Does brain structure and function causally determine mental disorder?
How mendelian randomisation can help causal insights in psychiatry

Graham Murray, University of Cambridge

REUTERS®

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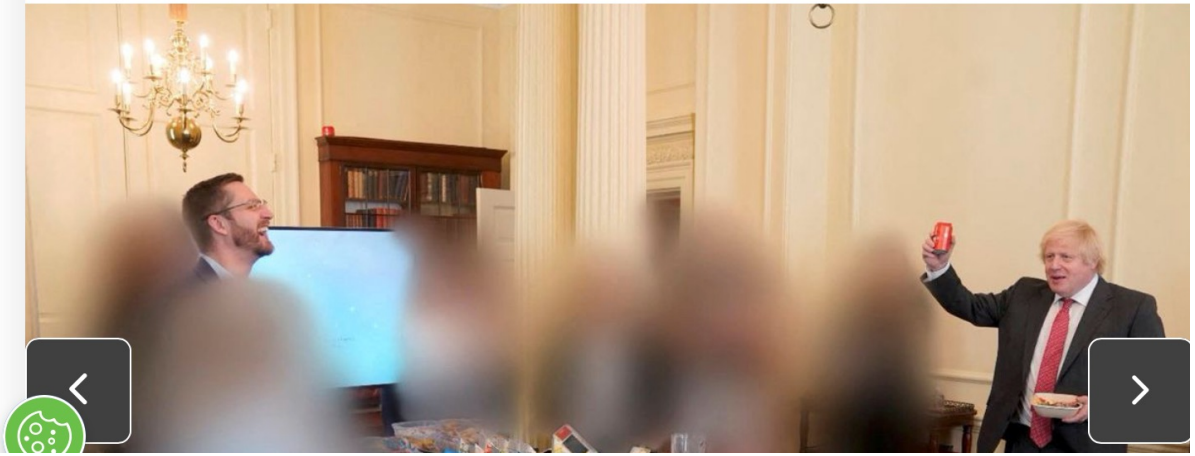
ago

Drunkenness, vomiting and a scuffle at UK government lockdown parties

By Andrew Macaskill and William James

3 minute read



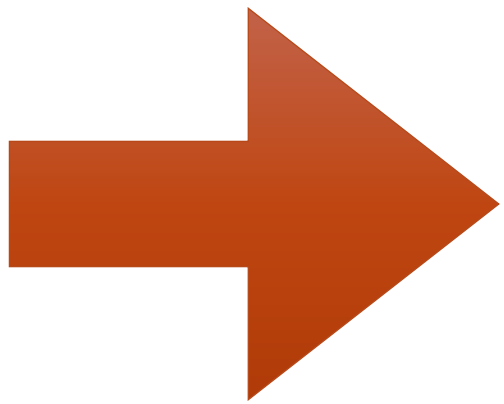
	Monday	Tuesday	Wednesday
Tonic	X		
Gin	X		
Vodka			
Whiskey			

	Monday	Tuesday	Wednesday
🤮	X		
Tonic	X		
Gin	X		
Vodka			
Whiskey			

	Monday	Tuesday	Wednesday
🤮	X	X	
Tonic	X	X	
Gin	X		
Vodka		X	
Whiskey			

	Monday	Tuesday	Wednesday
🤮	X	X	X
Tonic	X	X	X
Gin	X		
Vodka		X	
Whiskey			X


Schweppes
Indian
TONIC WATER
contains quinine
96
kcal

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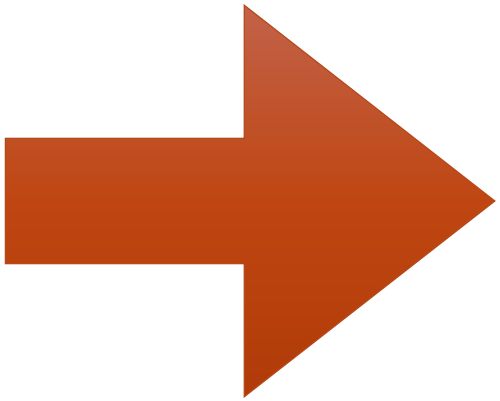


?

CEREBRAL VENTRICULAR SIZE AND COGNITIVE IMPAIRMENT IN CHRONIC SCHIZOPHRENIA

EVE C. JOHNSTONE T. J. CROW
C. D. FRITH JANET HUSBAND
L. KREEL

Divisions of Psychiatry and Radiology, Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ

Summary By comparison with age-matched controls in employment, 17 institutionalised schizophrenic patients were shown by computerised axial tomography of the brain to have increased cerebral ventricular size. Within the group of schizophrenic patients increased ventricular size was highly significantly related to indices of cognitive impairment.

THE LANCET, OCTOBER 30, 1976

Northwick Park Hospital and Clinical Research Centre who were matched with the index group for age, and as closely as possible for premorbid occupational attainment. The mental states of the patients and controls were assessed in terms of the rating scale devised by Krawiecka et al.[10] A total score of positive features of schizophrenia (delusions, hallucinations and thought disorder) and negative features of schizophrenia (retardation, flattening of affect, and muteness) was derived from this rating. The cognitive functioning of the patients and controls was assessed on the clinical tests devised by Withers and Hinton.[11] Physical examination was carried out and routine testing of all patients included full blood-count, erythrocyte-sedimentation rate, serum B_{12} and folate, specific serology, liver-function tests, and thyroid-function tests.

EMI scans of the brain were obtained in 17 of 18 schizophrenics and from 8 controls. Tomographic sections through the brain were taken beginning at, and continuing parallel to, the orbitomeatal line, at 1 cm intervals to the vertex. Two images at comparable levels were selected for each patient. One showed the body of the lateral ventricles and the other showed the anterior and posterior horns of the lateral ventricles together with the third ventricle. The images were photographed and the area of the ventricles in each photograph was measured with a planimeter, an instrument which measures the area contained within a circumference. These measurements were made blindly on two separate occasions by two independent investigators, giving four measurements on each subject. No attempt was made in this study to assess the size of the sulci, in view of the difficulties of finding an objective and reliable means of measurement.

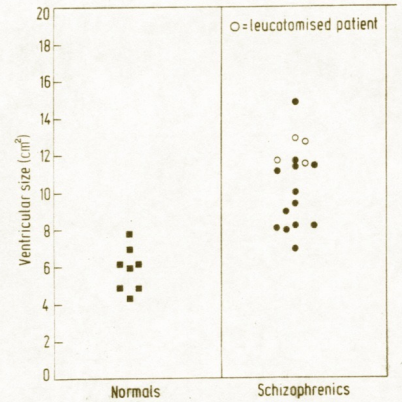
TABLE III—RELATIONSHIP OF CLINICAL FEATURES TO VENTRICULAR SIZE IN SCHIZOPHRENIC PATIENTS (LEUCOTOMISED CASES OMITTED)

Comparison	Correlation coefficient	No. of patients	Significance
Age v. ventricular size	r= 0·21	13	N.S.
Cognitive function[11] v. ventricular size	r=−0·70	13	P<0·01
Positive features v. ventricular size	r=−0·24	13	N.S.
Negative features v. ventricular size	r= 0·38	13	N.S.

Results

There were no obvious discrepancies between the ages and occupations of the control (table I) and patient (table II) groups. The mental states of the control group showed no abnormality on the Krawiecka scale. The schizophrenics performed significantly less well than the control group on the Withers and Hinton tests of cognitive function (P<0·001).

In the EMI-scan assessments there was a high correlation between the measurements obtained by the two separate observers (cut 1, r=0·96, P<<0·001; cut 2, r=0·94, P<<0·001) and apparently this is a reliable method of measuring ventricular size. The correlation between the measurements at the two levels in the same patient was high (cut 1 *v* cut 2, r=0·68, P<0·001), and this suggests that minor variation in exact site of the tomographic sections is unlikely significantly to affect assessment of ventricular size.



Ventricular size in patients and controls.

Each point represents average of four measurements on photographs.

The figure shows the mean of the four measurements of ventricular size. Leucotomy is associated with increased ventricular size and in some cases with distortion of the ventricles. For this reason the leucotomised patients were omitted from all calculations except those concerning the effects of leucotomy. Ventricular size in the schizophrenic group, with leucotomised patients excluded, is significantly greater than that in the control group (P<0·01). The relationship between ventricular size and clinical features within the schizophrenic group (leucotomised patients excluded) is shown in table III. In this group there is a significant association between increased ventricular size and poor performance on the Withers and Hinton test battery (P<0·01). This impairment emerges principally in those items in the battery that place greatest demands on memory—e.g., serial

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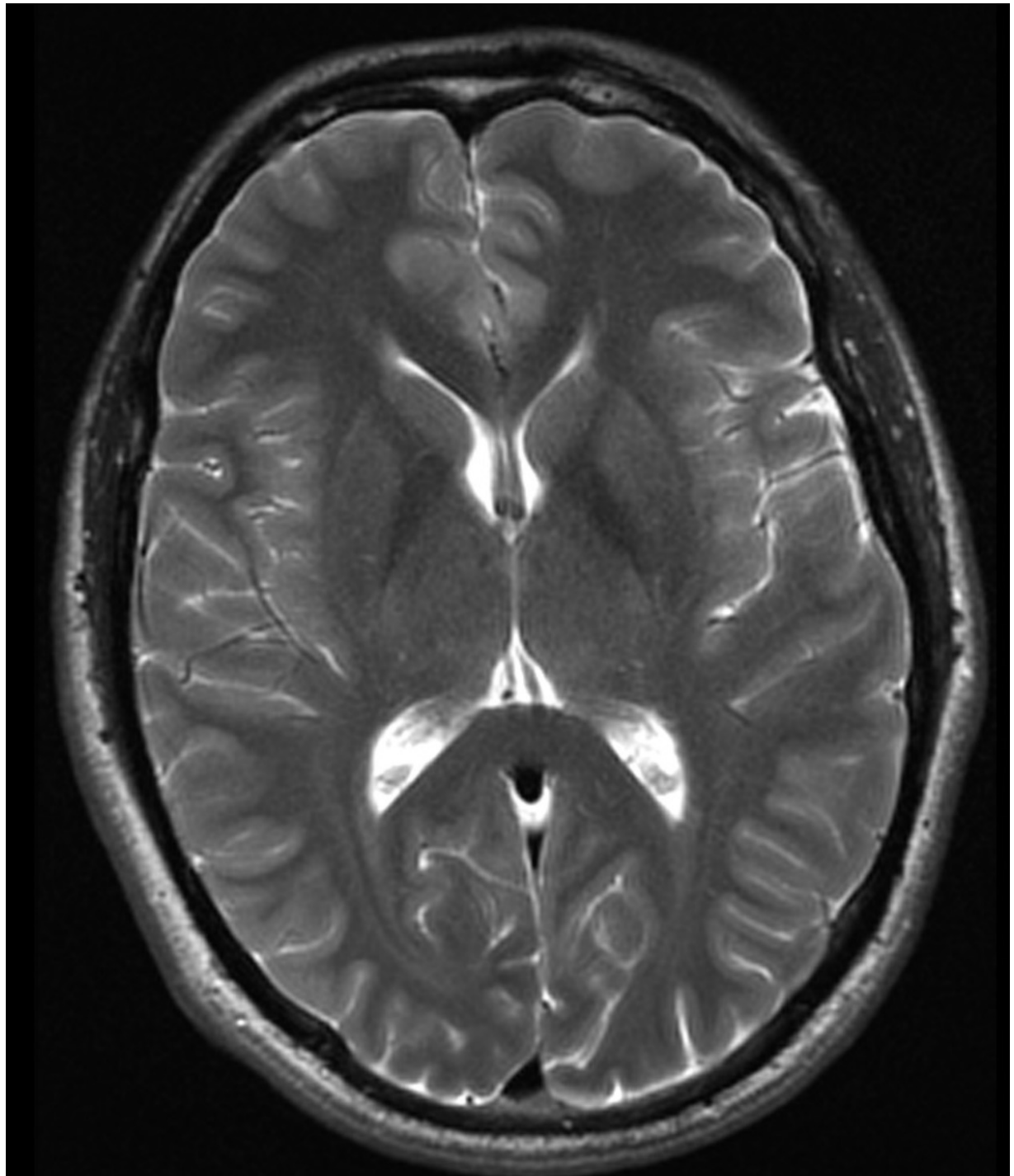
Form of treatment	Mean ventricular size 29 cm		No. of cases		t	P
	With treatment	Without treatment	With treatment	Without treatment		
Leucotomy	12·3 S.D. 0·70	9·9 S.D. 2·20	4	13	2·06	<0·05 (1 tailed)
E.C.T.	9·9 S.D. 2·96	9·97 S.D. 1·57	6	7	0·04	N.S.
Phenothiazines	9·3 S.D. 1·76	11·3 S.D. 2·76	9	4	1·57	N.S.
Institutionalisation	8·5 S.D. 1·45	11·2 S.D. 2·0	6	7	2·71	<0·05



