Digital phenotyping from wearables using AI characterizes psychiatric disorders and identifies genetic associations

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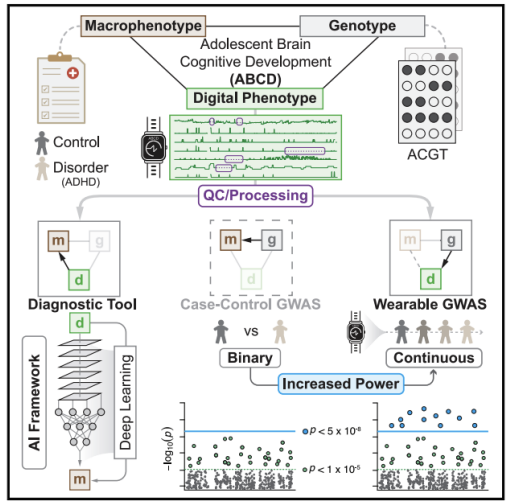
Article

Digital phenotyping from wearables using AI characterizes psychiatric disorders and identifies genetic associations

Graphical abstract



Authors

Jason J. Liu, Beatrice Borsari, Yunyang Li, ..., Matthew J. Girgenti, Walter Roberts, Mark Gerstein

Correspondence

walter.roberts@yale.edu (W.R.), mark@gersteinlab.org (M.G.)

In brief

Complex disorders require precise strategies for their characterization. AI-based digital phenotypes from biosensors can be used to predict psychiatric disorders and identify GWAS loci.

Highlights

- Uniform processing of wearable and genomic data and integration with AI modeling and GWAS
- AI framework uses wearable digital phenotypes to better predict psychiatric disorders
- Univariate and multivariate digital phenotypes can act as a continuous response for GWAS
- Wearable GWAS detects a larger number of loci compared with traditional case-control GWAS

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Article
Digital phenotyping from wearables using AI characterizes psychiatric disorders and identifies genetic associations

Jason J. Liu,[1,2,11] Beatrice Borsari,[1,2,11] Yunyang Li,[3,12] Susanna X. Liu,[1,2,12] Yuan Gao,[1,2] Xin Xin,[1,2] Shaoke Lou,[1,2] Matthew Jensen,[1,2] Diego Garrido-Martín,[4] Terril L. Verplaetse,[5] Garrett Ash,[6,7,8] Jing Zhang,[9] Matthew J. Girgenti,[5] Walter Roberts,[5,8,*] and Mark Gerstein[1,2,3,8,10,13,*]

[1]Program in Computational Biology and Biomedical Informatics, Yale University, New Haven, CT 06511, USA
[2]Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, CT 06511, USA
[3]Department of Computer Science, Yale University, New Haven, CT 06511, USA
[4]Department of Genetics, Microbiology and Statistics, Universitat de Barcelona (UB), Barcelona 08028, Spain
[5]Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06511, USA
[6]Section of General Internal Medicine, Yale University School of Medicine, New Haven, CT 06511, USA
[7]Center for Pain, Research, Informatics, Medical Comorbidities and Education Center (PRIME), VA Connecticut Healthcare System, West Haven, CT 06516, USA
[8]Department of Biomedical Informatics and Data Science, Yale University, New Haven, CT 06511, USA
[9]Department of Computer Science, University of California, Irvine, Irvine, CA 92697, USA
[10]Department of Statistics and Data Science, Yale University, New Haven, CT 06511, USA
[11]These authors contributed equally
[12]These authors contributed equally
[13]Lead contact
*Correspondence: walter.roberts@yale.edu (W.R.), mark@gersteinlab.org (M.G.)
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SUMMARY

Psychiatric disorders are influenced by genetic and environmental factors. However, their study is hindered by limitations on precisely characterizing human behavior. New technologies such as wearable sensors show promise in surmounting these limitations in that they measure heterogeneous behavior in a quantitative and unbiased fashion. Here, we analyze wearable and genetic data from the Adolescent Brain Cognitive Development (ABCD) study. Leveraging >250 wearable-derived features as digital phenotypes, we show that an interpretable AI framework can objectively classify adolescents with psychiatric disorders more accurately than previously possible. To relate digital phenotypes to the underlying genetics, we show how they can be employed in univariate and multivariate genome-wide association studies (GWASs). Doing so, we identify 16 significant genetic loci and 37 psychiatric-associated genes, including *ELFN1* and *ADORA3*, demonstrating that continuous, wearable-derived features give greater detection power than traditional case-control GWASs. Overall, we show how wearable technology can help uncover new linkages between behavior and genetics.

INTRODUCTION

Psychiatric disorders of childhood and adolescence currently affect 1 in 7 youths in the United States and globally.[1,2] Externalizing disorders such as attention-deficit/hyperactivity disorder (ADHD) and internalizing disorders such as anxiety are among the most prevalent and represent a wide spectrum of dysfunctional behavior patterns.[3] Treatment barriers are complex and multifaceted, but major contributors include our limited understanding of psychiatric phenotypes and difficulty identifying youth individuals that experience these disorders.

Traditionally, psychiatric disorders have been conceptualized as categorical macrophenotypes based on clinical manifestations of a disease, which are defined according to the number and type of symptoms and the presence of distress or impairment.[4–6] While this has practical benefits in terms of reliability and ease of diagnosis, it poses several challenges to the research of these disorders and, consequently, to the development of treatments. Furthermore, given the high heritability of psychiatric disorders, dissecting their underlying genetic architecture is of interest to researchers.[7–10] While cost-effective and accurate genotyping technologies in large cohorts of individuals have significantly advanced the field, barriers associated with missing heritability and the need for improved phenotyping strategies are still present.[10–13] In fact, many psychiatric genome-wide association studies (GWASs) to date rely on

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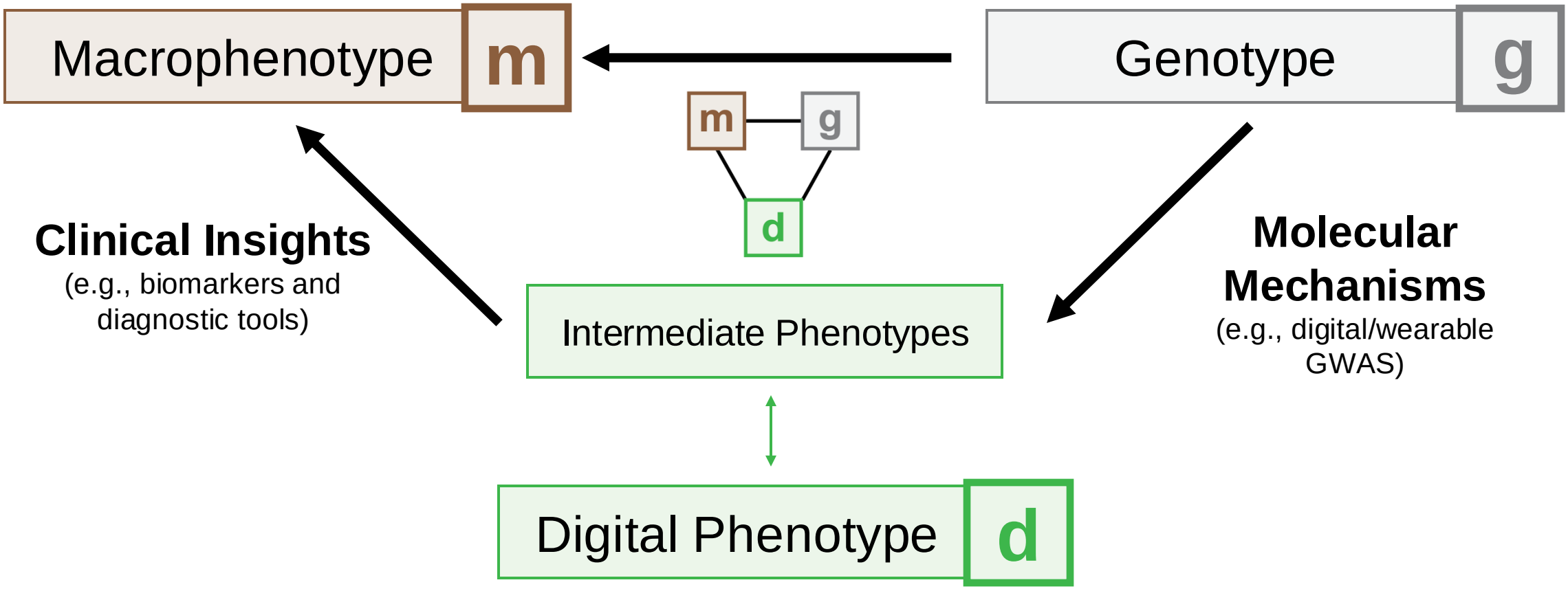
Using wearable biosensors for “digital phenotypes”



