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Linear Mixed Models minimise false positive rate and enhance precision of mass-univariate vertex-wise analyses of grey-matter

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Program in Complex Trait Genomics

ARAMIS LAB BRAIN DATA SCIENCE

The University Of Queensland AUSTRALIA | IMB Institute for Molecular Bioscience

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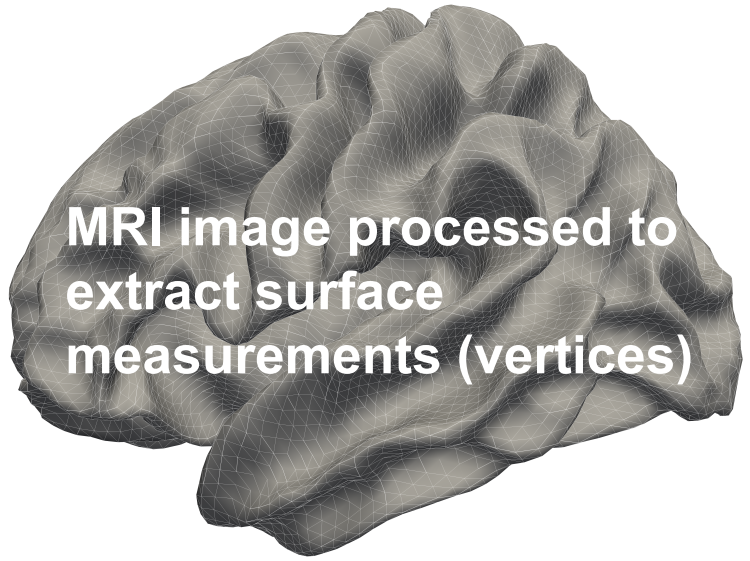
Mass-univariate vertex-wise analyses

Disease / trait

(e.g. Alzheimer's, cognition score, smoking status…)



Objective: find brain regions associated with phenotype

Context: "big-data" problem with more vertices/feature than participants

Current approach: test association with each vertex in turn (using **Generalised Linear Models: GLM**)

Rationale

- Vertices are correlated with each other due to factors unrelated to the phenotype of interest (e.g. geometry, MRI artifacts, age, sex)
- Vertices correlated with truly associated ones may also reach significance
- **PROBLEM**: **confounded association, pointing to "wrong" brain regions and redundant**

- **Linear Mixed Models (LMM)** can control for factors that cause correlation between features, leading to more robust association results (evidence from the OMICs literature)

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Advantages and pitfalls in the application of mixed model association methods

ic-data-based complex

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Aims

Compare state of the art (GLM) to Linear Mixed Models (LMM) for association studies of the brain

- False positive rate
- Statistical power
- Precision (size of associated regions/clusters)
- Prediction accuracy

1) **Using phenotypes simulated from real MRI images**
2) **Using real phenotypes (age, sex, BMI, fluid IQ and smoking status)**

T1w MRI image

DATA:

Processed T1w and T2 FLAIR MRI images

Vertices measure grey-matter structure (thickness and surface area)

UK Biobank: 10,102 volunteers from the UK, aged 44-80

For prediction and validation:

OASIS3: 732 adults some with Alzheimer's disease, aged 42-95

UK Biobank: another 4,942 participants from the UK

Simulation scenarios

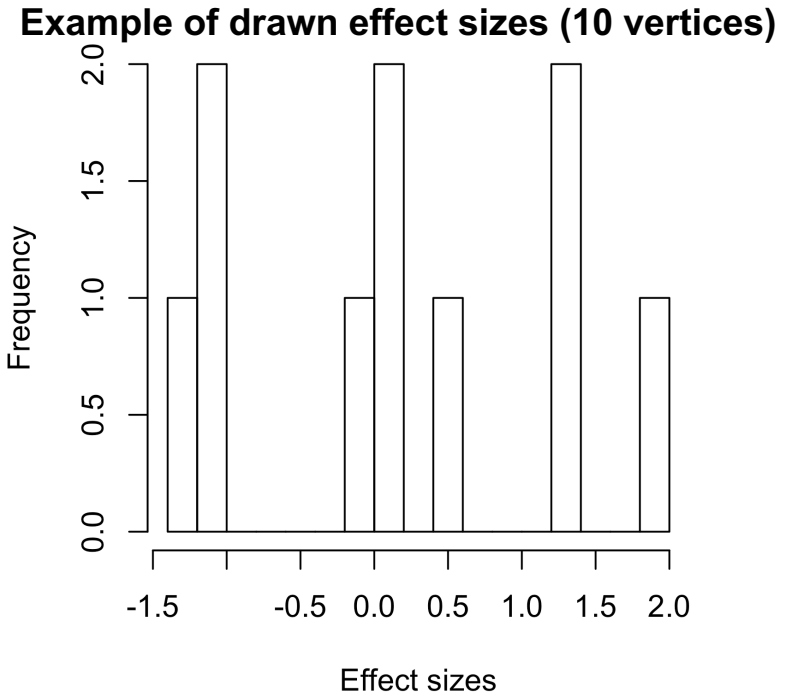
Phenotype simulation

- Randomly select associated vertices
- draw effect sizes (b_i) from a normal distribution
- Set the total association between vertices and phenotype (R^2 a.k.a. morphometricity)
- Construct simulated phenotype y as

y = sum($\mathbf{x}_i b_i$)+**ε** **with:**

$\mathbf{x}_i$ vector of standardised vertex measurement, at the i-th associated vertex

ε ~ N(0,var(sum($\mathbf{x}_i b_i$))(1/R^2-1))