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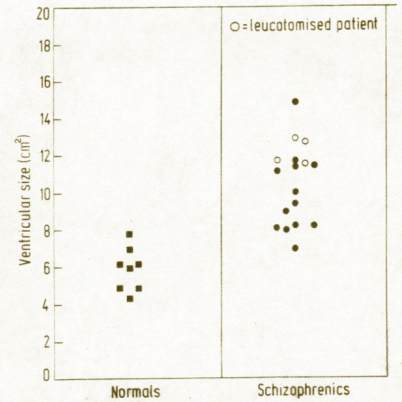

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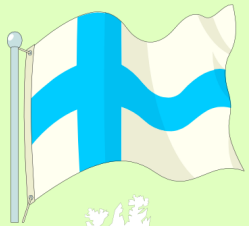
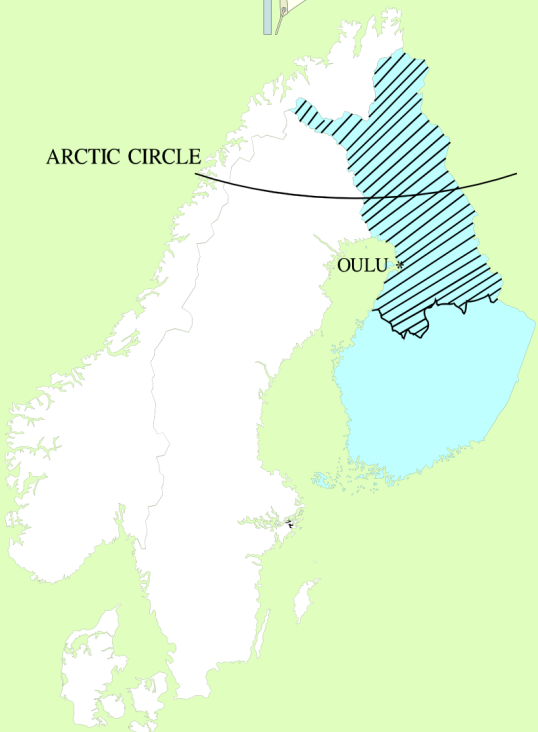
Take home message 1

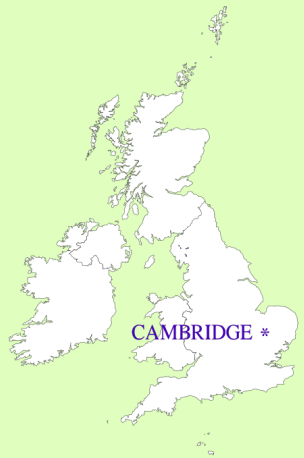
Cross sectional imaging* studies don't tell you much about causality

* nothing special about imaging here - the point is relevant to most observational association studies

THE NORTHERN FINLAND 1966 BIRTH COHORT STUDY

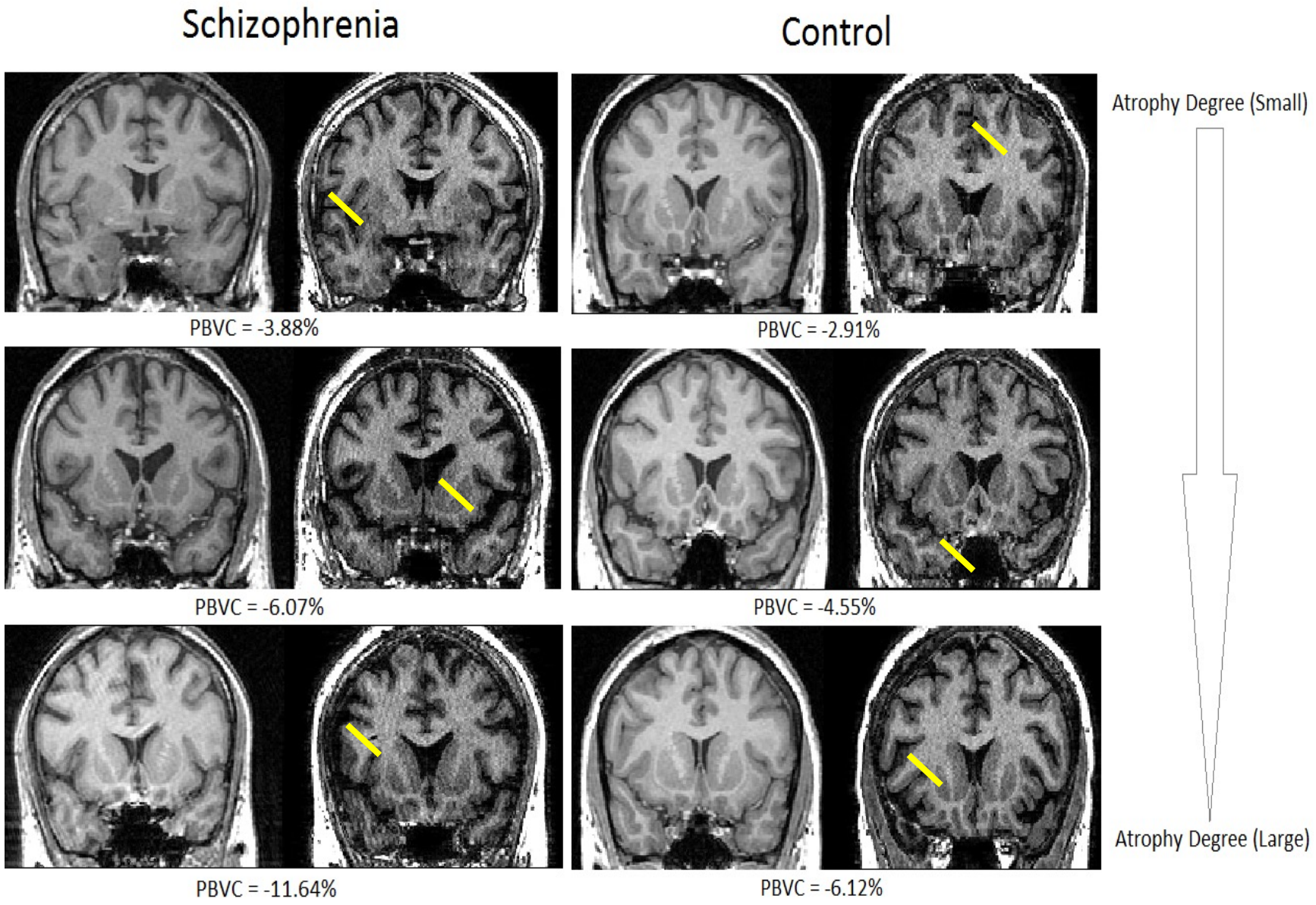






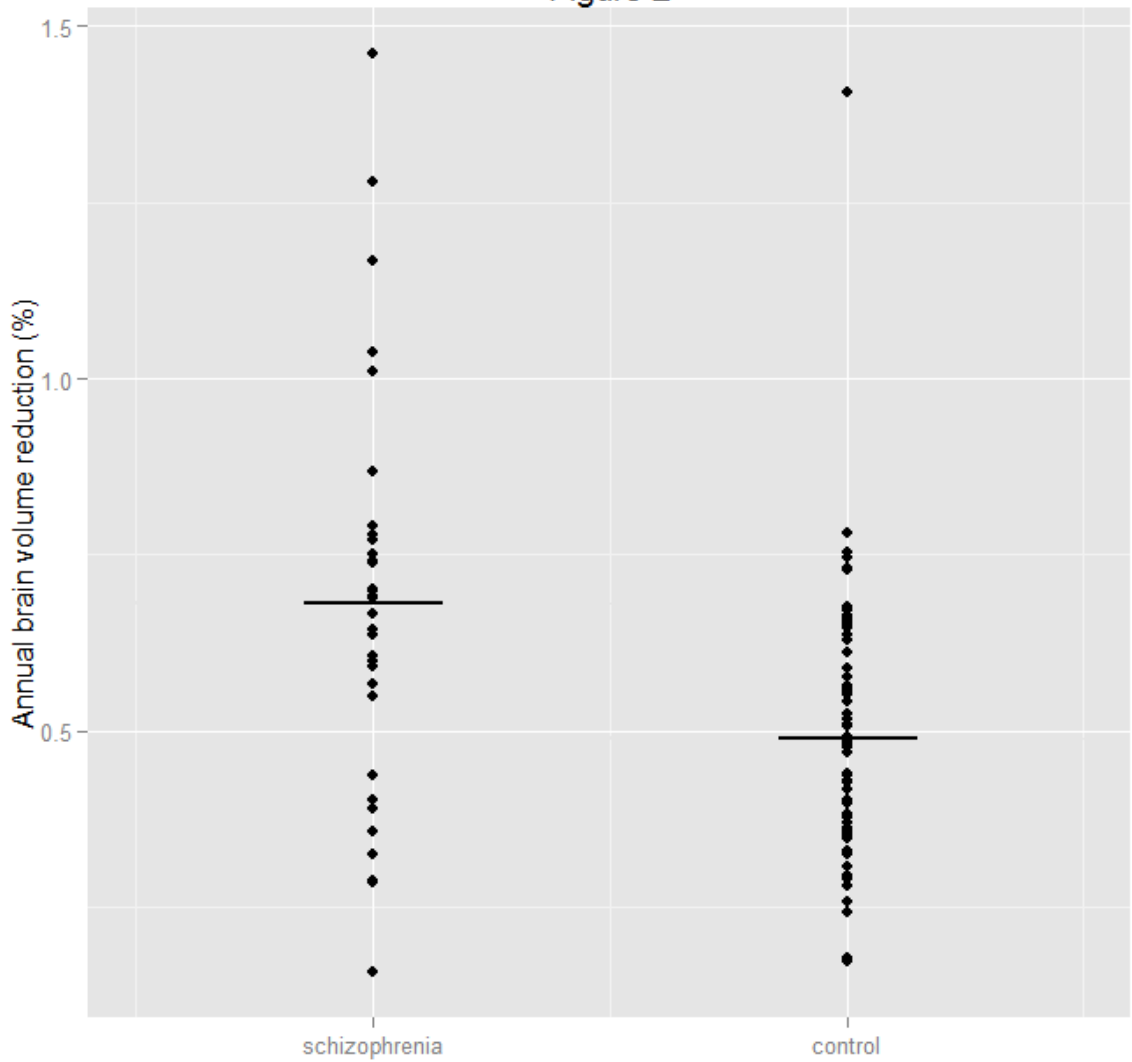
Methods

- All members of the Northern Finland Birth Cohort 1966 with any psychotic disorder and a random sample not having psychosis invited
- Assessment during 1999-2001 at the age of 33-35 years.
- Follow-up 9 years later during 2008-2010.
- Brain scans at both time points from 33 people with schizophrenia and 71 controls



PBVC: **P**ercent **B**rain **V**olume **C**hange

Figure 2


Annual brain volume reduction (%)
1.5
1.0
0.5
schizophrenia
control

Do antipsychotics cause loss of brain volume?