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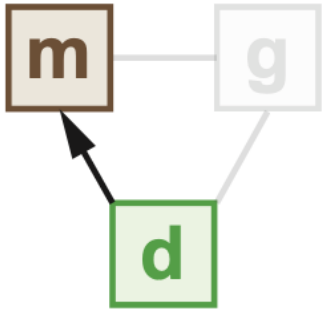
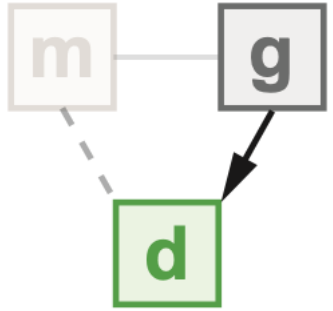
Goals

- Leverage wearable biosensors to generate **digital phenotypes** (including processing of raw data and feature engineering)

- Develop AI and statistical framework that uses **digital phenotypes** to aid in **macrophenotype** diagnosis and clinical characterization.



- Identify linkages between **digital phenotypes** and **genotype** (digital/wearable GWAS)



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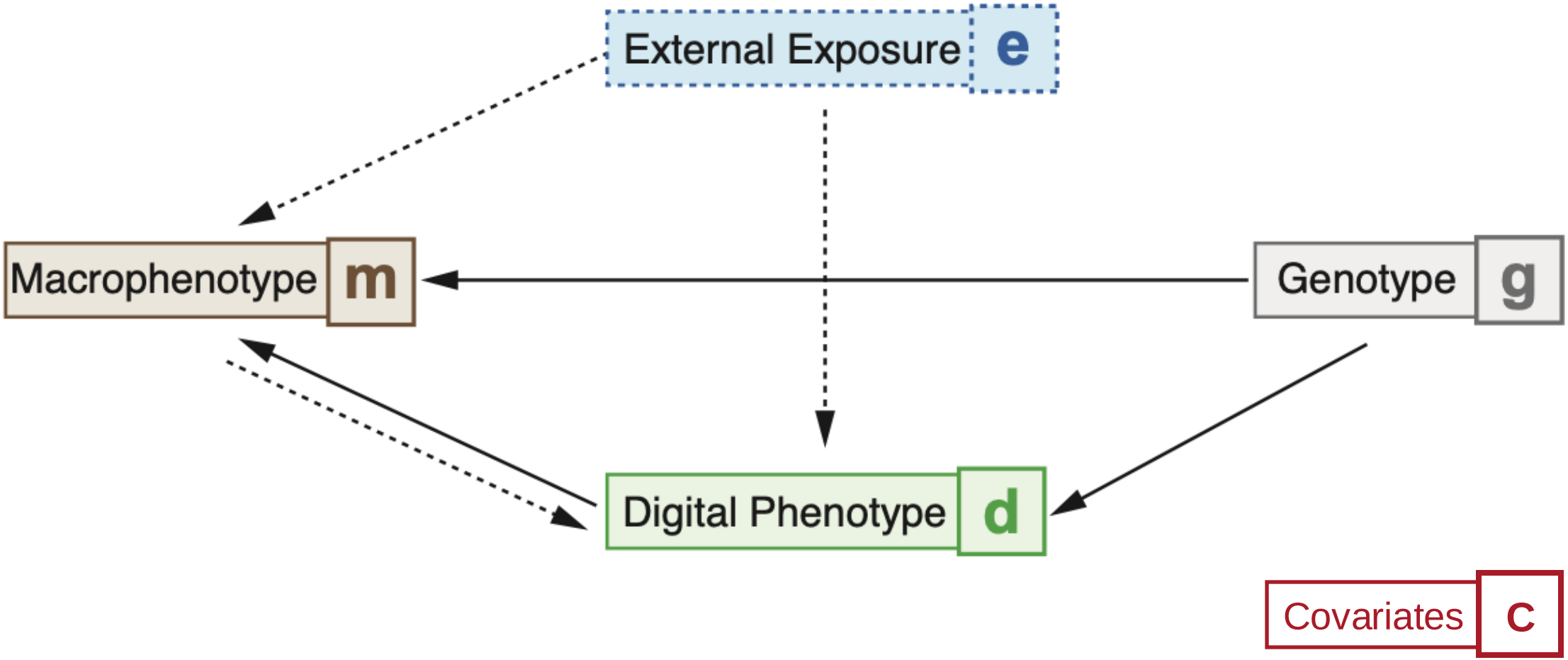
A note on causality



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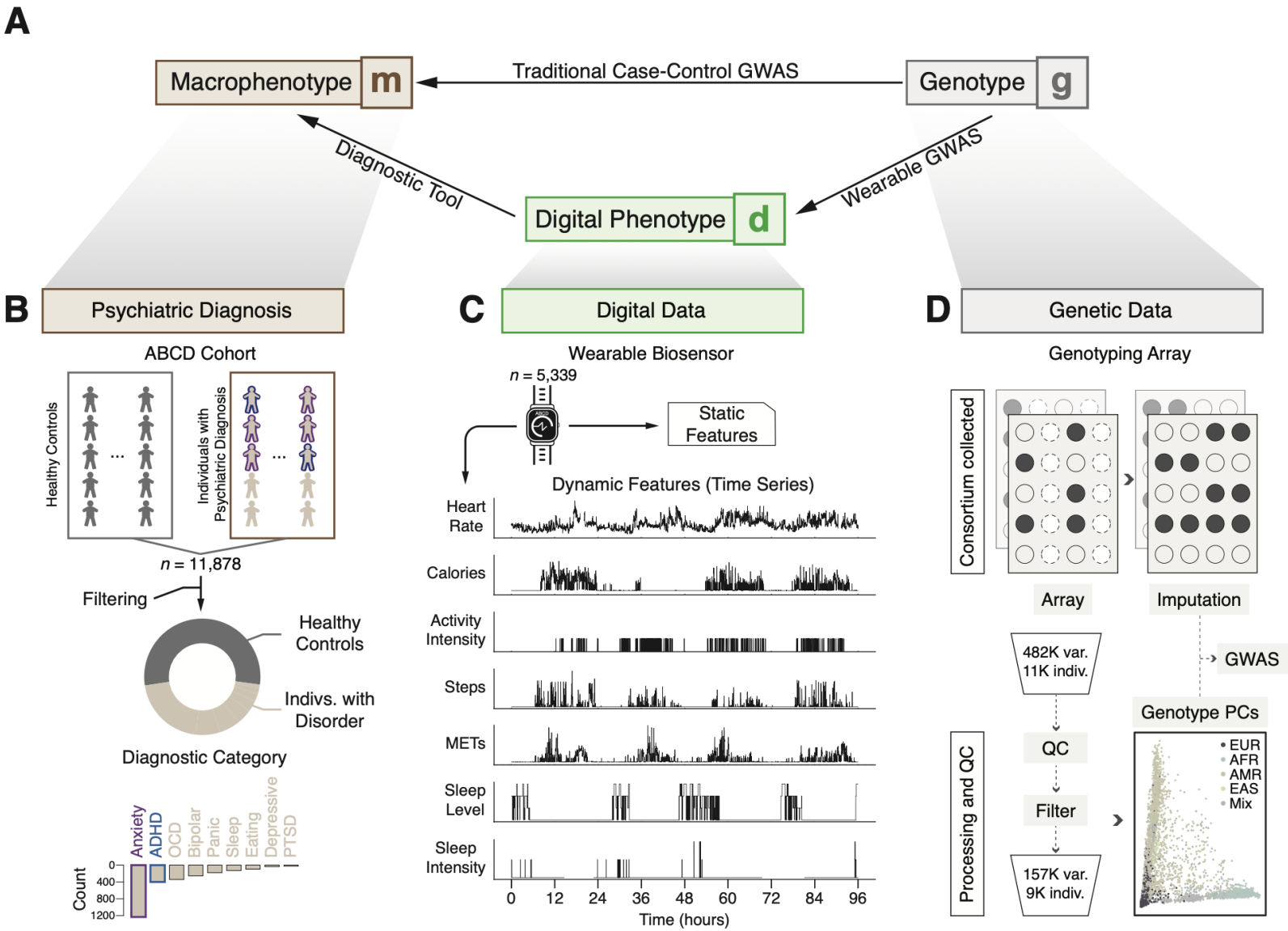
Adolescent Brain Cognitive Development (ABCD) Study