Scenario 1:
10 associated vertices
Total R^2=0.2

⇒ Average vertex association r^2=0.02

Scenario 2:
100 associated vertices
Total R^2=0.5

⇒ r^2=0.005

Scenario 3:
1000 associated vertices
Total R^2=0.4

⇒ r^2=0.0004

For each scenario, we simulated 100 phenotypes

Models considered

GLM no covariates: pheno = u + b*vertex + ε

GLM with age, sex and ICV: pheno = u + b1*age + b2*sex + b3*ICV + b*vertex + ε

GLM with 5 principal components: pheno = u + b1*PC1 + … + b5*PC5 + b*vertex + ε

GLM with 10 principal components: pheno = u + b1*PC1 + … + b10*PC10 + b*vertex + ε

GLM with 10 modality specific Principal components: pheno = u + b1*$PC1_j$ + … + b10*$PC10_j$ + b*$vertex_j$ + ε

With j the modality (cortical thickness, area, subcortical thickness or area) of the vertex

LMM (global BRM) pheno = u + b*vertex + β + ε

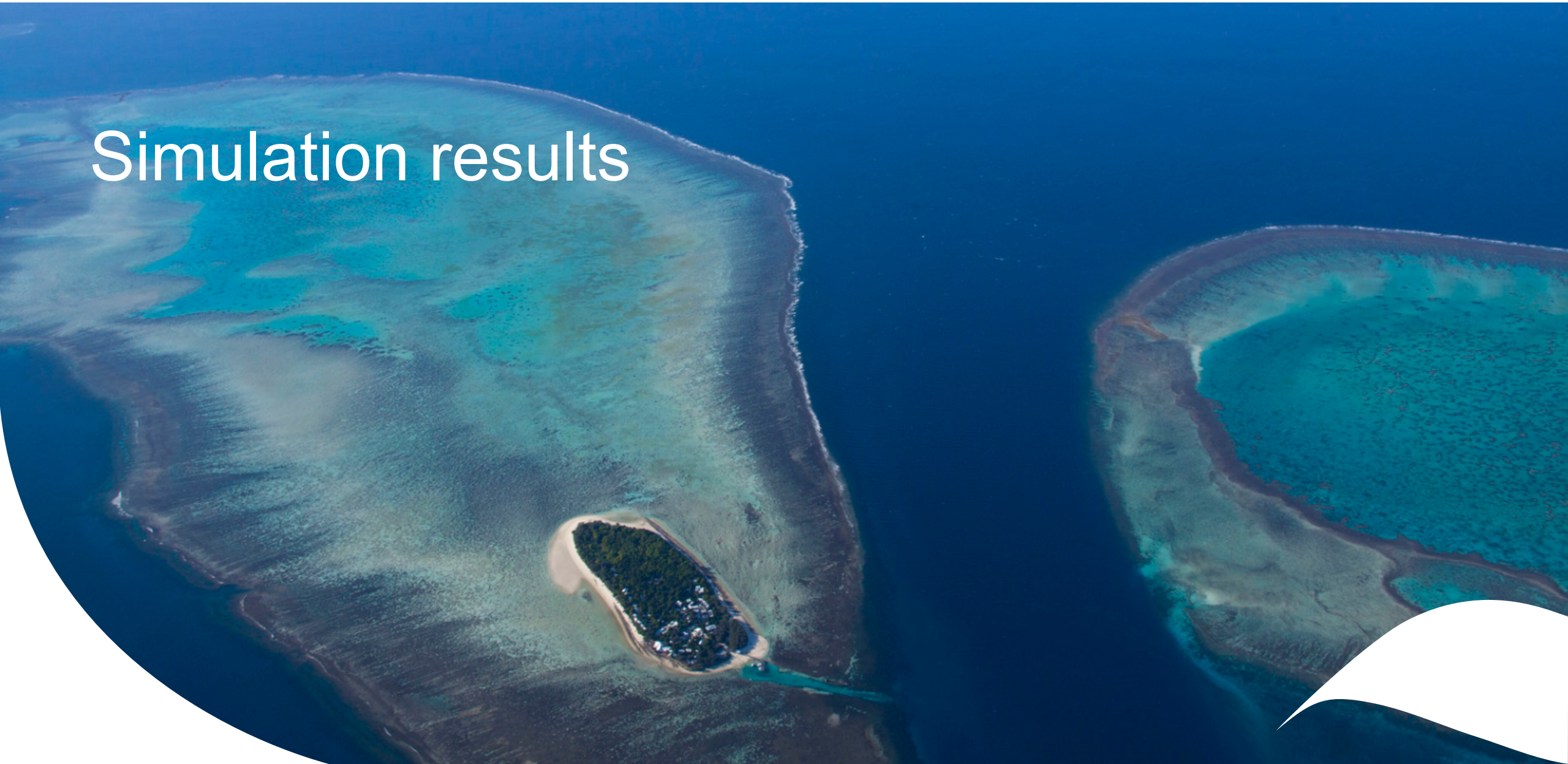
with $\beta \sim N(0, \mathbf{BRM} * \sigma^2)$

LMM (modality specific BRM) pheno = u + b*$vertex_j$ + $\beta_1 + \beta_2 + \beta_3 + \beta_4 + \varepsilon$

with $\beta_j \sim N(0, \mathbf{BRM_j} * \sigma_j^2)$ the random effect corresponding to a single modality

We apply **Bonferroni correction for multiple testing** in all the following

Simulation results



Inflation of ("null") test statistics

Compare observed and expected distribution of test statistics of non-associated vertices