R^2=0.24, p=0.004

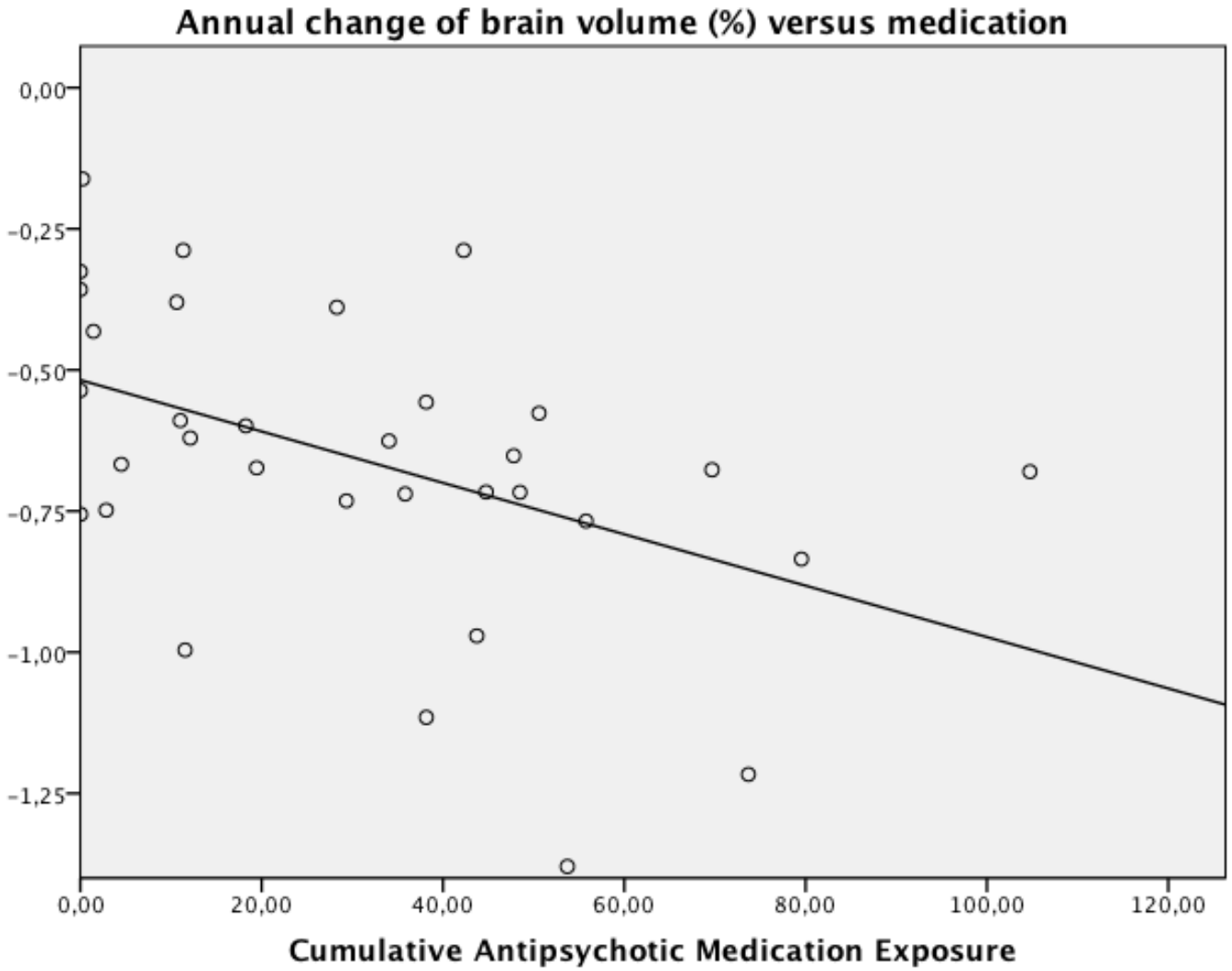
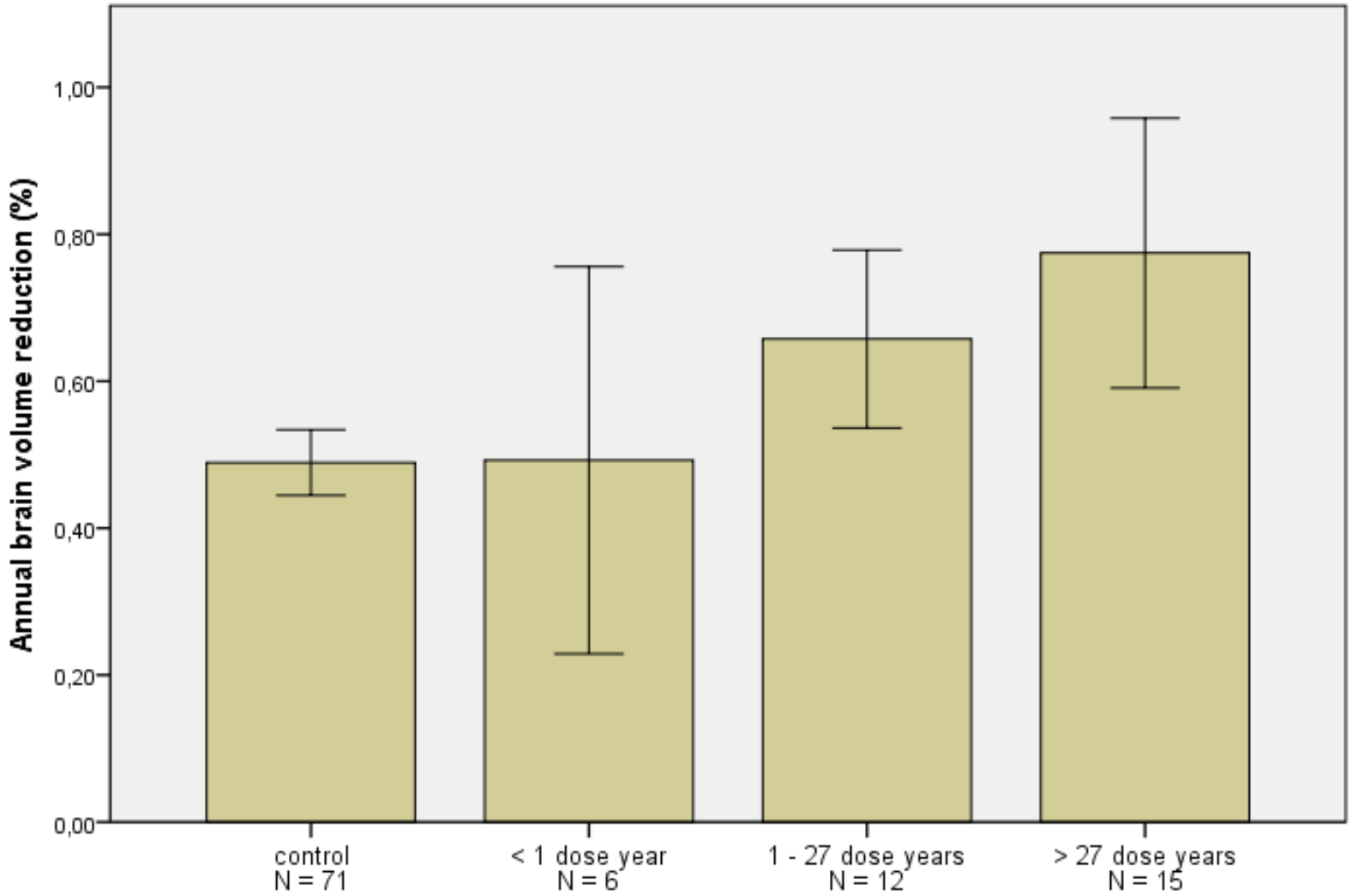


Figure 4



Control subjects and subjects with schizophrenia in three dose years categories of antipsychotic medication

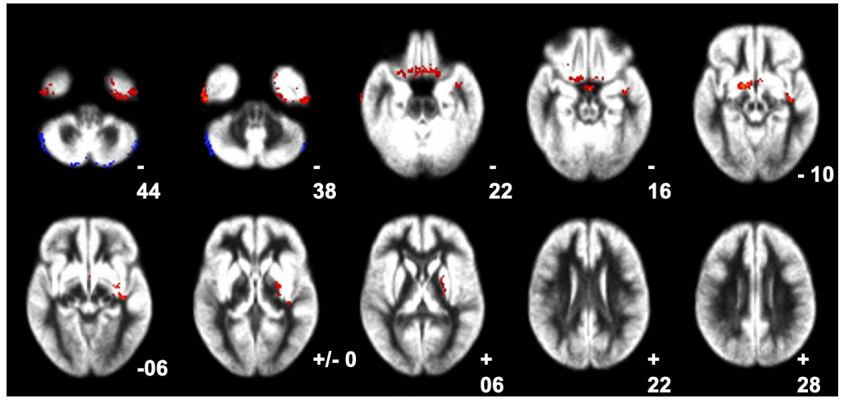
Error Bars: 95% CI

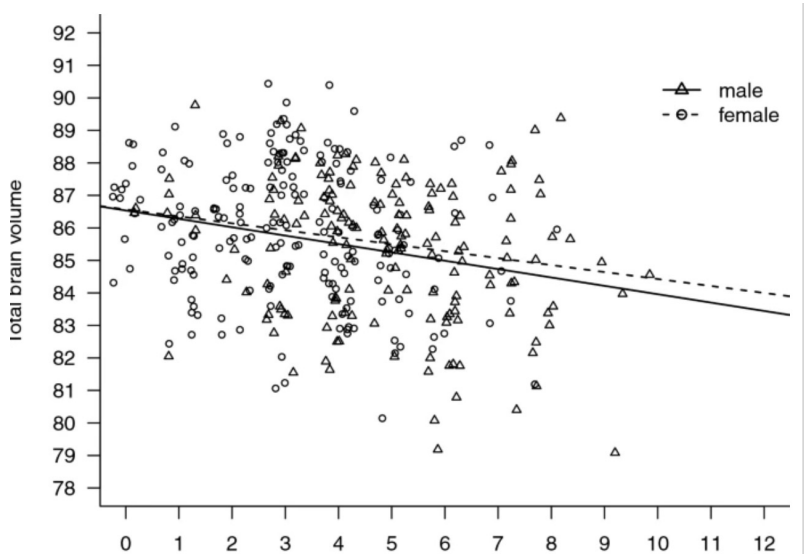
Take home message 2

Longitudinal imaging* studies don't tell you much about causality either

* nothing special about imaging here: the point holds for most longitudinal observational association studies

Brain Areas Associated with “being a people person”