- ~12k adolescents
- 21 sites in USA
- Collecting clinical, genetic, and digital data
- Focusing on neuropsychiatric disorders and brain development



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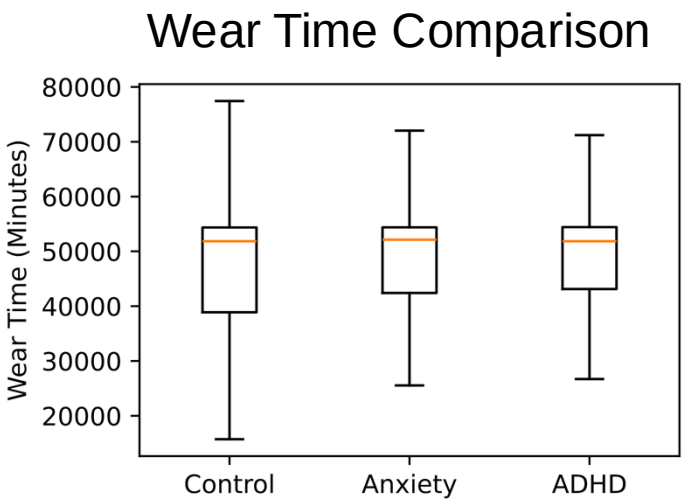
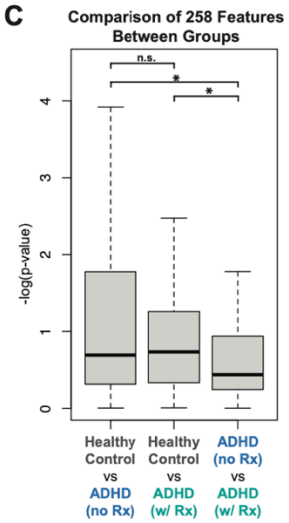
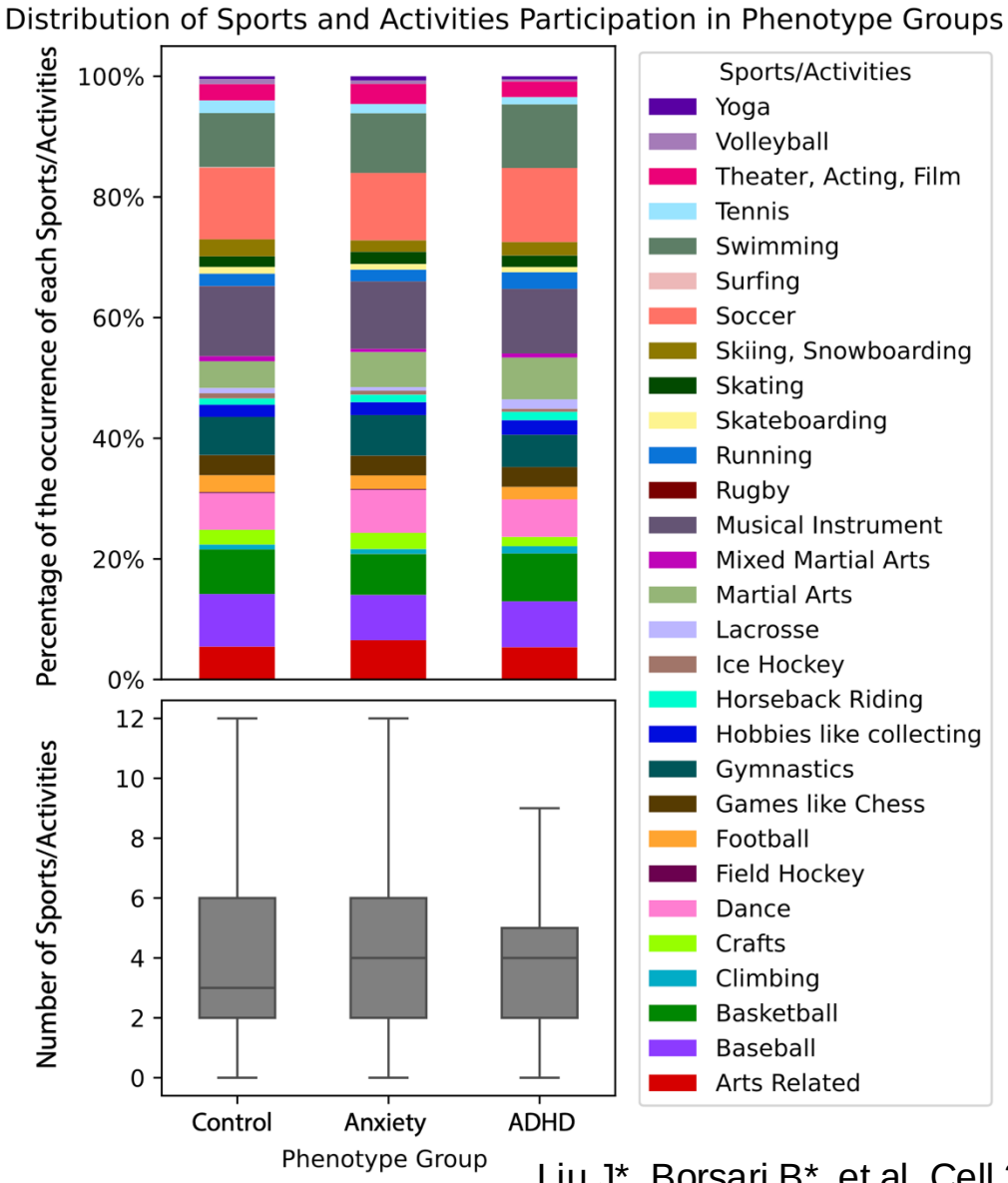
Covariates used in the study

Covariate	Description
Sex	M/F
Race/Ethnicity	Categorical Race / Ethnicity
Age	Numeric Age
Parent Divorce Status	Divorce Status
Parent Grade	Parent Grade
Family Income	Numeric Income
Family History	Bipolar
	Schizophrenia
	Antisocial
	Nerves
	Treatment
	Hospital
	Suicide
Adopted	Adopted
Cognitive Test Scores	stopsigreactiontime
	stopsignolgort
	standevgort
	picvocab
	flanker
	precessspeed
	picmemory
	readingscore
Child Behavior Checklist, CBCL	CBCL score
Relatedness	Identify by descent
Medication	Medication and dosage
Wear time	Time worn
Sports/Activity Participation	29 categories