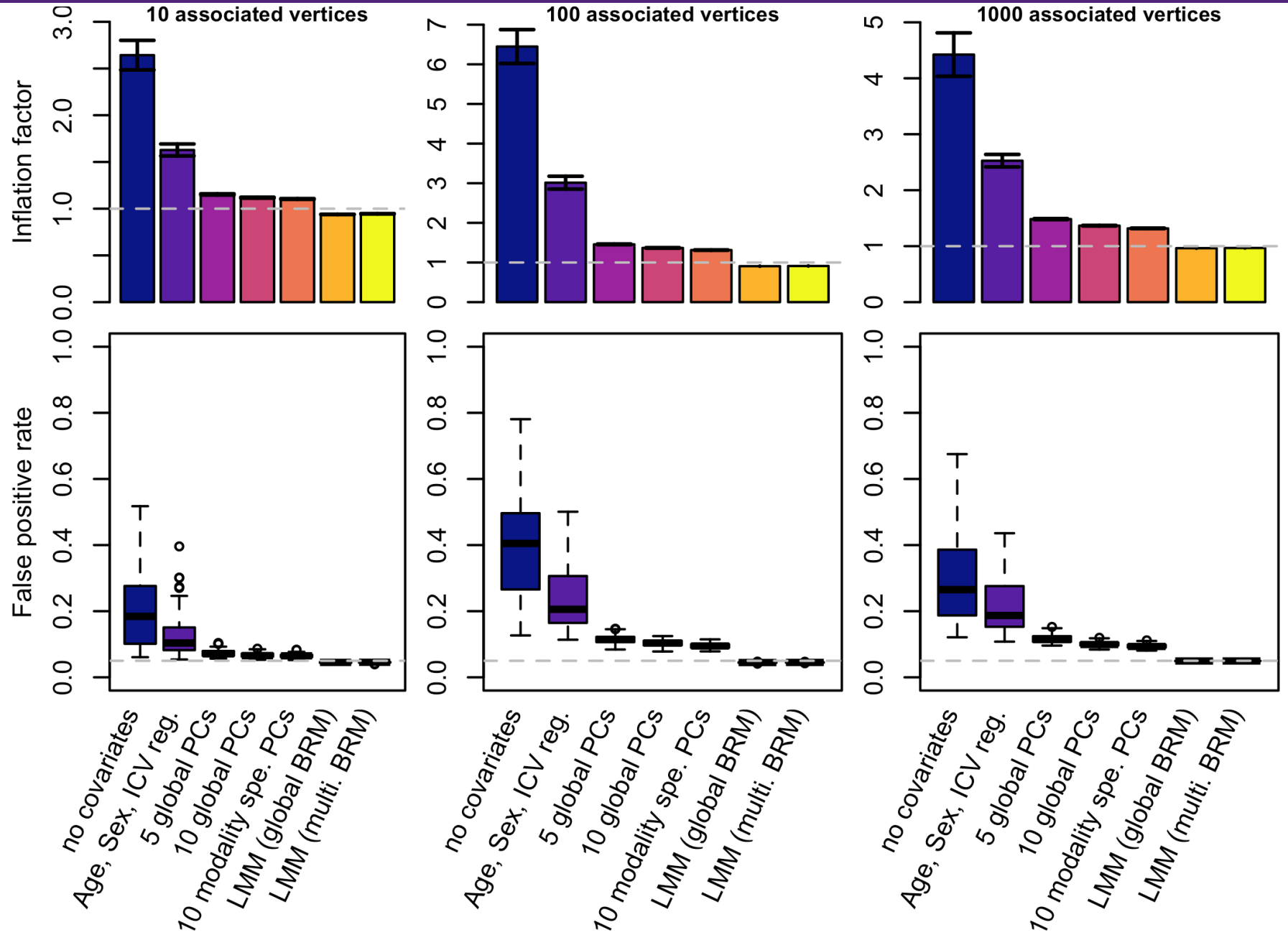
Inflation factor: median of observed test statistic divided by the expected (under the null)

False positive rate: in each replicate the proportion of null vertices with $p<0.05$

Inflation of statistics in GLM

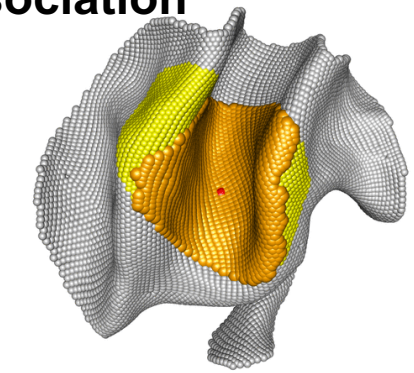
⇒ Null vertices are correlated with true associations