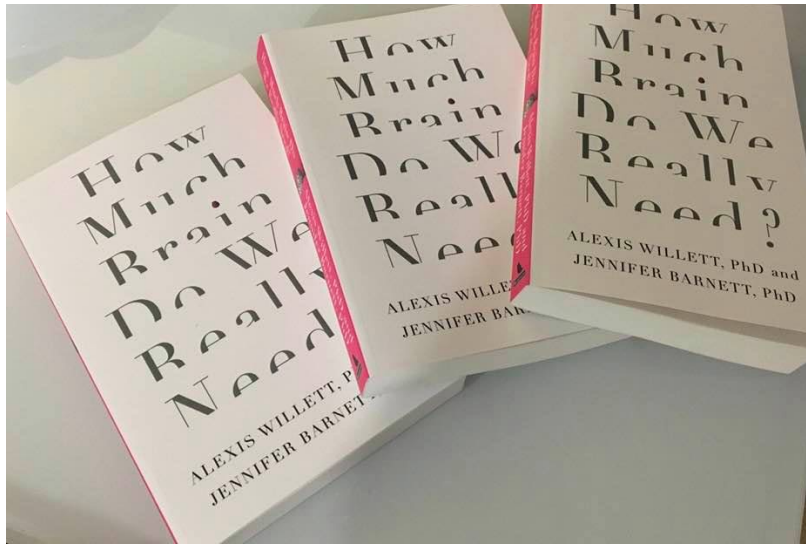




ELSEVIER

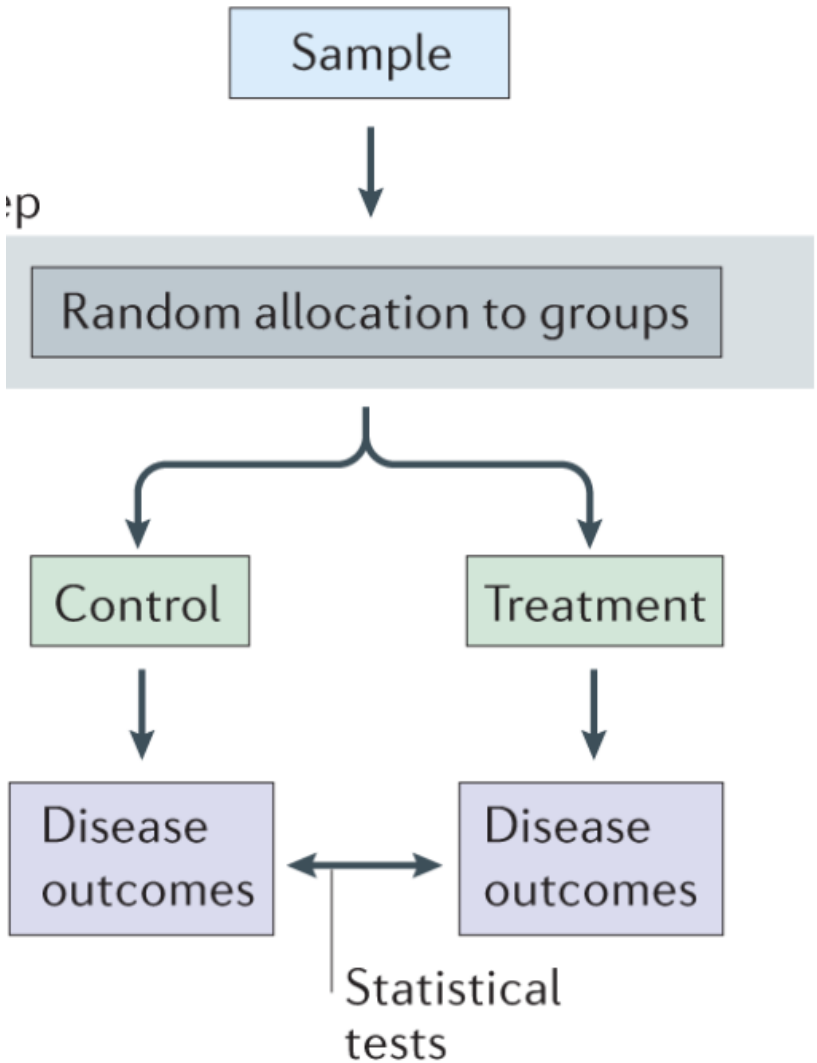
International Journal of Hygiene and Environmental Health

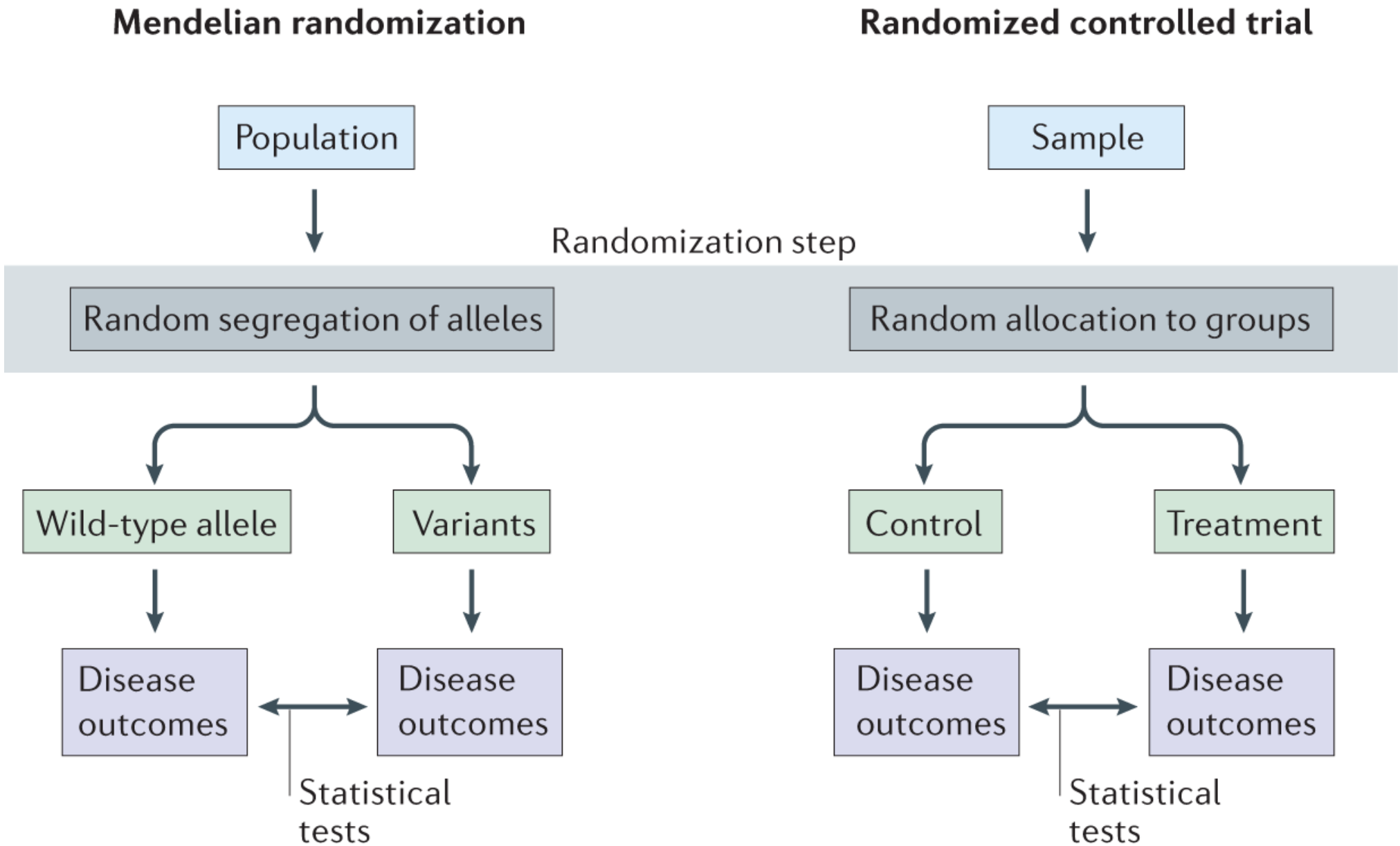
Volume 239, January 2022, 113867



Long-term air pollution, noise, and structural measures of the Default Mode Network in the brain: Results from the 1000BRAINS cohort

Randomized controlled trial





Sanderson et al 2022

Limitations of observational studies

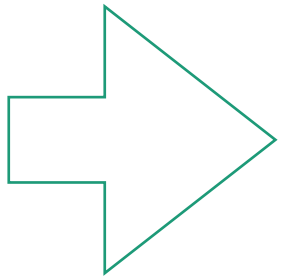
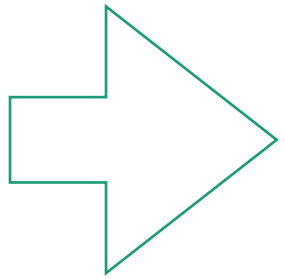
- Residual and/or unmeasured confounding
- Measurement error
- Reverse causation
- Limited opportunity to explore mediating relationships

Mendelian randomisation (MR)

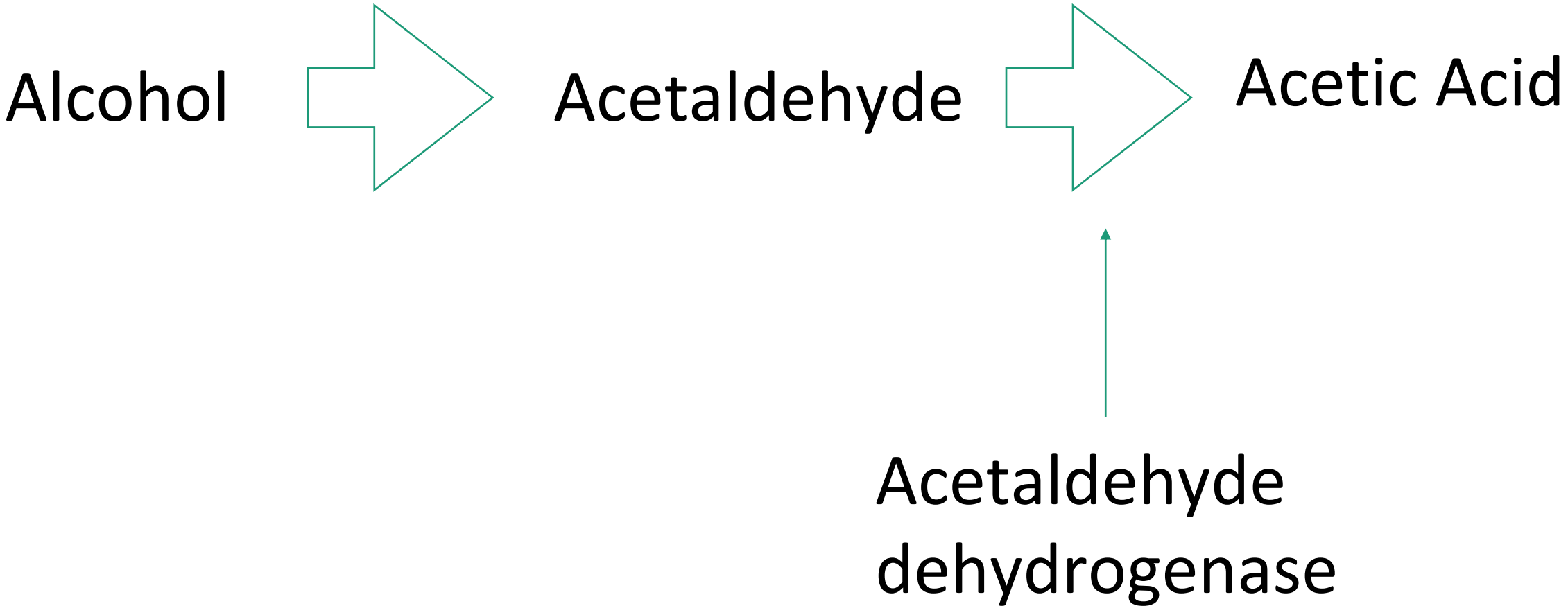
- A form of instrumental variable analysis
- Uses genetic variants as proxies for environmental exposures
- Robust to many limitations of observational study designs
- Provides evidence of lifetime causal effects of exposures on disease risk
- In a RCT, randomly assigned treatment evaluates the effect of treatment on the outcome, whereas in MR, a genetic variant is treated as a naturally occurring form of randomization.

