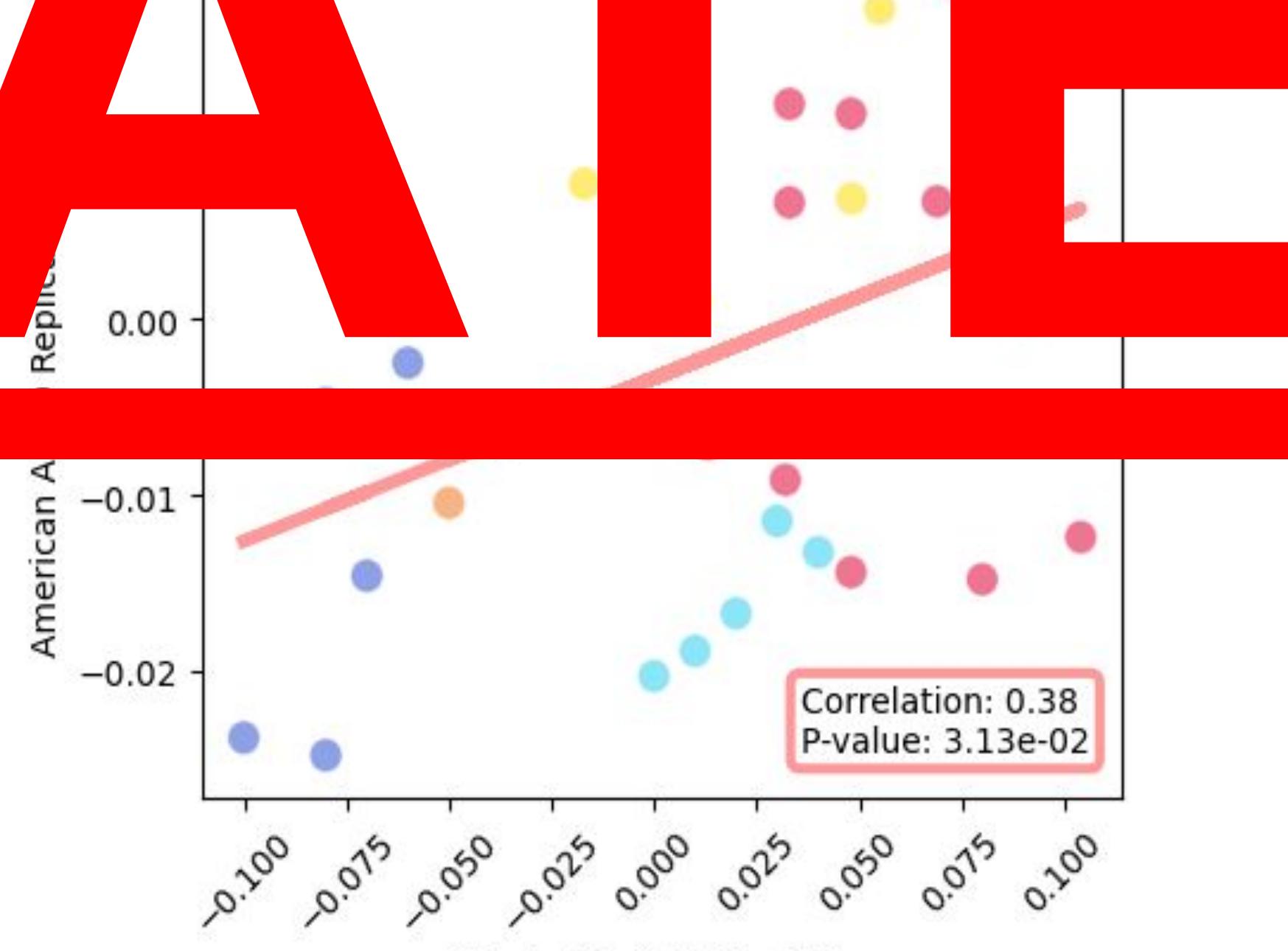
European-like Ancestry

Baseline n = 5,472



European-like Ancestry