⇒ Possible false positives



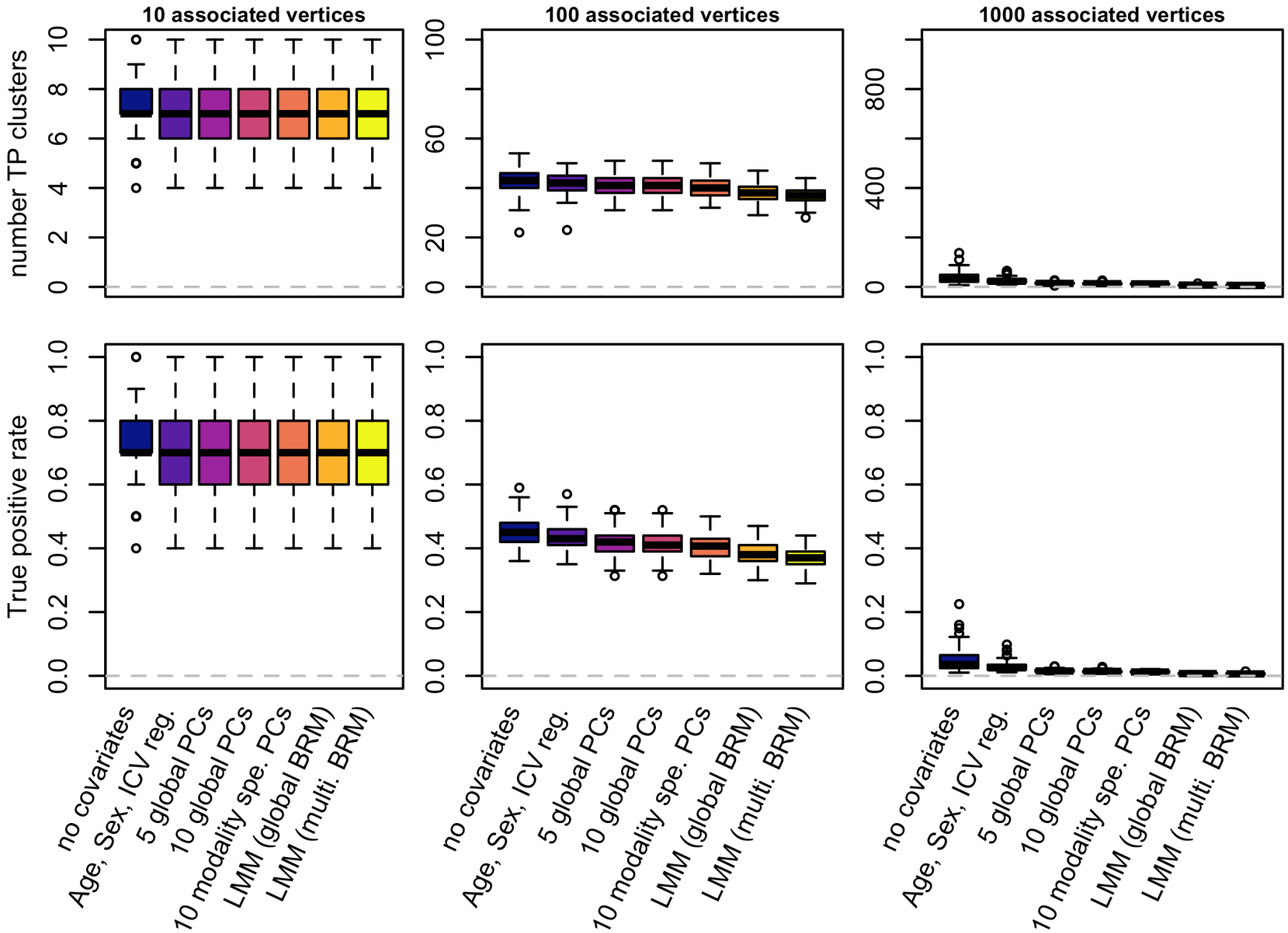
Statistical Power

Number of significant clusters that contain a true association



True positive rate: in each replicate, the proportion of truly associated vertices significant