Anderson, Int J Epidemiol, 2020; Raghavan, Neurol Genet, 2019; Larsson, BMJ, 2017 ; Sanderson 2022

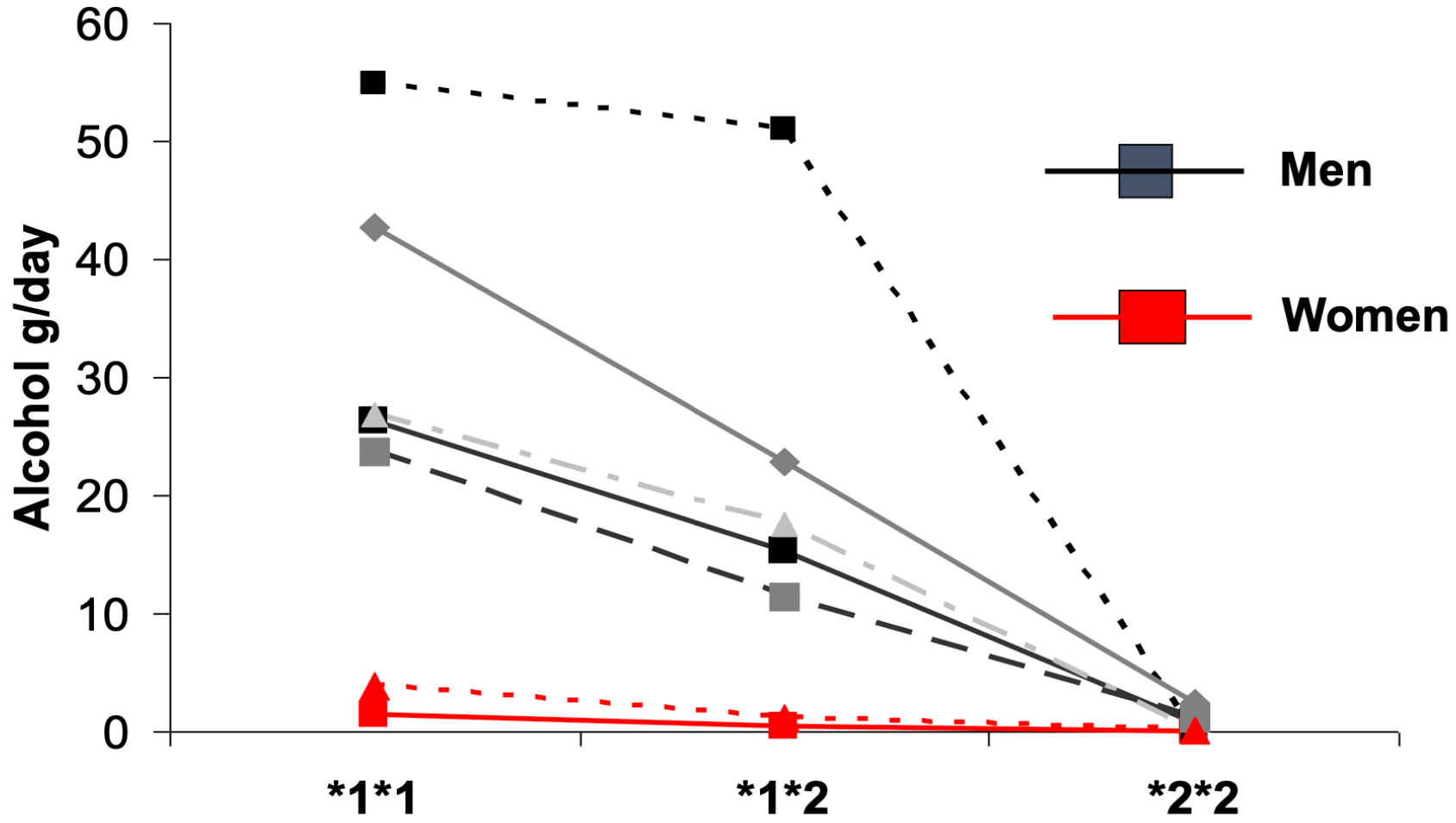
Metabolism of Alcohol in the Liver

Alcohol  


Alcohol
Acetaldehyde

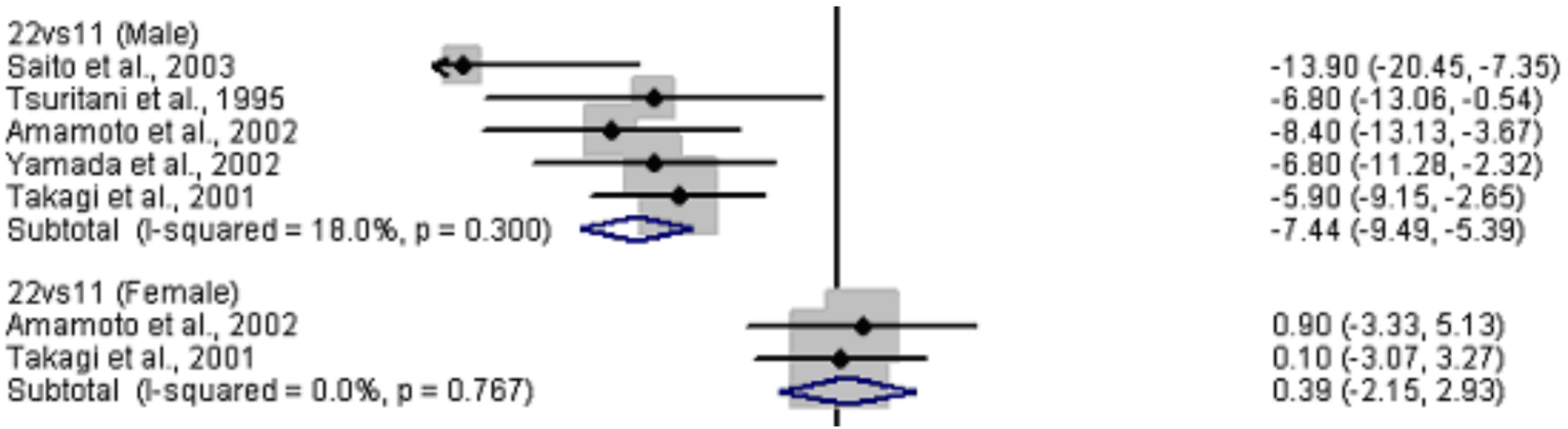

Alcohol
Acetaldehyde
Acetic Acid
Acetaldehyde dehydrogenase

ALDH2 genotype by alcohol consumption, g/day: 5 studies, n=6815

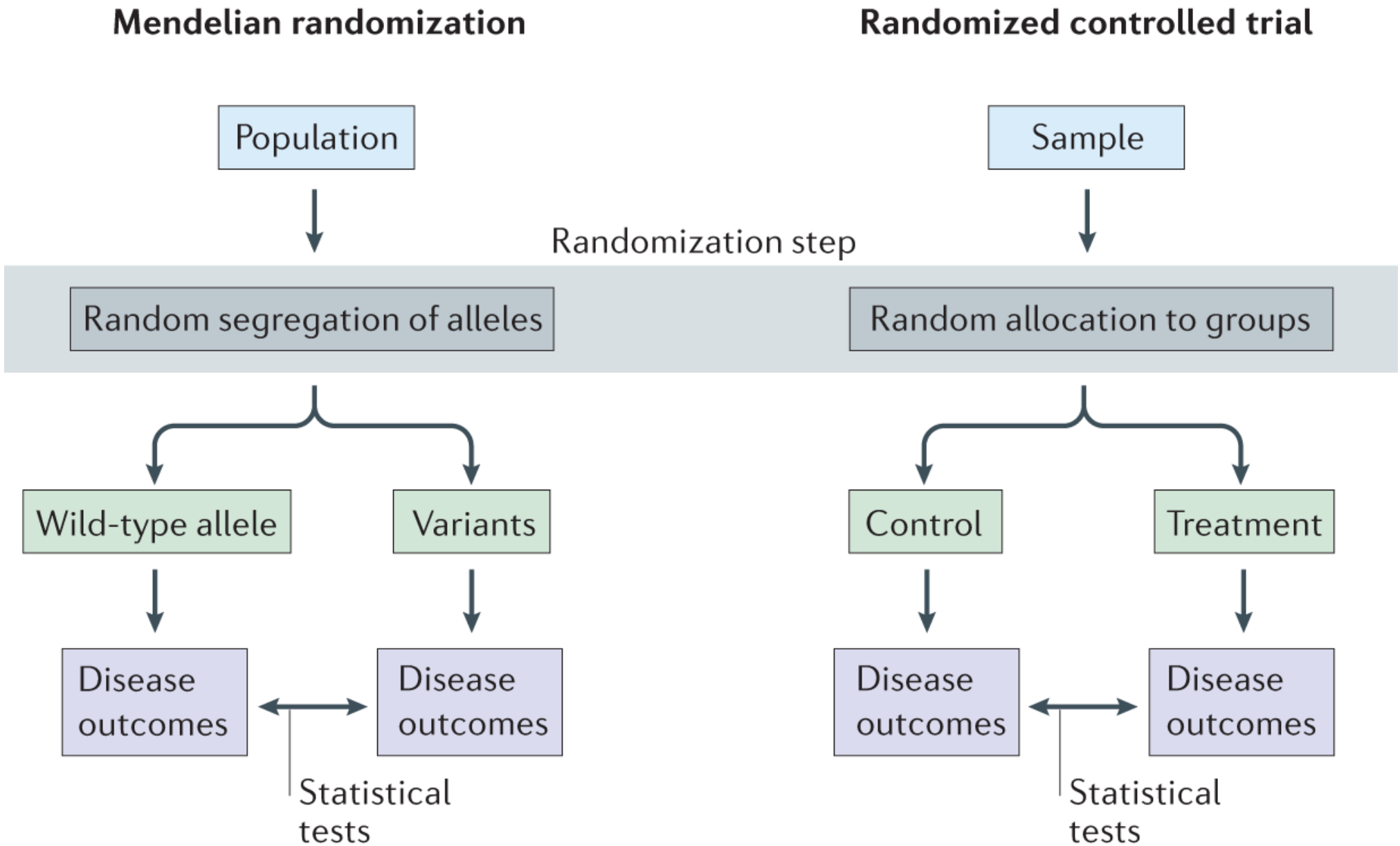


Chen, Davey Smith et al, PLoS Med 2008

ALDH2 genotype and systolic blood pressure



Chen et al, PLoS Medicine 2008

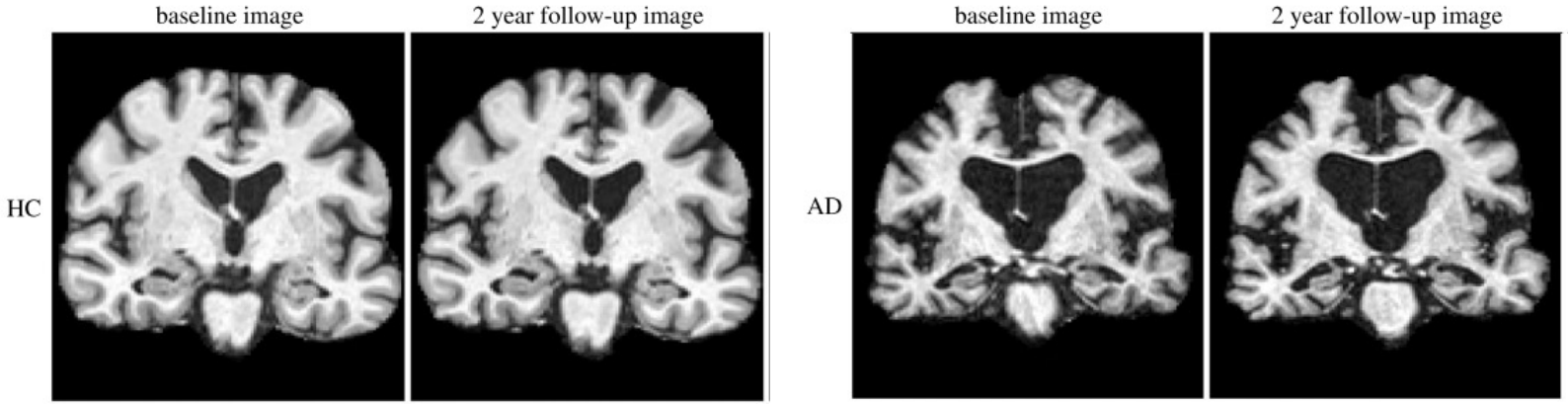


Sanderson et al 2022

Can optimising brain health prevent dementia?