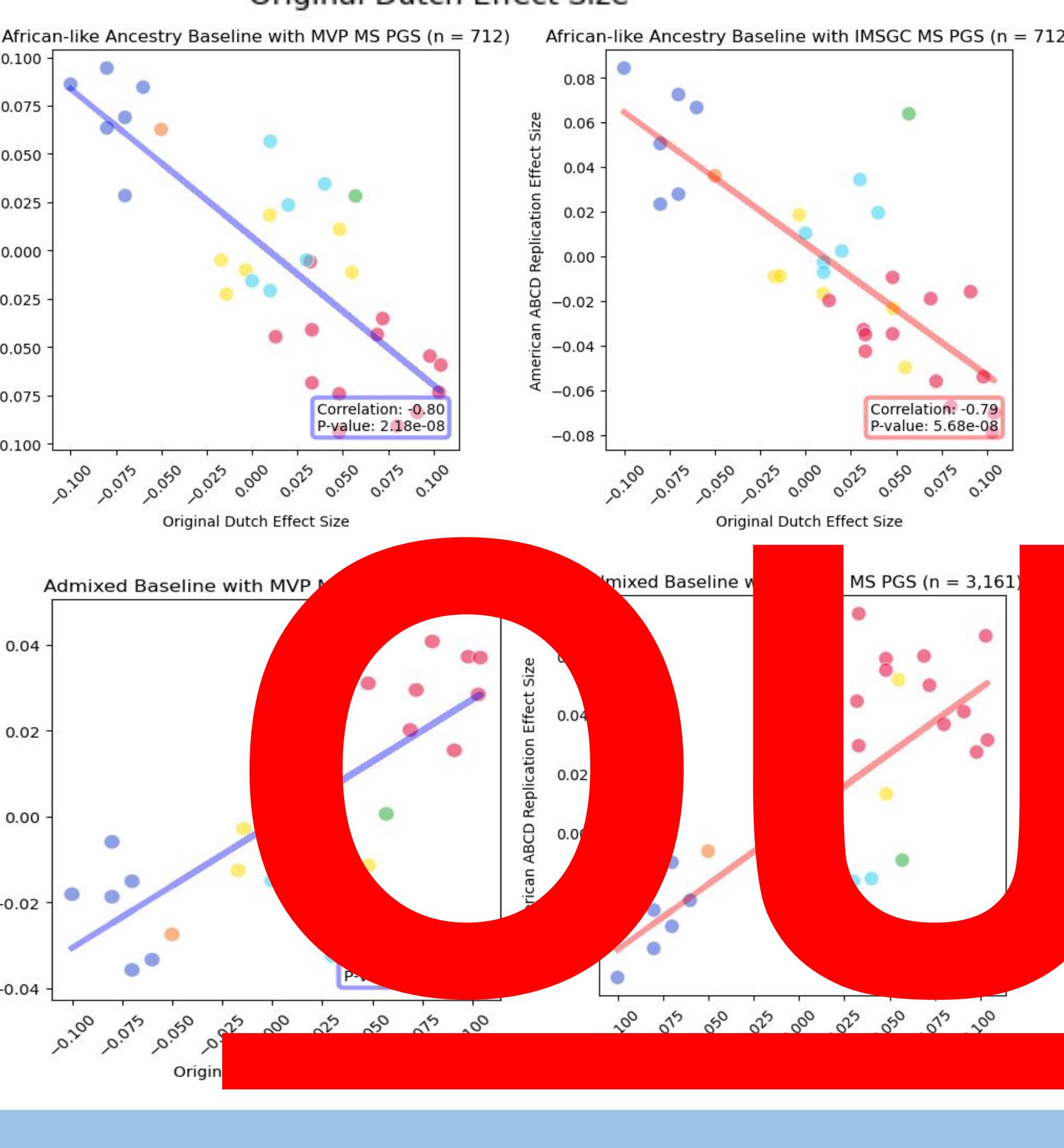
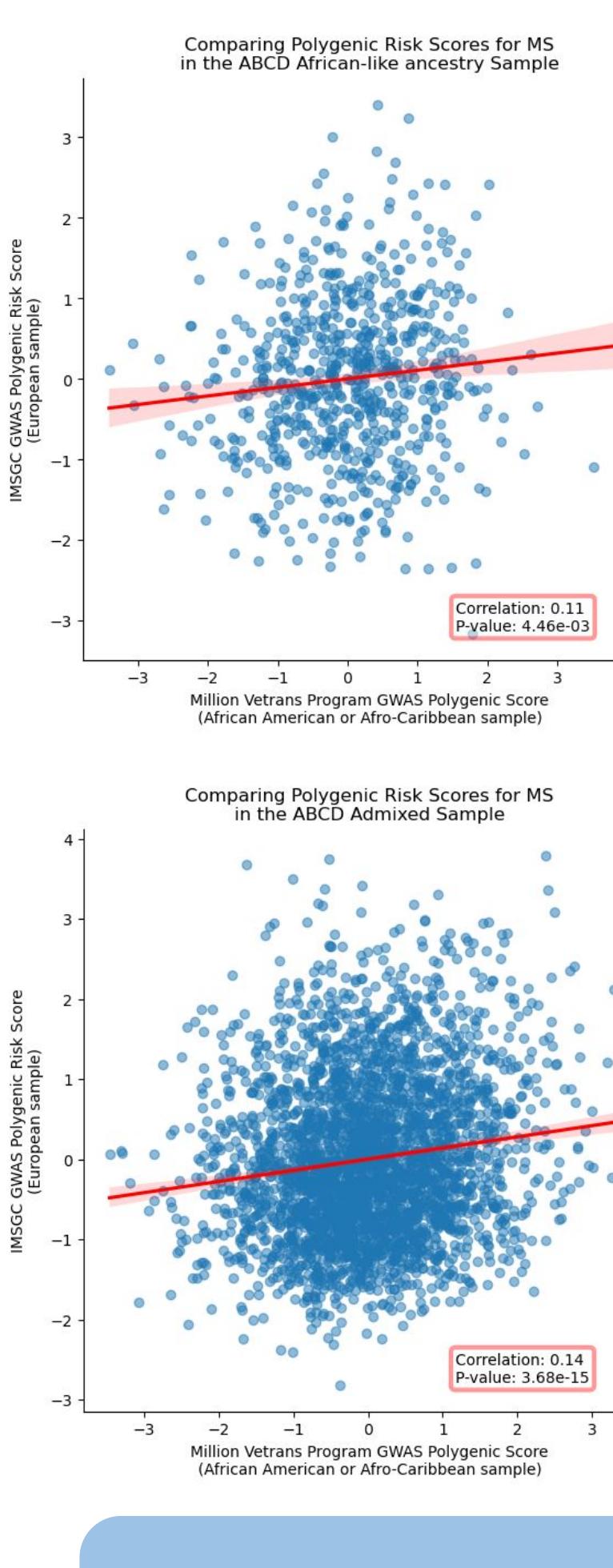
Year 2 Follow Up