Power slightly reduced for LMM compared to GLM

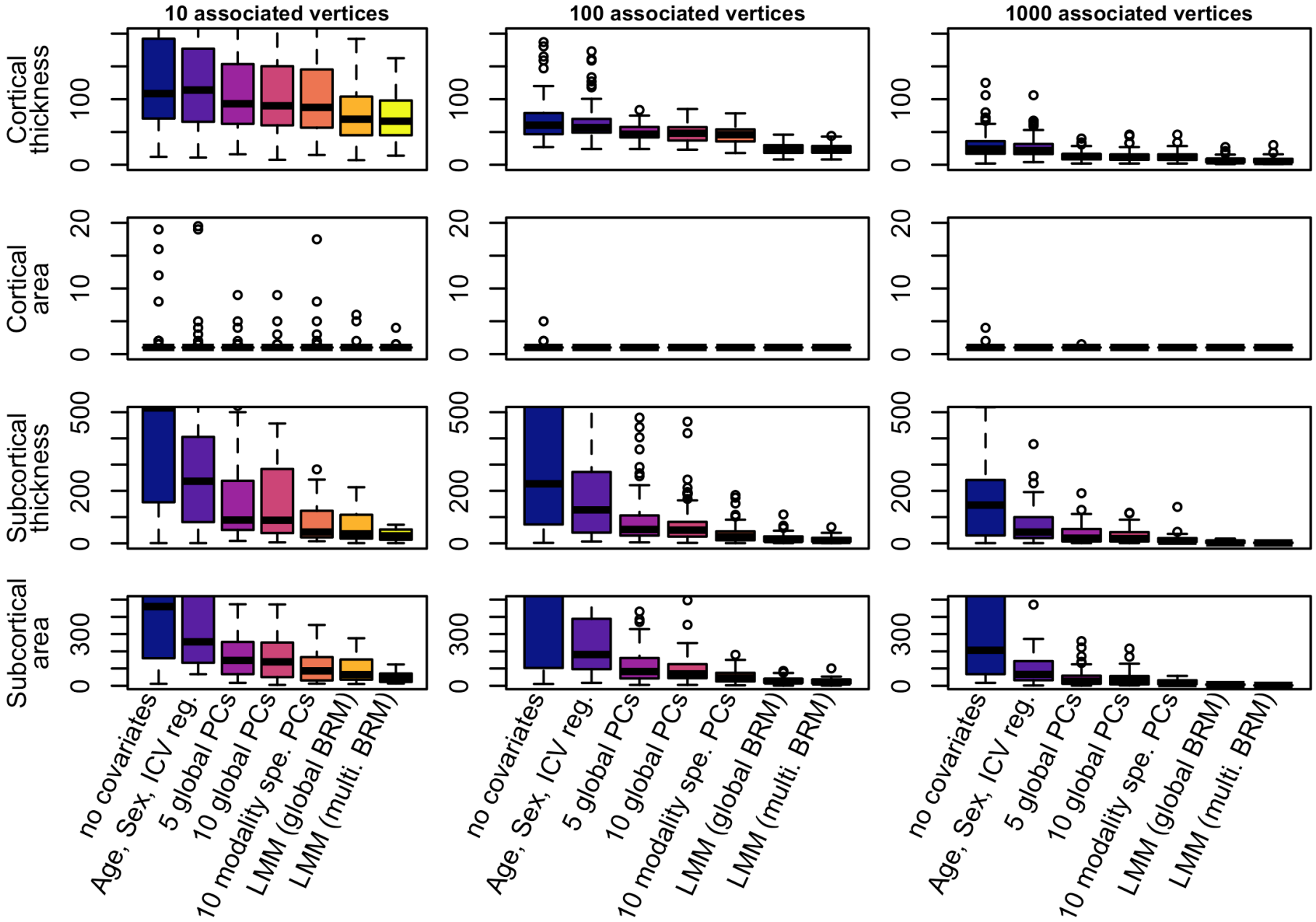


Precision

Median size of True Positive clusters
By modality

LMM yield true positive clusters much smaller than GLM
⇒ More precise identification of associated brain region

For cortical area more than half the TP clusters contain a single vertex
⇒ Suggests little local/long range correlations with those vertices

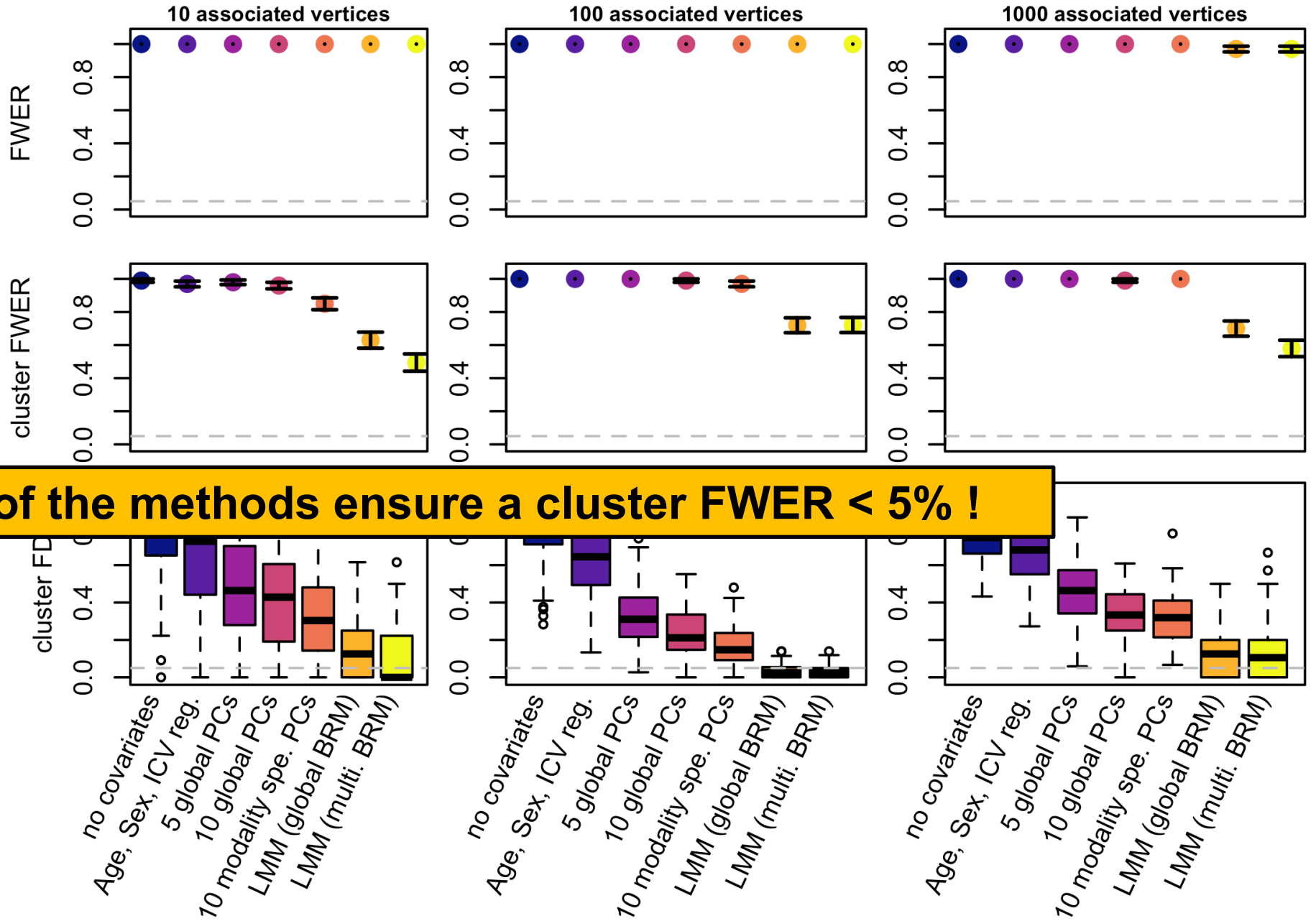


False positive rate

FWER (family wise error rate): proportion of replicates with at least 1 false positive vertex

Cluster FWER: proportion of replicates with at least 1 false positive cluster

Cluster FDR: proportion of FP clusters among significant clusters



Yet, none of the methods ensure a cluster FWER < 5% !