Structural brain changes in Alzheimer's Dementia

- Reduced grey matter volume (Mak, Neuroimage Clin 2015)
- Cortical thinning (Koval, Sci Rep 2021)
- Reduced surface area (Yang, Gen Psychiatr 2019)



Policy context

BRAIN HEALTH:
A NEW WAY TO THINK ABOUT DEMENTIA RISK REDUCTION

January 2021

Alzheimer's Research UK

RSPH
ROYAL SOCIETY FOR PUBLIC HEALTH
VISION, VOICE AND PRACTICE

THINK BRAIN HEALTH

Valenzuela, Curr Opin Psychiatry 2008; Foubert-Samier, Neurobiol Aging 2012; Teipel, J Alzheimers Dis 2009; Cox Neurology 2016; Noble, 2012

Background: Alzheimer's disease & educational attainment

Educational attainment (EA) is a potentially modifiable protective factor for AD

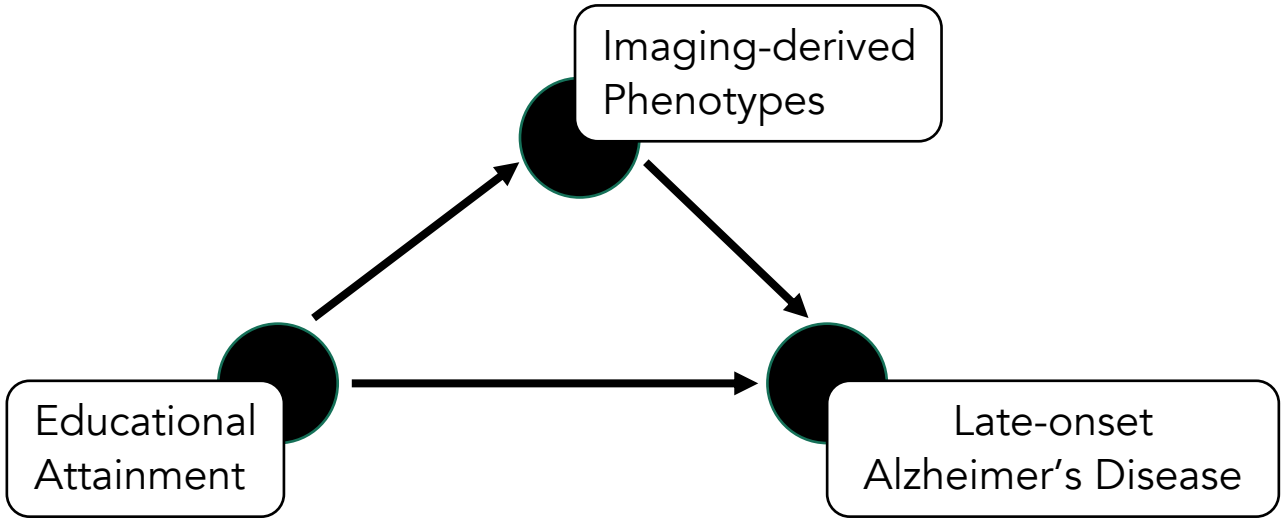
- Norton, Lancet Neurol 2014
  - Low EA associated with increased risk of AD (RR = 1.59, 95% CI 1.35–1.86)
  - Worldwide population attributable risk = 19.1% (95% CI 12.3–25.6%)
- Aetiological mechanisms unclear – insight into the biological underpinning of the association between EA and AD can inform the development of prevention strategies

Livingston, Lancet 2020; Meng, PLoS One 2012; Sharp, Alzheimer Dis Assoc Disord 2011; Kremen, Proc Natl Acad Sci USA 2019

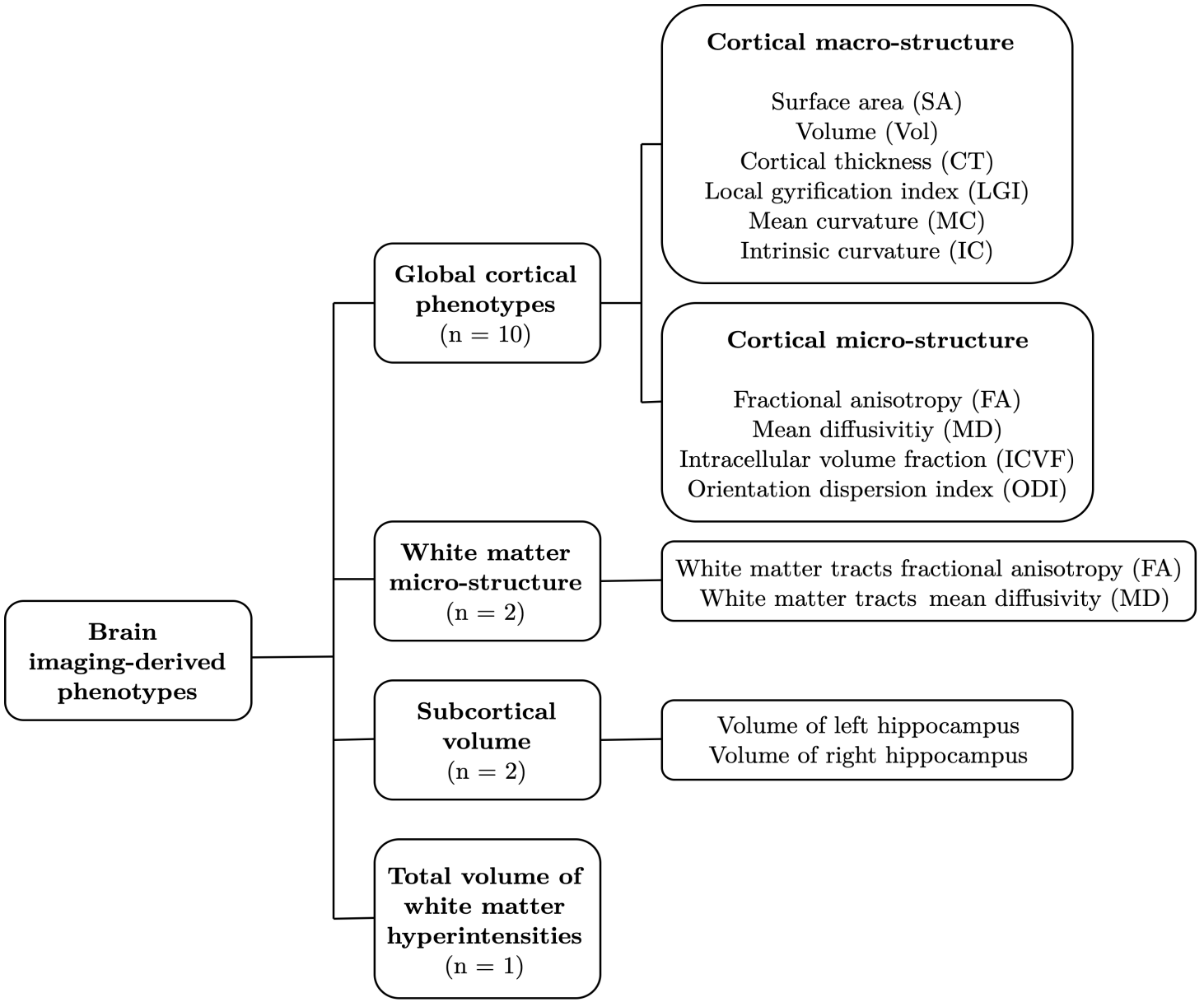
Objectives

Primary aims of investigation

- Test protective causal effect of educational attainment (EA) on late-onset Alzheimer's disease (AD)
- Assess whether brain structural phenotypes have a causal effect on late-onset AD
- Assess whether EA has a causal effect on brain structural phenotypes
- Assess whether the protective causal effect of EA on late-onset AD is mediated via changes to brain structure



Overview of imaging-derived phenotypes



Methods: Data sources & Instrumental variable selection

Summary statistics from the following GWAS:

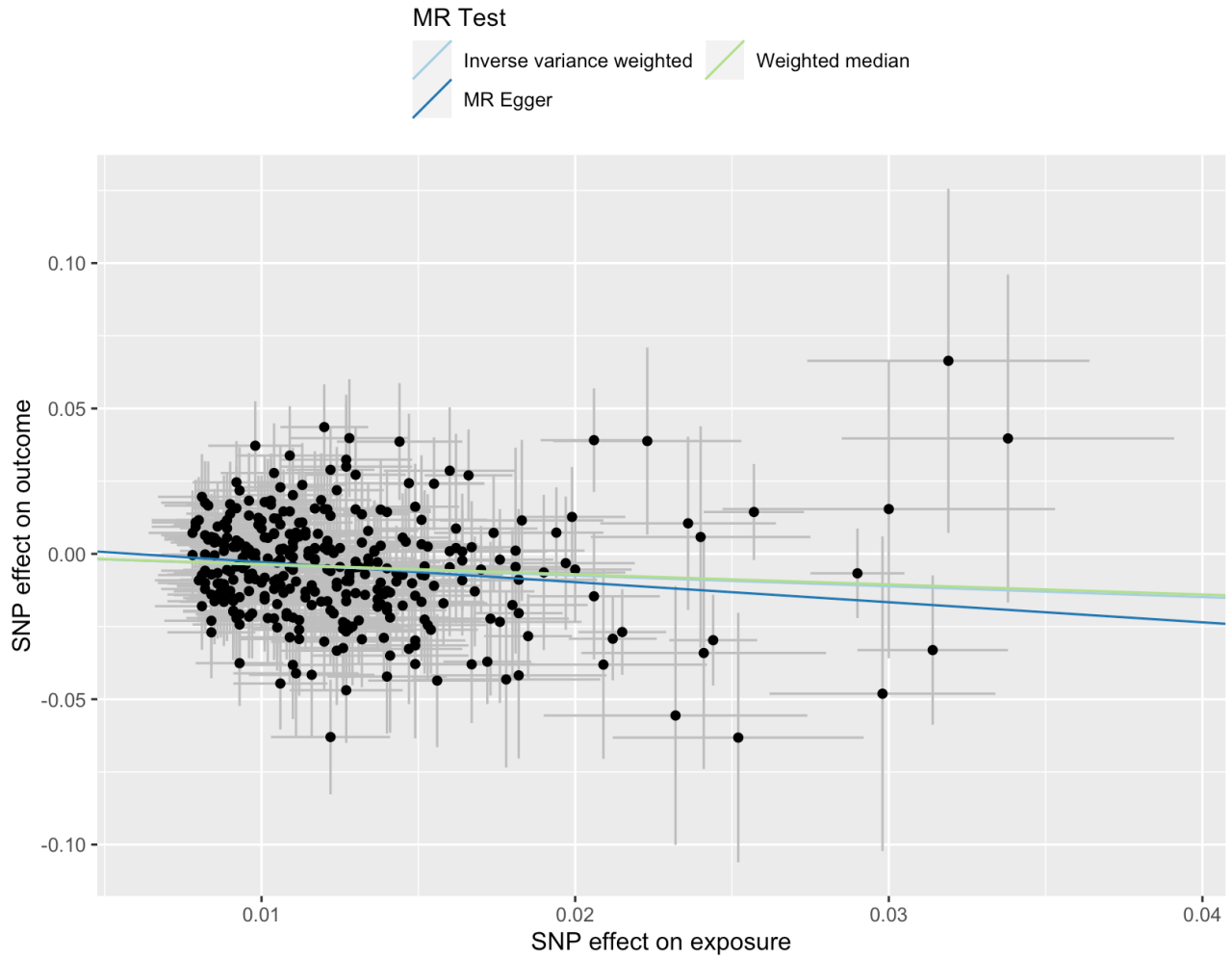
Phenotype	Source	Description	N
Late-onset Alzheimer's disease (LOAD)	Kunkle et al., Nat Genet, 2019	Clinical and autopsy-documented LOAD (onset age >65 years	35,274 AD cases and 59,163 controls
Educational attainment (EA)	Lee et al., Nat Genet, 2018	Number of years of schooling completed, measured at an age of at least 30 years	1,131,881
Brain imaging-derived phenotypes (IDPs)	Oxbridge GWAS: Smith et al Oxford Warrier/Bethlehem Cambridge	UK Biobank early-2020 release of combined multi-modal neuroimaging and genetic data	~40,000