European-like Ancestry (EUR)

- We were unable to replicate any of the significant results from the original paper.
- We did identify trending associations between the MS PRS and lower global average mean diffusivity (MD) and decreased longitudinal diffusivity (LD) superior longitudinal fasciculus at baseline and increased thalamus volume at the 2 year follow up. Results did not remain significant after multiple comparisons correction.
- Our effect sizes were weakly but significantly correlated with those of the original study at baseline and the year-2 follow-up.
- Results are not significantly changed when accounting for socioeconomic status.

Legend:
● FA
● MD
● Volume
● Nonverbal IQ
● LD
● TD



Performance Across Ancestry

MS PRSs change based on the GWAS they are generated on. MS PRSs show varied performance in diverse ancestries reflecting the need for greater representation in all levels of genetics and methods improvements.

CONCLUSIONS

- We were unable to replicate the findings of the original paper and failed to identify any significant associations between MS PGSs and white matter integrity in a similar sample from ABCD.
- More research is needed to understand potential differences in environmental factors and gene-environment interactions between the Netherlands and the United States that could be leading to difference in findings identified here.
- MS PGSs generated tested in different ancestries in ABCD show differential performance underscoring the limitations of polygenic translation across ancestries and the need to include more diverse populations at all levels of genetic research.

QR CODE MAYBE

Works Cited:

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