- Adderall
- Concerta
- Vyvanse



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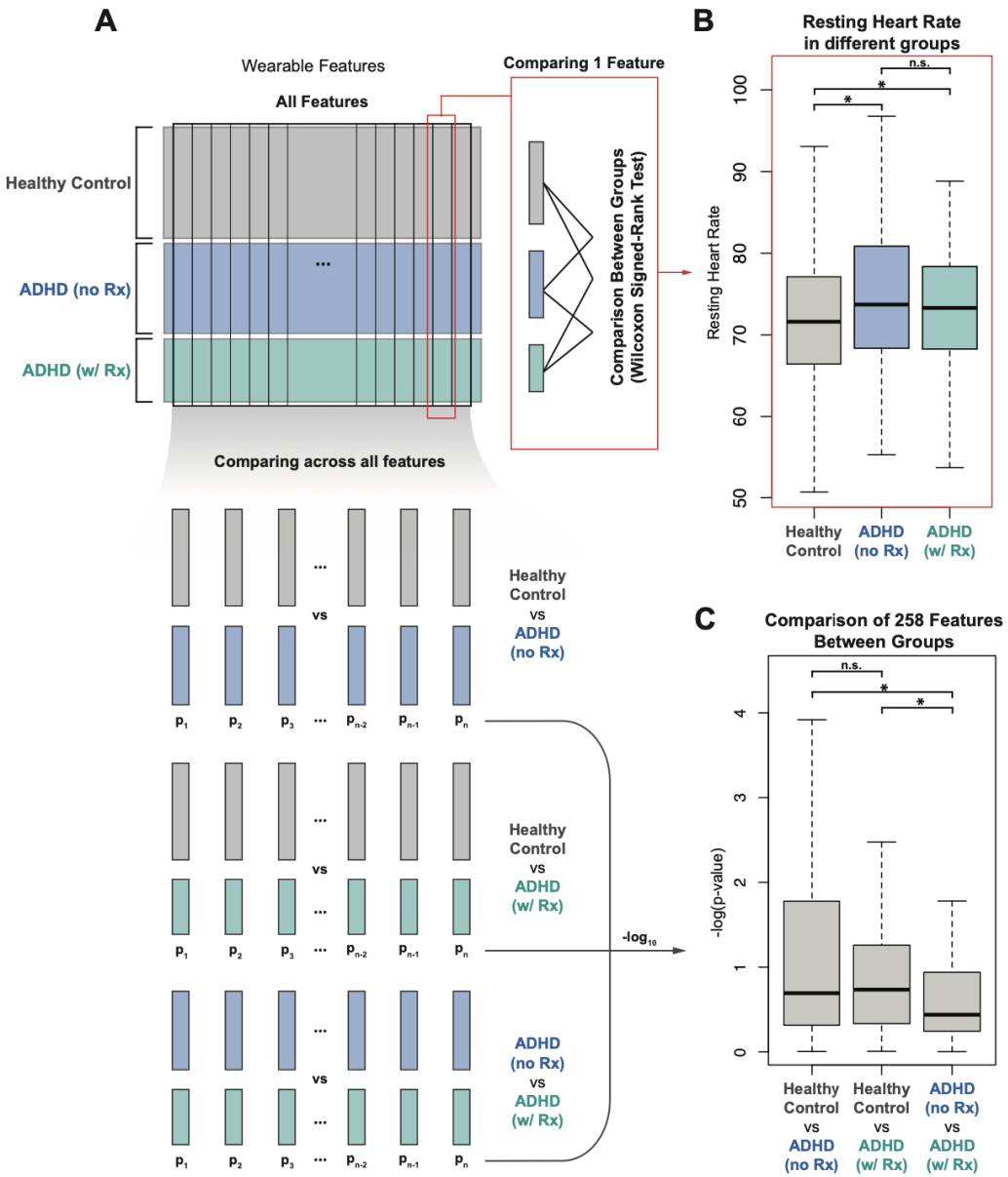

A) Analysis for comparing wearable features across healthy controls, ADHD (no Rx), and ADHD (w/ Rx). ADHD (no Rx) denotes a subset of individuals with ADHD not treated with medication and "ADHD (w/ Rx)" denotes a subset of individuals with ADHD who were treated with medication (e.g., Adderall, Concerta, Vyvanse). P-values were determined using a Wilcoxon Signed-Rank Test.

B) Comparison of resting heart rate across the three different groups. Healthy controls were significantly different when compared to either the "ADHD (w/ Rx)" or "ADHD (no Rx)" groups (p=0.017 and p=0.00163, respectively). No significant difference was determined when comparing between "ADHD (w/ Rx)" and "ADHD (no Rx)" groups.

C) For each feature, a p-value was determined for each of the pairwise comparisons between groups. Overall, the most significant differences across all features were found when comparing healthy controls to either the "ADHD (w/ Rx)" or "ADHD (no Rx)" groups. Comparison of "ADHD (w/ Rx)" or "ADHD (no Rx)" groups yields the least significance across all features.

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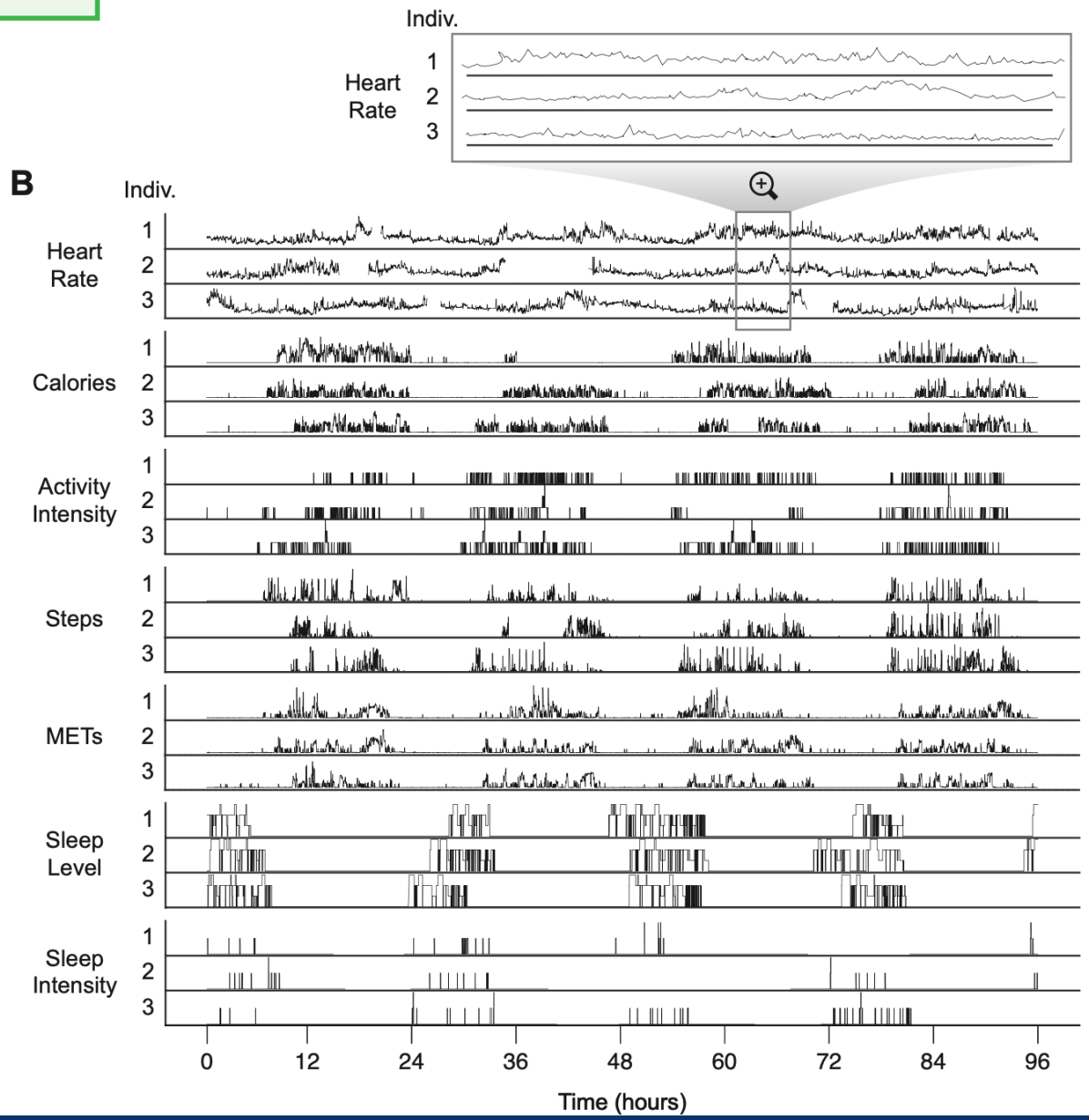
Wearable Data from the ABCD Study