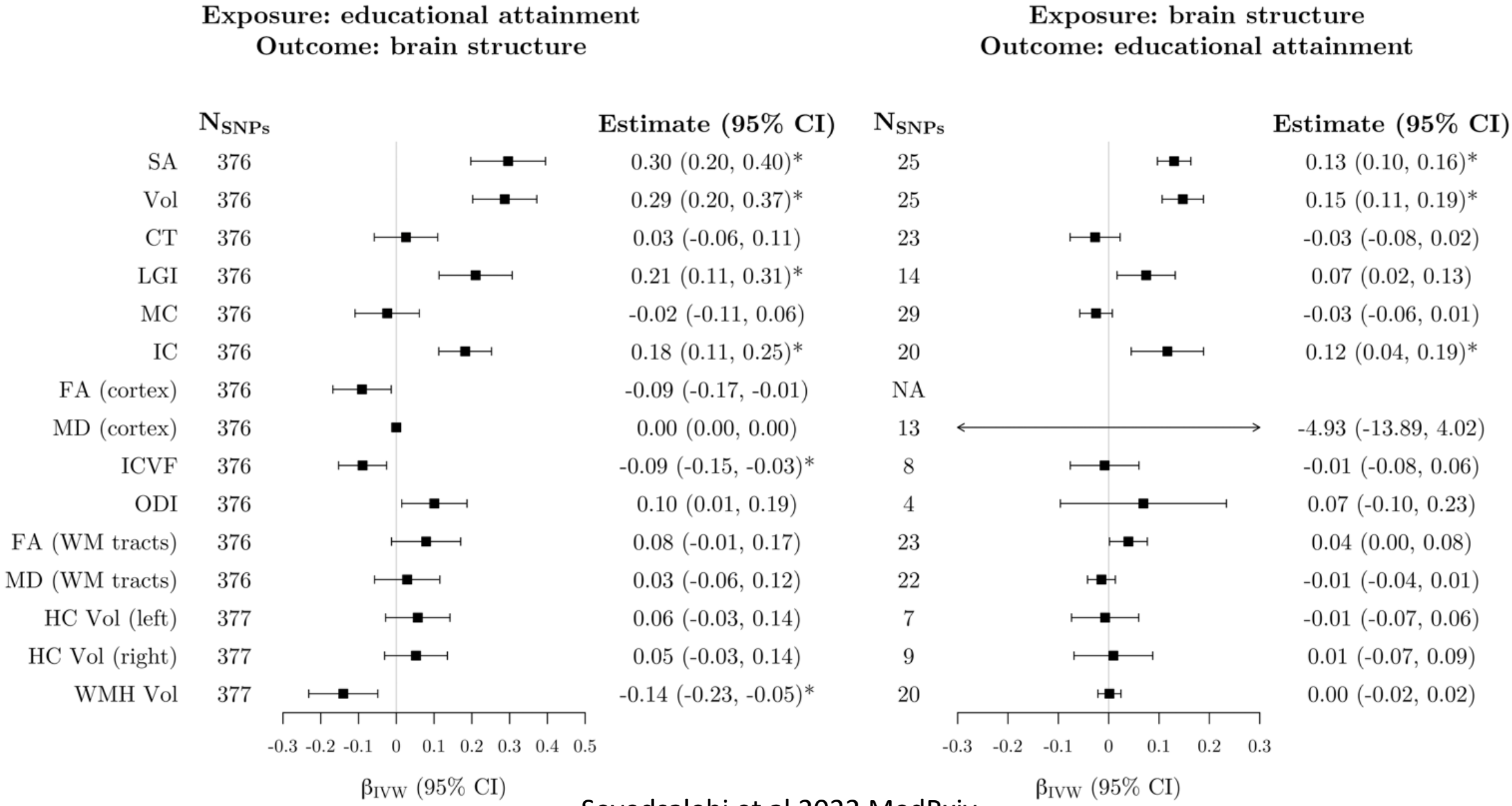
Instrumental variable selection

- All variants associated with the exposure at a genome wide significance threshold, $p < 5\times10^{-8}$
- To ensure independence amongst IVs, variants will be clumped using the following parameters: kb = 10000, $r^2 = 0.001$, $p = 5\times10^{-8}$
- Exclusion criteria: SNPs with known pleiotropy (ApoE region)

Protective causal effect of educational attainment on late-onset Alzheimer's disease

Analysis	Odds ratio (95% CI)	P-value	N SNPs
Inverse-variance weighted (IVW)	0.69 (0.60, 0.80)	$5.02\ 10^{-7}$	331
MR-Egger	0.50 (0.30, 0.85)	1.0510^{-2}	331
Weighted median MR	0.70 (0.56, 0.89)	$2.69\ 10^{-3}$	331





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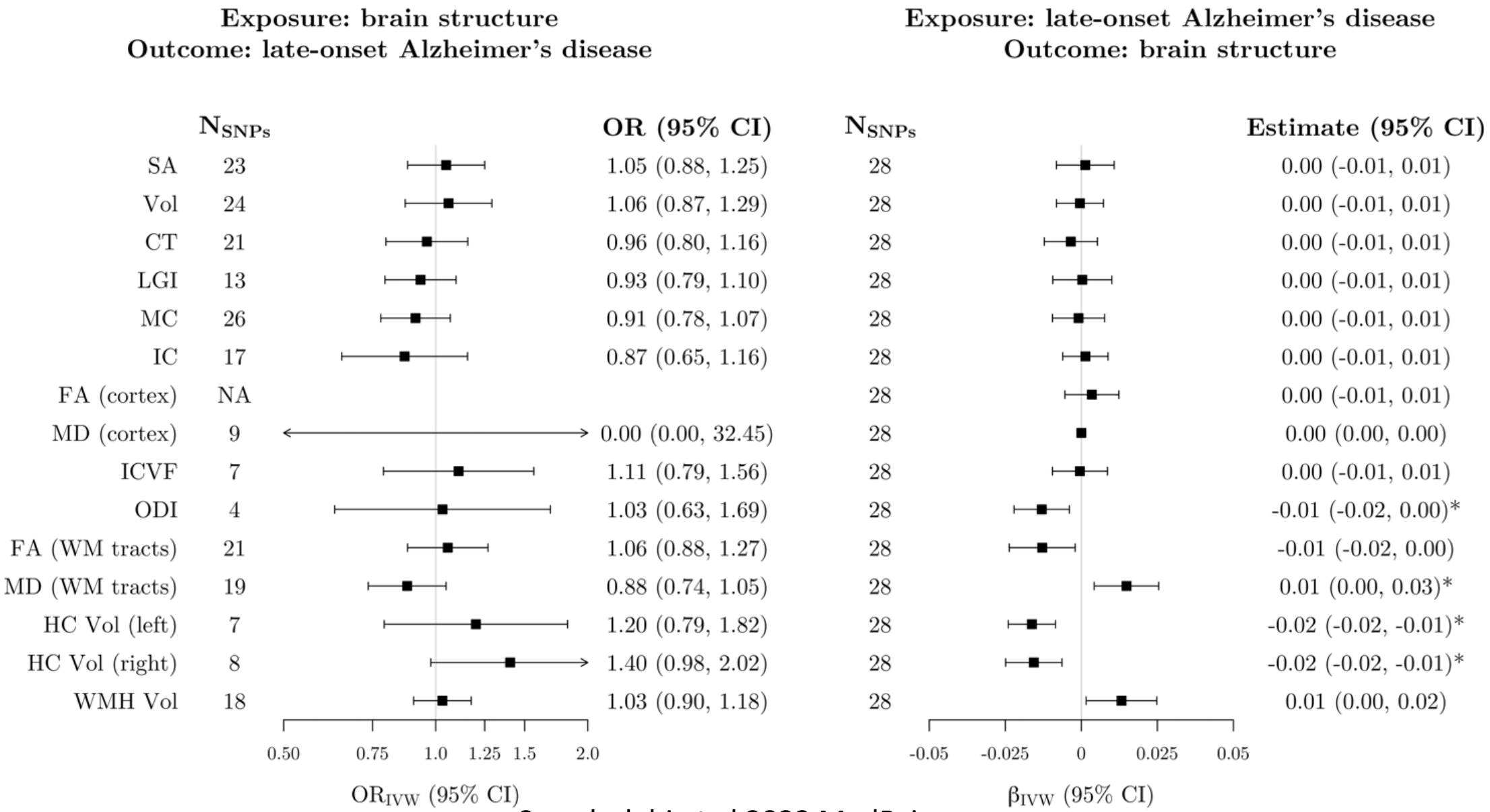

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Education's protective effect against AD is not mediated by (our measures of) brain structure

Table 2 Effect of educational attainment on Alzheimer's disease risk, estimated after n adjustment and after adjustment for brain structure phenotypes.

Adjustment	$OR_{MR\text{-}IVW}$ (95% CI)	*p*-value
None (univariable analysis)	0.70 (0.60, 0.80)	9.98×10^{-7}
Surface area	0.71 (0.62, 0.82)	3.68×10^{-6}
Volume	0.72 (0.62, 0.83)	6.12×10^{-6}
Cortical thickness	0.69 (0.60, 0.80)	3.62×10^{-7}
Local gyrification index	0.71 (0.61, 0.81)	1.39×10^{-6}
Mean curvature	0.69 (0.60, 0.79)	1.80×10^{-7}
Intrinsic curvature	0.71 (0.62, 0.82)	2.74×10^{-6}
Mean diffusivity (cortical)	0.70 (0.61, 0.81)	9.35×10^{-7}
Intracellular volume fraction	0.71 (0.62, 0.82)	2.72×10^{-6}
Orientation dispersion index	0.70 (0.61, 0.81)	8.65×10^{-7}
Fraction anisotropy (white matter)	0.71 (0.61, 0.81)	1.53×10^{-6}
Mean diffusivity (white matter)	0.71 (0.61, 0.82)	2.42×10^{-6}
Volume of left hippocampus	0.70 (0.61, 0.80)	5.66×10^{-7}
Volume of right hippocampus	0.70 (0.61, 0.81)	7.74×10^{-7}
White matter hyperintensities volume	0.71 (0.61, 0.81)	1.43×10^{-6}