All methods yield 1+ false positive vertex

LMM minimise probability of false positive clusters and proportion of false positive clusters

Prediction – into UKB left out sample

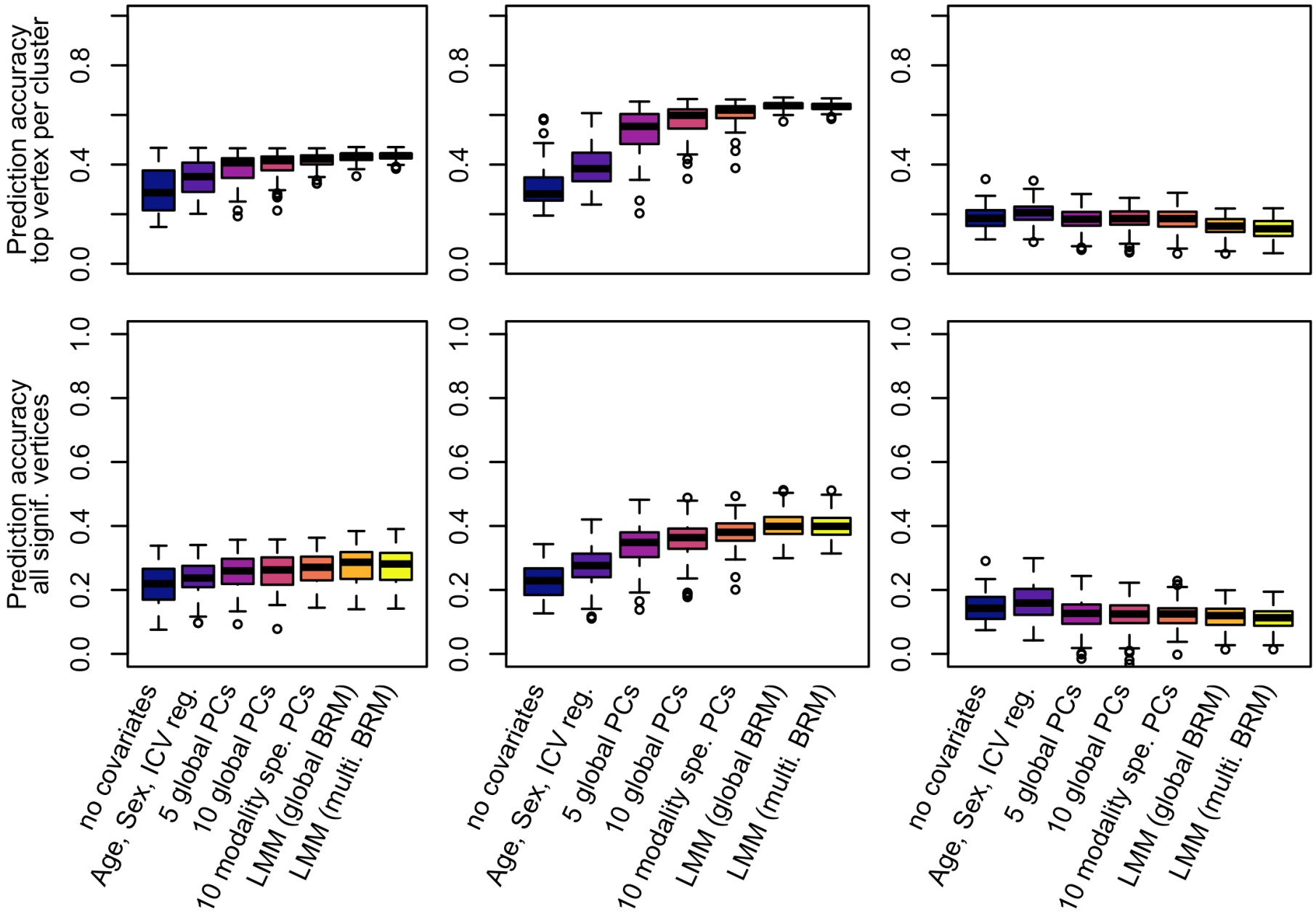
Prediction accuracy (correlation) from significant brain regions

- Using the top vertex (smallest pvalue) per significant cluster

- Using all significant vertices

LMM derived scores offer equivalent to superior prediction accuracy

GLM based prediction decreased by false positives and redundant associations



Summary of the simulations

As in OMICs analyses, LMM control for unaccounted factors that contribute to correlation between features which can cause false positive

LMM offer a more parsimonious and conservative characterisation of the brain-trait associations

	GLM	LMM
Inflation of "null" test statistics	**Yes**	**No**
Statistical power	**Maximal**	**Slightly reduced**
Precision	**Poor**	**Good**
FWER	**Large (~1)**	**Large (~1)**
Cluster FWER	**Large (0.85 - 1)**	**Reduced (0.49 - 0.72)**
Cluster FDR	**High (0.17-0.78)**	**Small (0.03 - 0.16)**
Computation	**Quick (minutes)**	**Longer (hours)**
Prediction accuracy	**Better than chance**	**Equivalent to superior**

Analyses of real phenotypes

Summary of significant associations

		BMI	Fluid Intelligence	Age	Sex	Smoking status
GLM no covariates	*N assoc. vertices*	10,977	24,809	136,348	355,127	712
	N assoc. clusters	232	640	970	714	34
	Max cluster size	862	2,030	22,358	130,651	116
GLM - Age, sex, ICV	*N assoc. vertices*	10,262	196	130,189	56,575	88
	N assoc. clusters	237	15	1,270	1,154	6
	Max cluster size	494	112	19,450	2,955	37
GLM - 10 global PCs	*N assoc. vertices*	8,565	30	16,772	26,912	91
	N assoc. clusters	174	5	297	492	6
	Max cluster size	518	9	894	1,782	43
Single random effect LMM	*N assoc. vertices*	**11**	0	**47**	**27**	0
	N assoc. clusters	**5**	0	**8**	**6**	0
	Max cluster size	**5**	NA	**15**	**11**	NA
	Morphometricity (SE)	**0.59 (0.026)**	0.16 (0.023)	**0.91 (0.021)**	**0.99 (0.020)**	0.15 (0.022)
Multiple random effect LMM	*N assoc. vertices*	0	0	0	**9**	0
	N assoc. clusters	0	0	0	**1**	0
	Max cluster size	NA	NA	NA	**9**	NA
	Morphometricity (SE)	0.51 (0.031)	0.17 (0.034)	0.83 (0.026)	**1.06 (0.024)**	0.12 (0.029)