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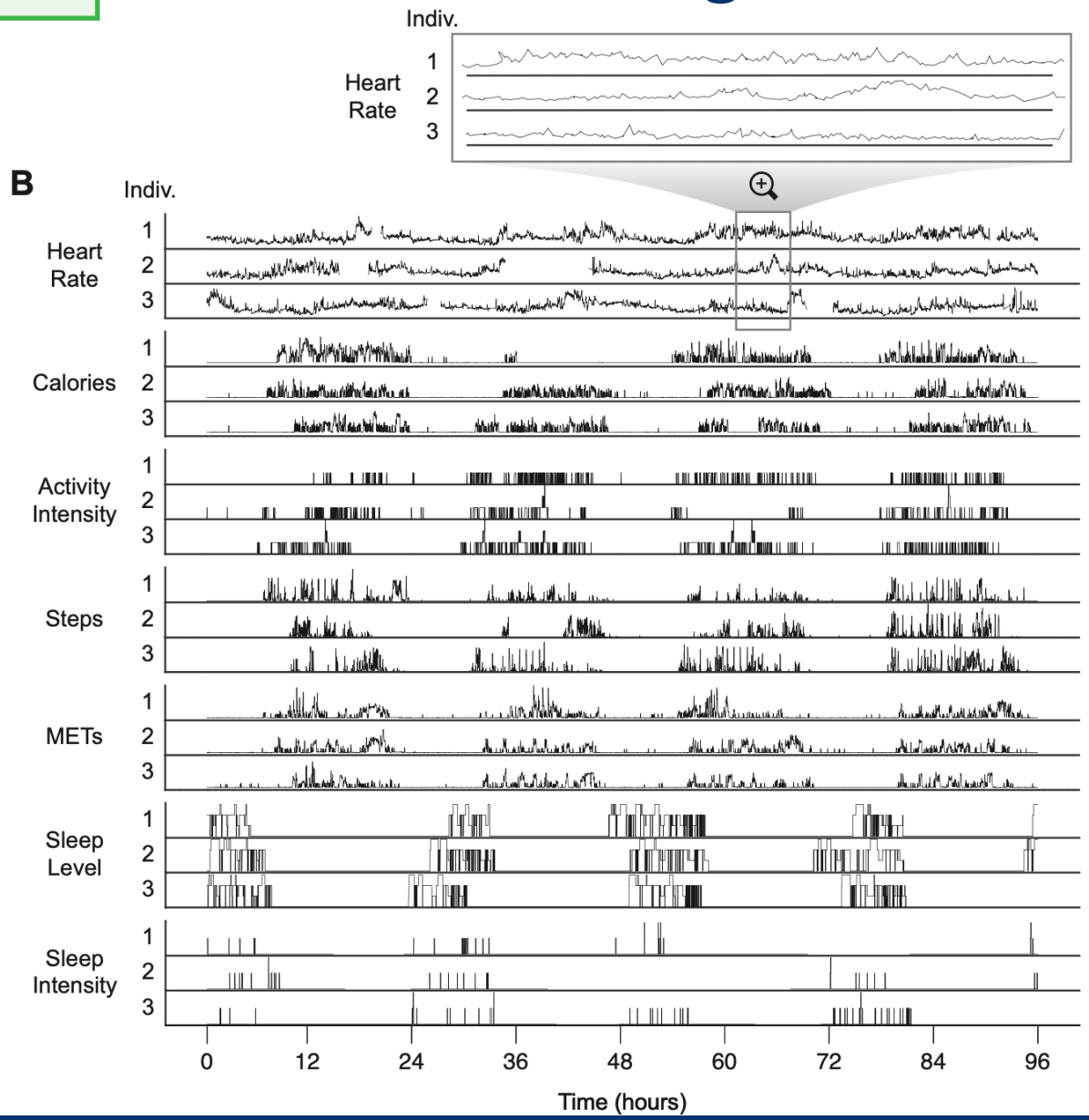
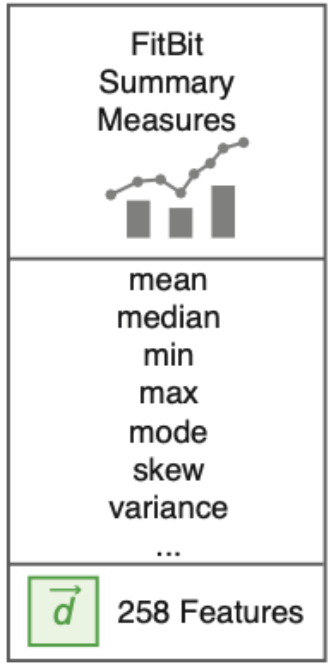
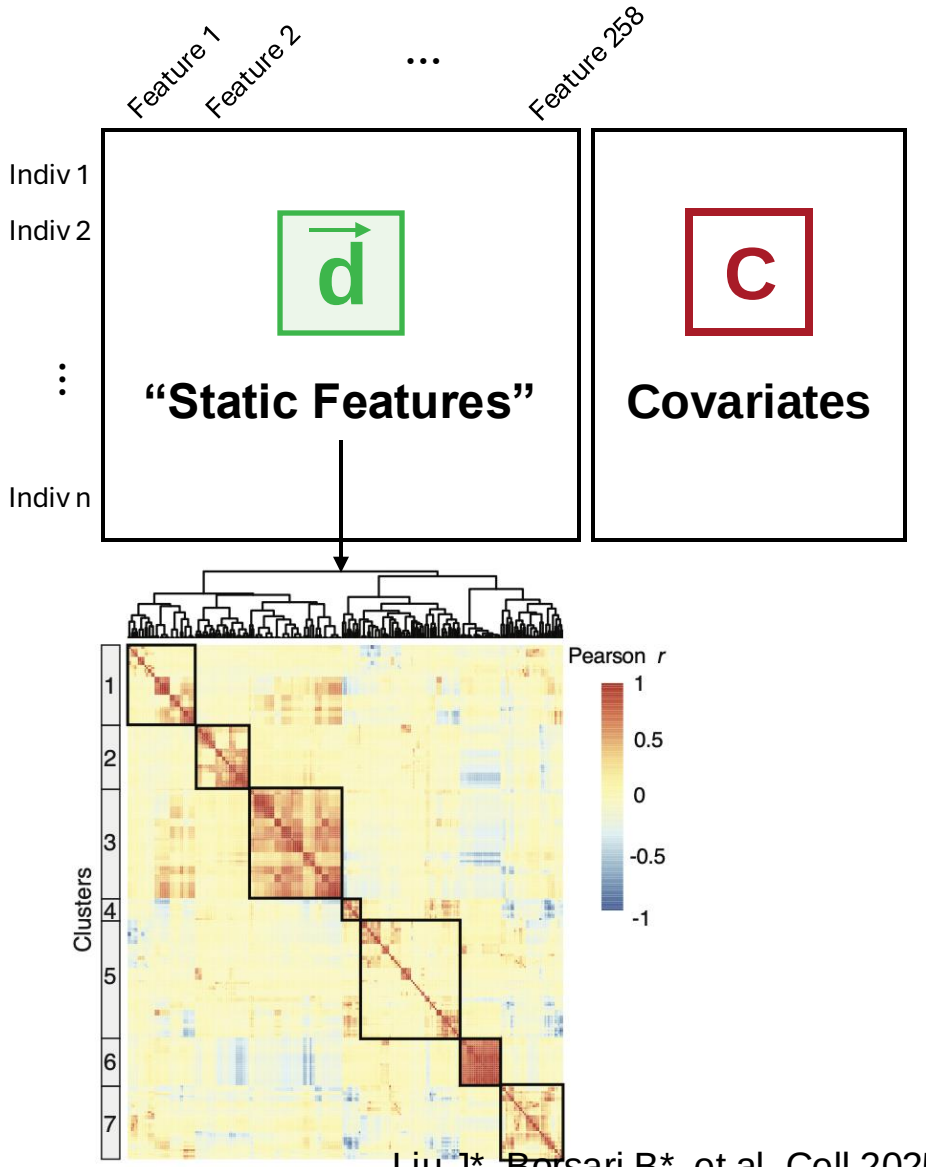
Processing Wearable Data from the ABCD Study