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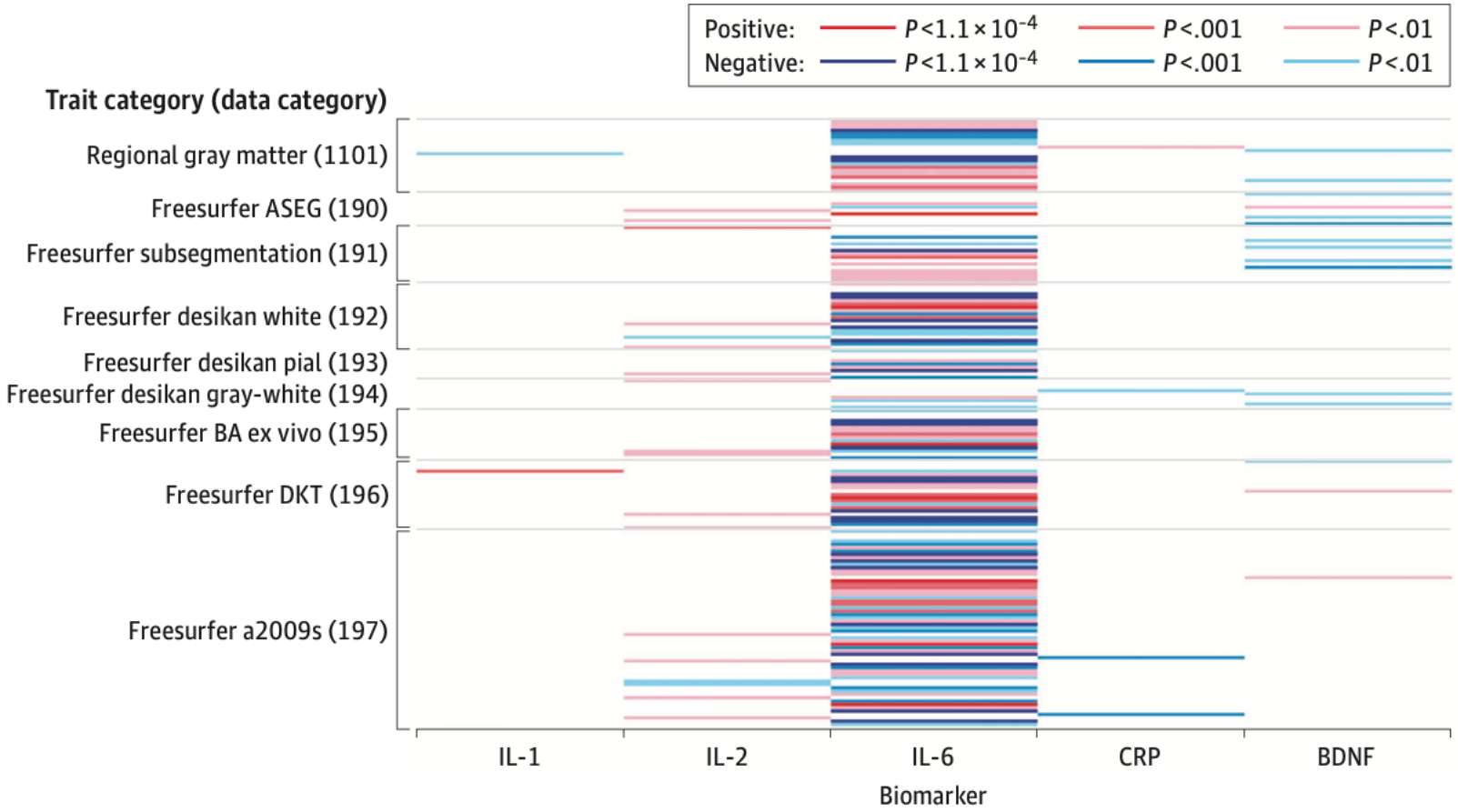
Discussion

- **No evidence that brain structure, as measured here, has a causal effect on AD risk**
- No evidence for the primary mediation hypothesis
- Some interesting observations relating education to brain structure

Discussion

- Our brain imaging measures are imperfect and necessarily our brain phenotypes reflect only what our MRI technology can currently measure
- We could have looked at brain regions at a finer resolution (but were concerned about multiple testing)
- In spite of imaging GWAS sample size of >30,000, the number of independent genetic SNP instruments was modest, and power calculation suggested we only had power to detect moderate or large effects of genetically predicted brain structure on AD.
- We weren't able to identify an anatomical measure of brain reserve in this study

Figure 2. Heat Map of Associations Between Genetically Predicted Inflammatory Biomarkers and Brain Imaging Measures



Brain imaging measures from UK Biobank, with data categories from the UK Biobank Brain Imaging Catalogue, and their association with inflammatory biomarkers are shown. Brain imaging measures having no associated inflammatory biomarkers at $P < .01$ are omitted from presentation; only the 166 measures with at least 1 associated biomarker are plotted. BDNF indicates brain-derived neurotrophic factor; CRP, C-reactive protein; IL-1, interleukin 1; IL-2, interleukin 2; IL-6, interleukin 6.

Williams et al 2022 JAMA psychiatry

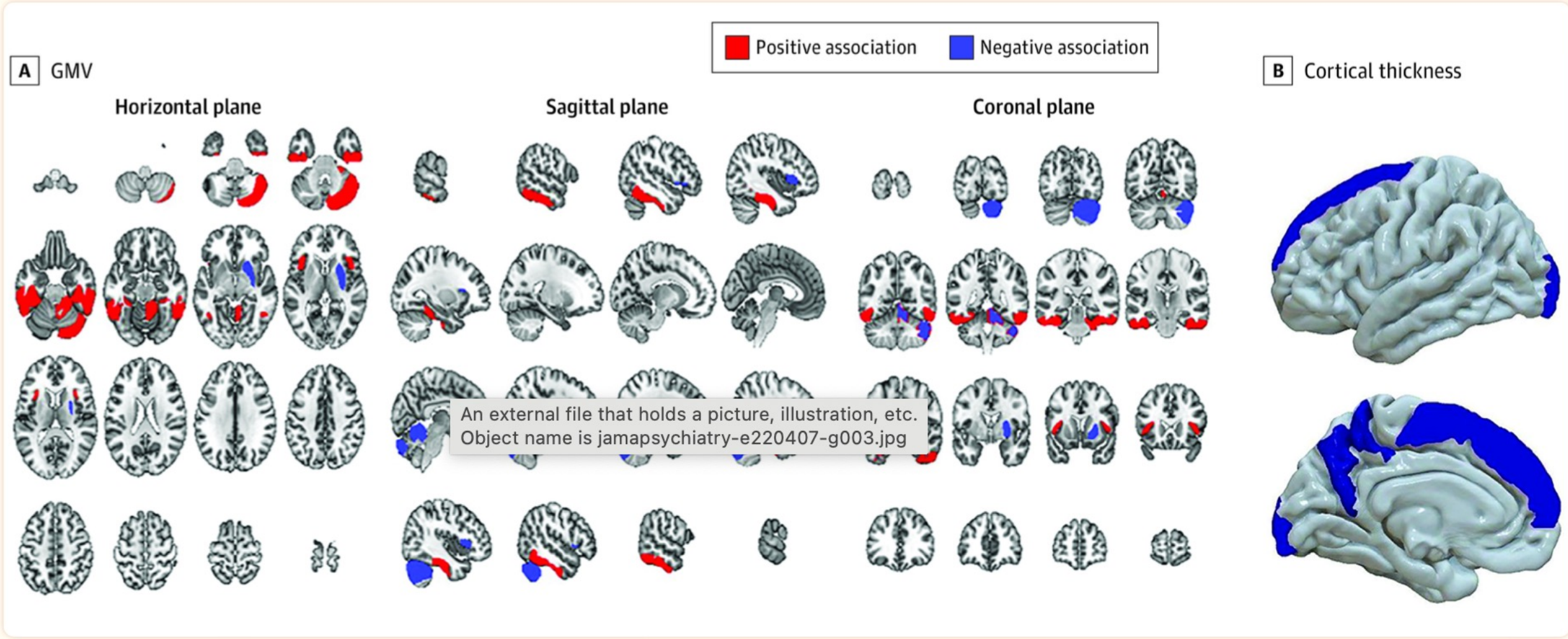
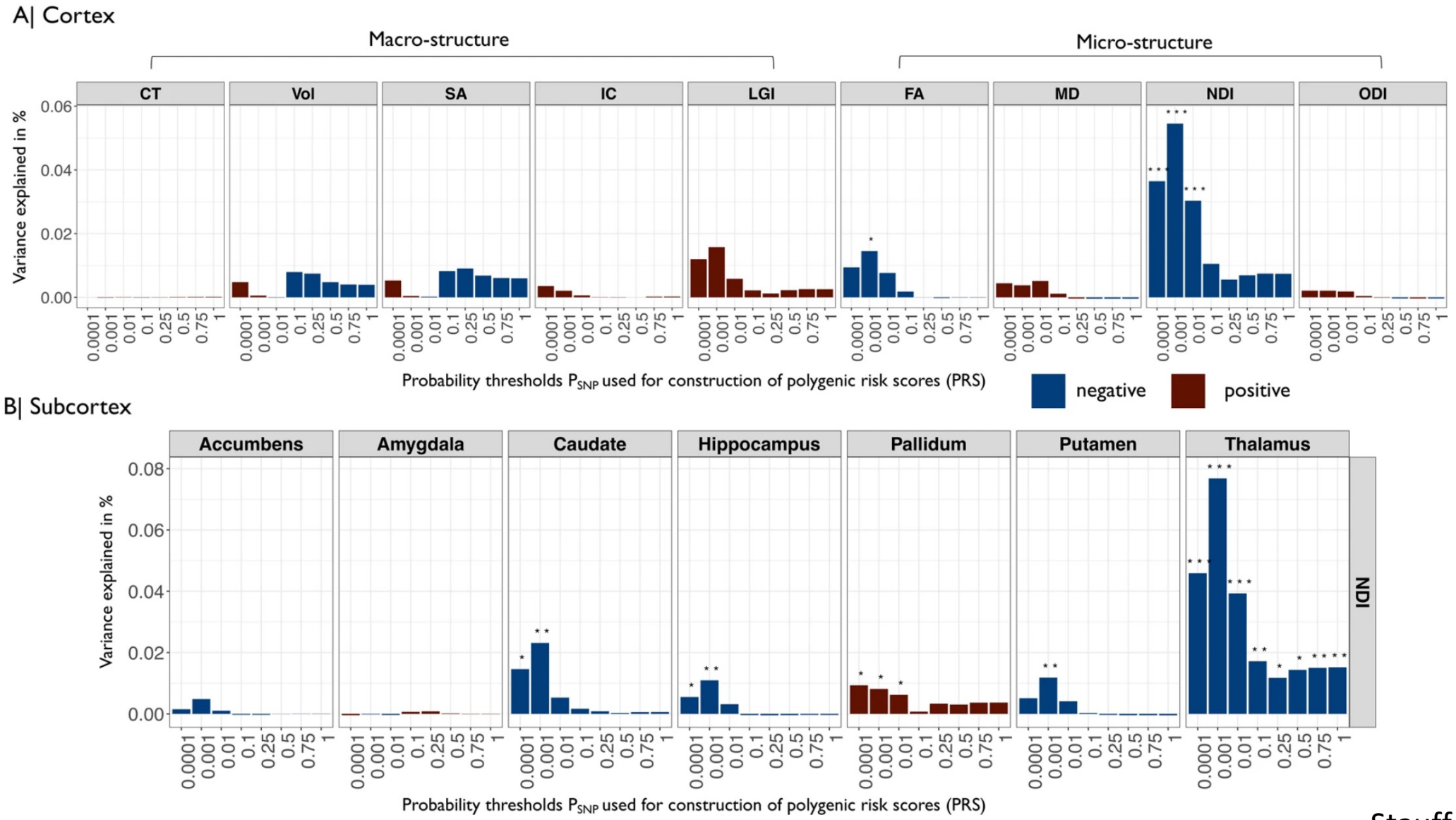


Figure 3.

Williams et al 2022 JAMA psychiatry

Brain Imaging Measures Associated With Genetically Predicted Levels of Interleukin 6 and Interleukin 6 Receptor Through Mendelian Randomization



Stauffer et al 2021

Lower genetically predicted NDI in the thalamus was associated with increased genetically predicted risk for schizop

Summary

- Observational studies are hard to interpret causally

- Mendelian randomisation offers potential insights into causal relations between brain structure and outcomes that matter to patients and clinicians
- Preliminary evidence that the IL-6 inflammatory pathway influences brain structure
- Preliminary evidence that educational attainment and brain structure are reciprocally causal, but that brain structure does not causally influence Alzheimer's risk.

THANK YOU

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