As expected from simulations:
LMM yield fewer significant vertices or clusters than GLM, as well as smaller clusters
LMM with multiple random effects may suffer from limited power

Prediction from significant brain regions

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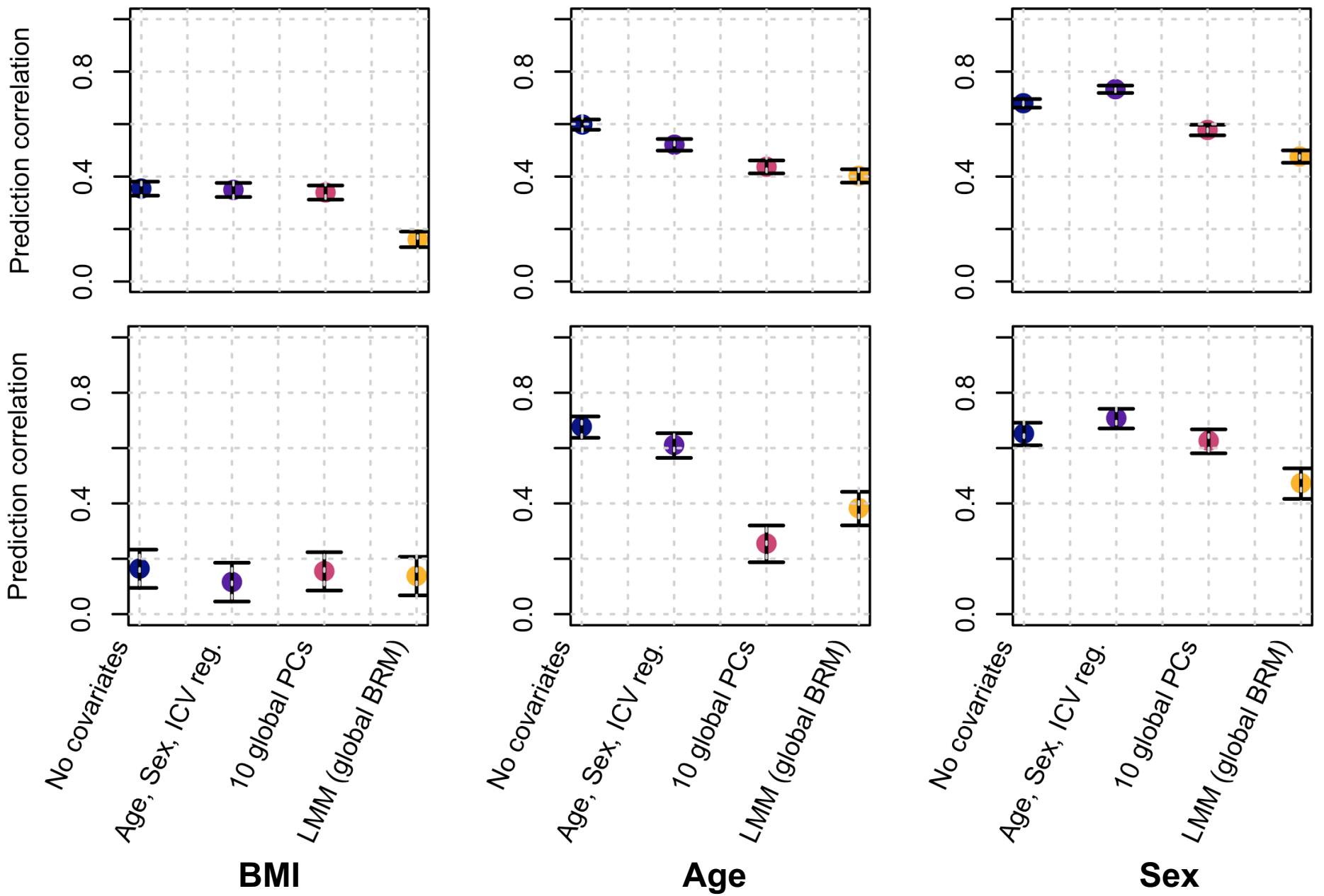
Prediction into UKB left out sample

Prediction into OASIS3



BMI:
GLM based prediction superior in UKB
But GLM fail to generalise in OASIS
where the pattern of correlation between vertices may be different