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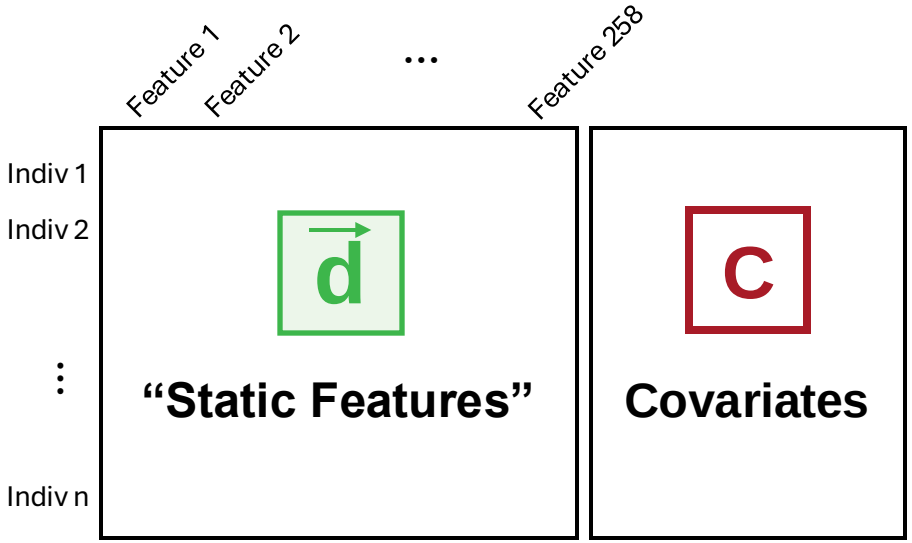
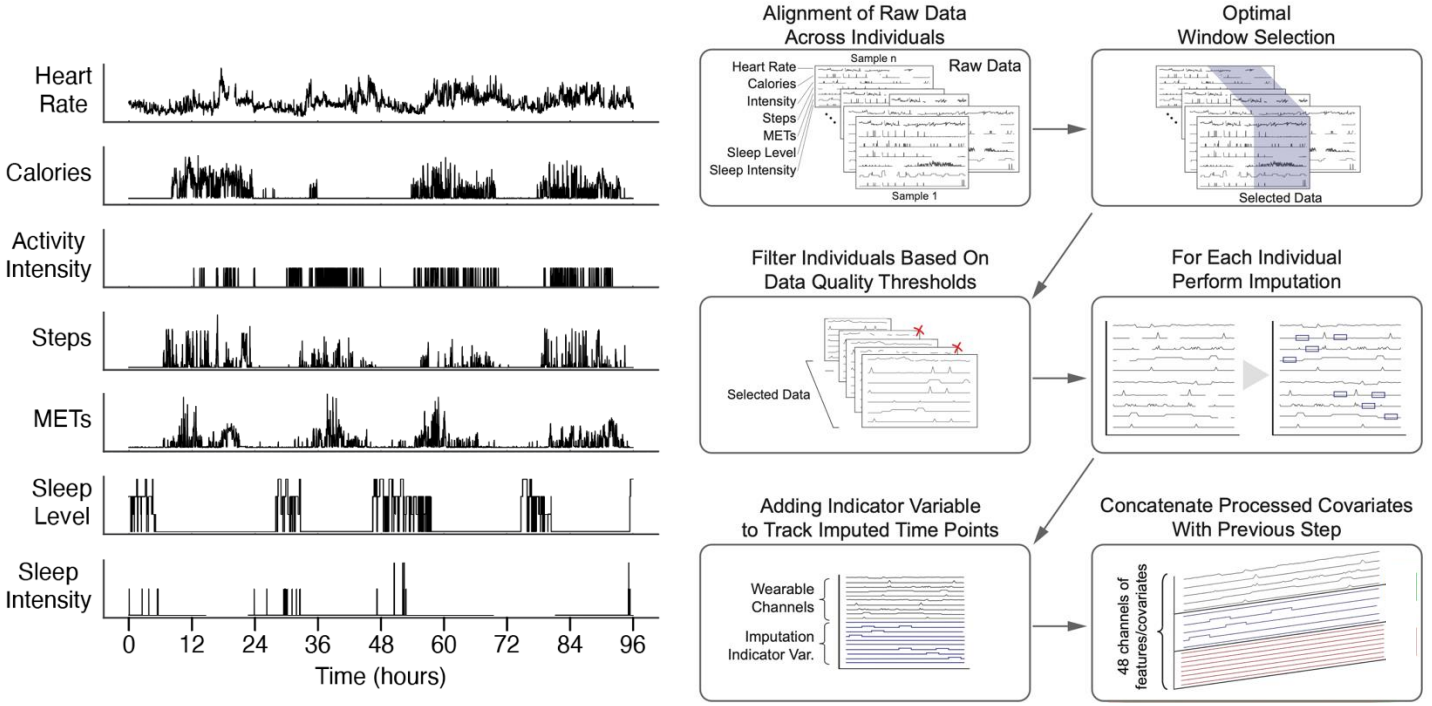
Processing Wearable Data from the ABCD Study



Loss of some temporal dynamics



"Dynamic Features"

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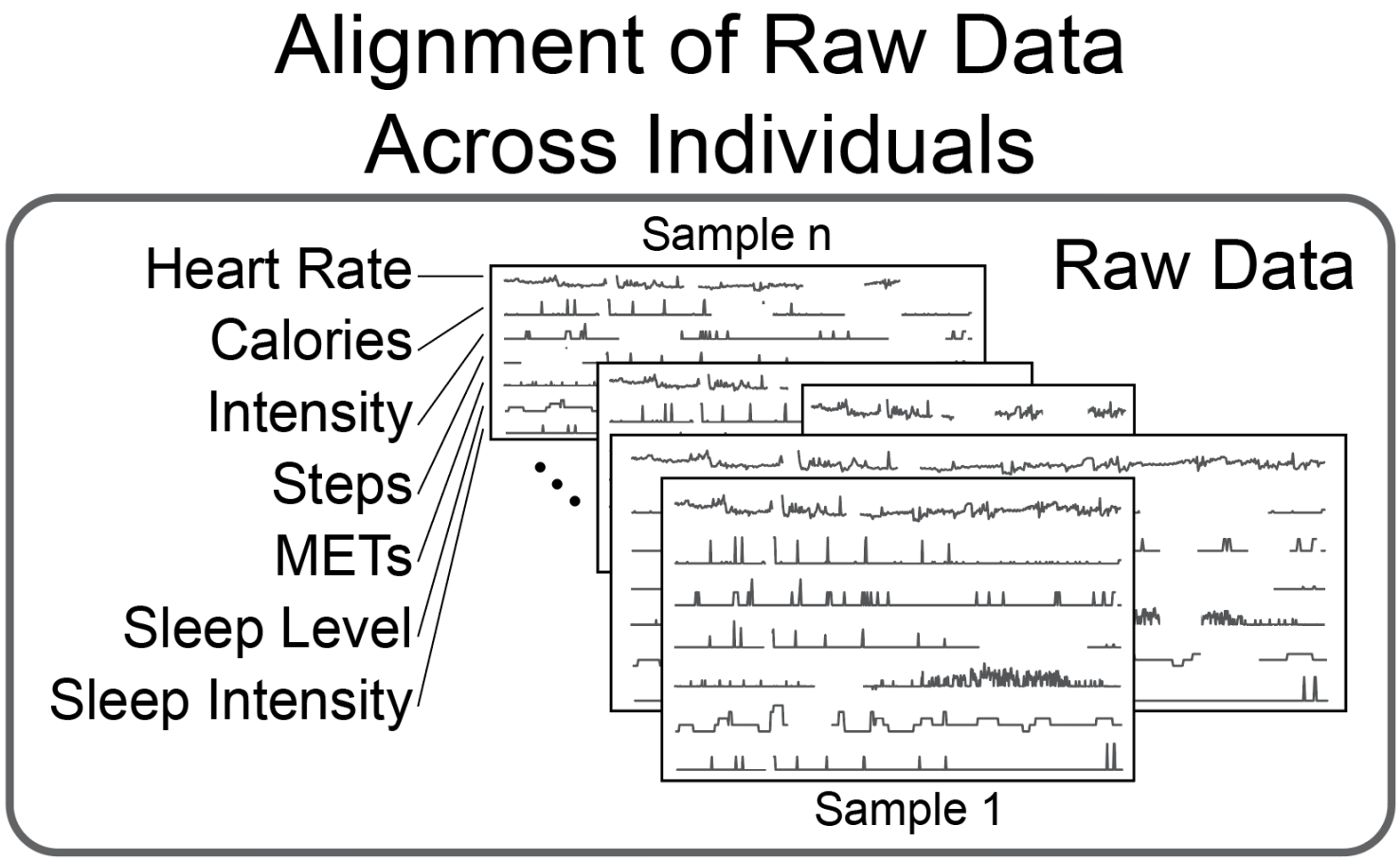
Processing Wearable Data from the ABCD Study



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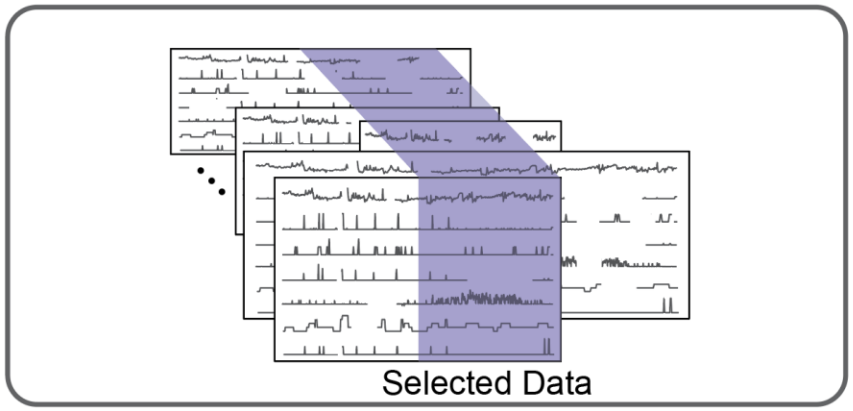
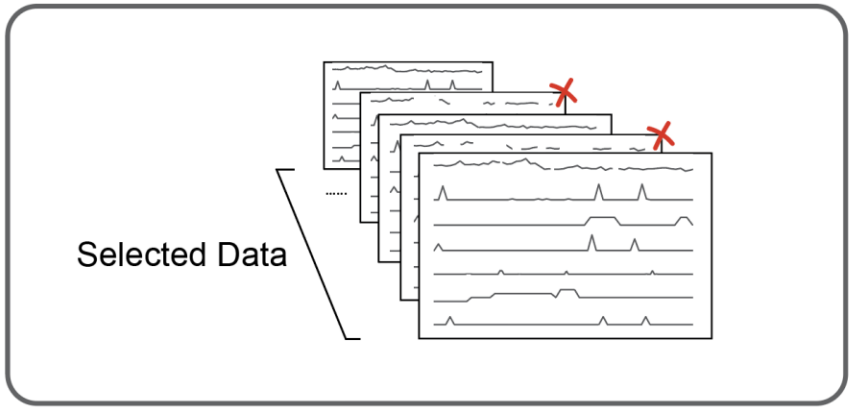
Processing Wearable Data from the ABCD Study

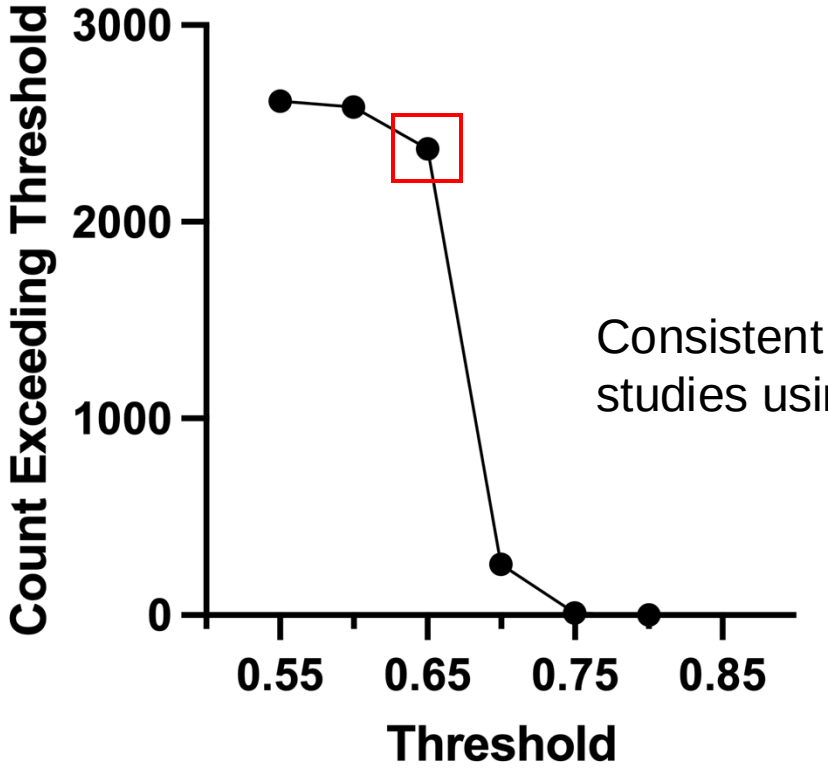
Optimal
Window Selection



Filter Individuals Based On
Data Quality Thresholds



Number of Individuals Exceeding Threshold



Consistent with other studies using wearables

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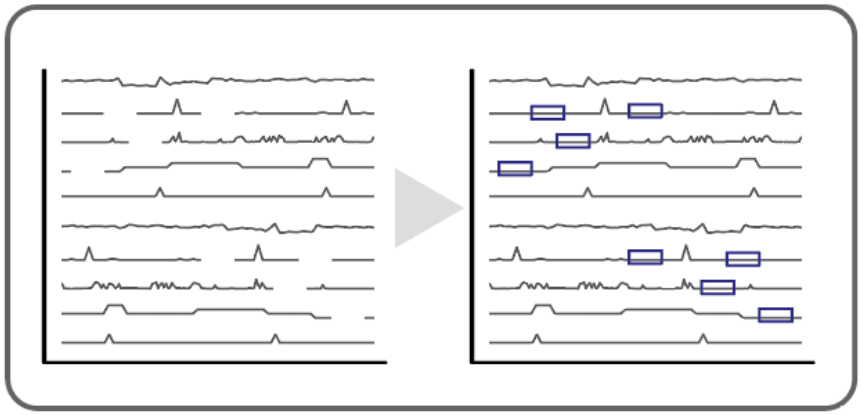
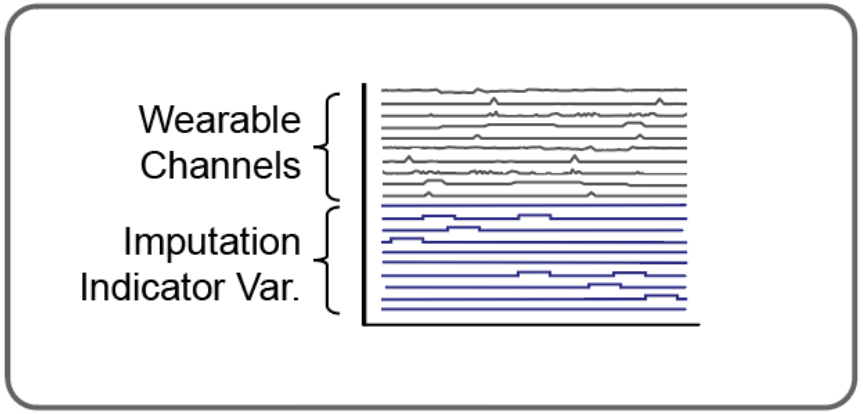
Processing Wearable Data from the ABCD Study

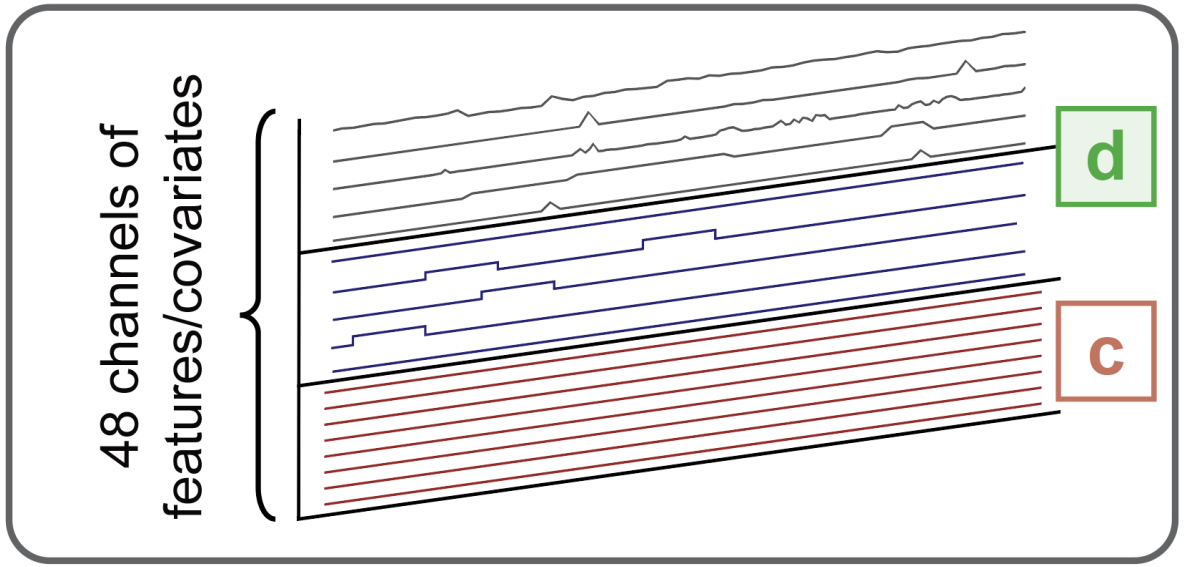
For Each Individual
Perform Imputation



Adding Indicator Variable
to Track Imputed Time Points



Concatenate Processed Covariates
With Previous Step



“Dynamic Features”