Prediction from significant brain regions

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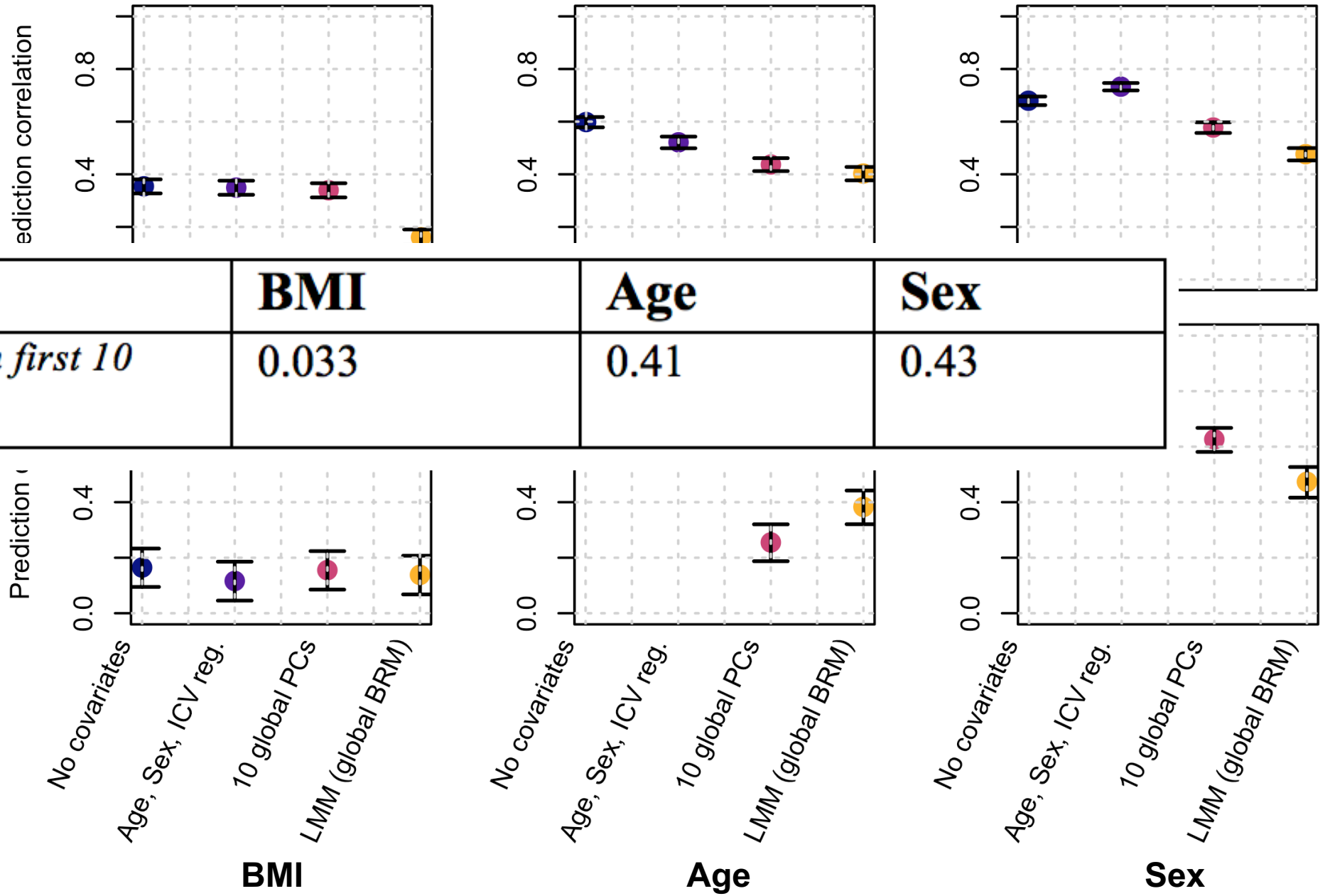
Prediction into UKB left out sample



	BMI	Age	Sex
Adj. R^2 with first 10 PCs	0.033	0.41	0.43

Prediction int

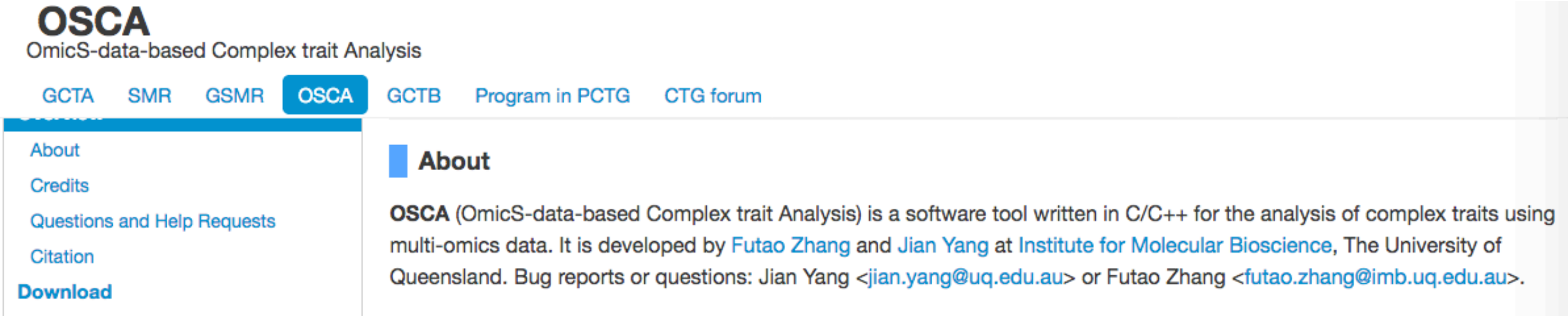
Age and sex

GLM based prediction superior in UKB and OASIS

Possible explanation: correlation between vertices dependent on age and sex (not BMI) => LMM always result in loss of power

Conclusions

LMM offer a more parsimonious and conservative characterisation of the brain-trait associations
Yet the inflated FWER suggests replication may be necessary to safely conclude about an association



https://cnsgenomics.com/software/osca/#Overview

For all analyses, including data management, phenotype simulation and LMM from any OMICs, brain imaging or big-data

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Thank you

To all participants and data managers of the UKB and OASIS studies
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Kathryn E. Kemper
Julia Sidorenko

Paris Brain Institute
Olivier Colliot

OSCA software
https://cnsgenomics.com/software/osca/#Overview

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