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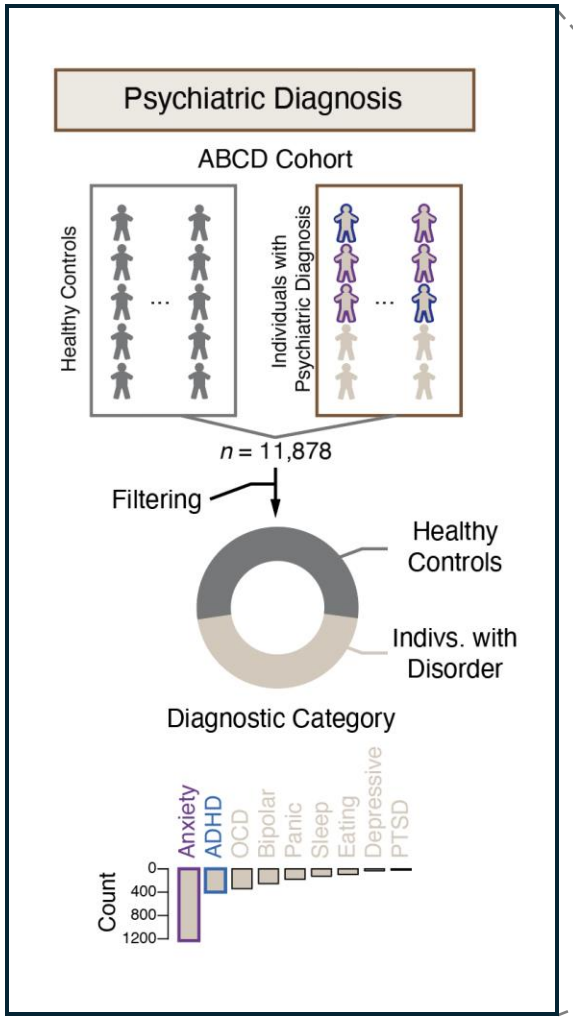
Classifying Individuals With/Without Disorders (Static)



Diagnostic Tool / Clinical Insights

Macrophenotype

Digital Phenotype

Class Balancing

Y		~	"Static Features"				+	Covariates			
0	0.2		1	3	…	1		M	10	…	2
1	0.9		2	9	…	5		F	9	…	3
1	0.8		5	2	…	2		M	12	…	2
0	0.1		2	2	…	11		M	12	…	1
1	0.9		3	14	…	6		F	13	…	5
0	0.1		1	8	…	3		F	11	…	2

~ XGBoost (RF) ~ +

d_{score}

AI-generated risk score

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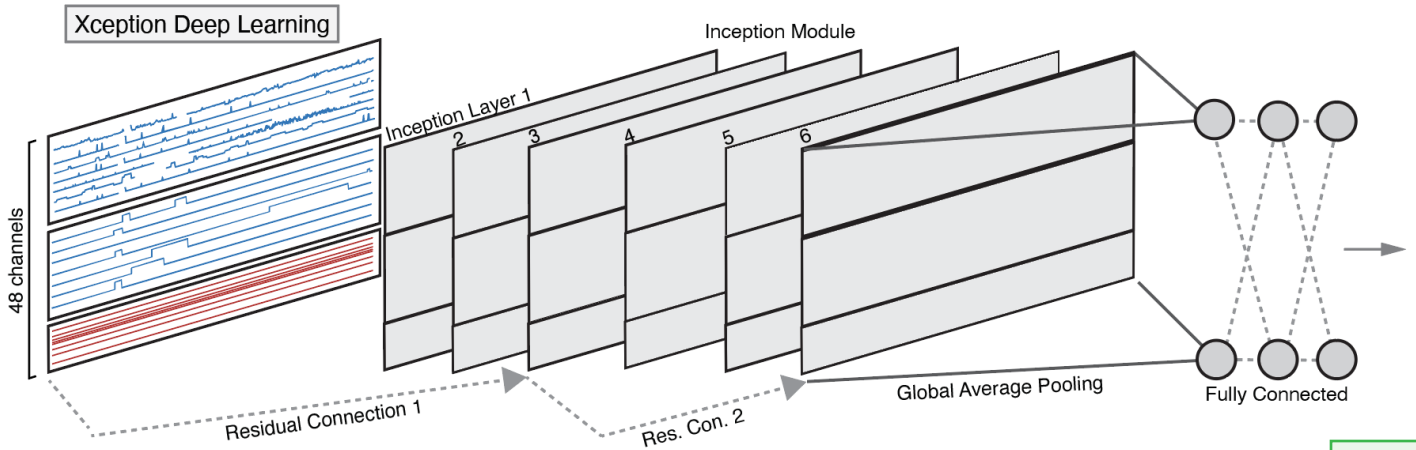
Classifying Individuals With/Without Disorders (Dynamic)

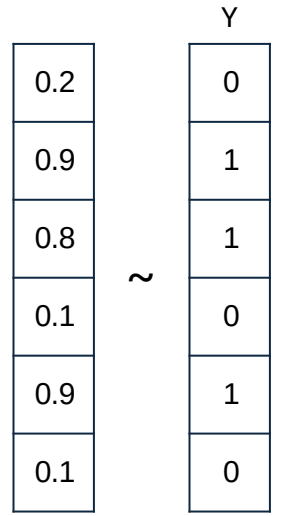
Digital Phenotype

Diagnostic Tool / Clinical Insights

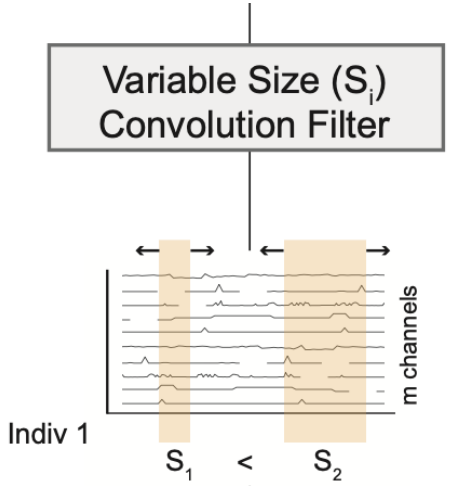
Macrophenotype

Dynamic Features

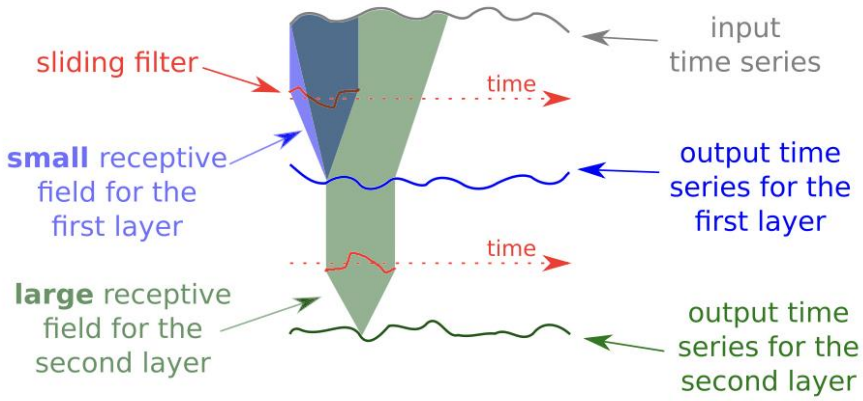




AI-generated risk score d_{score}



[Fawaz et al. Data Min. and Knowledge Disc. ('20)]



[Li et al. NeurIPS ('18)]

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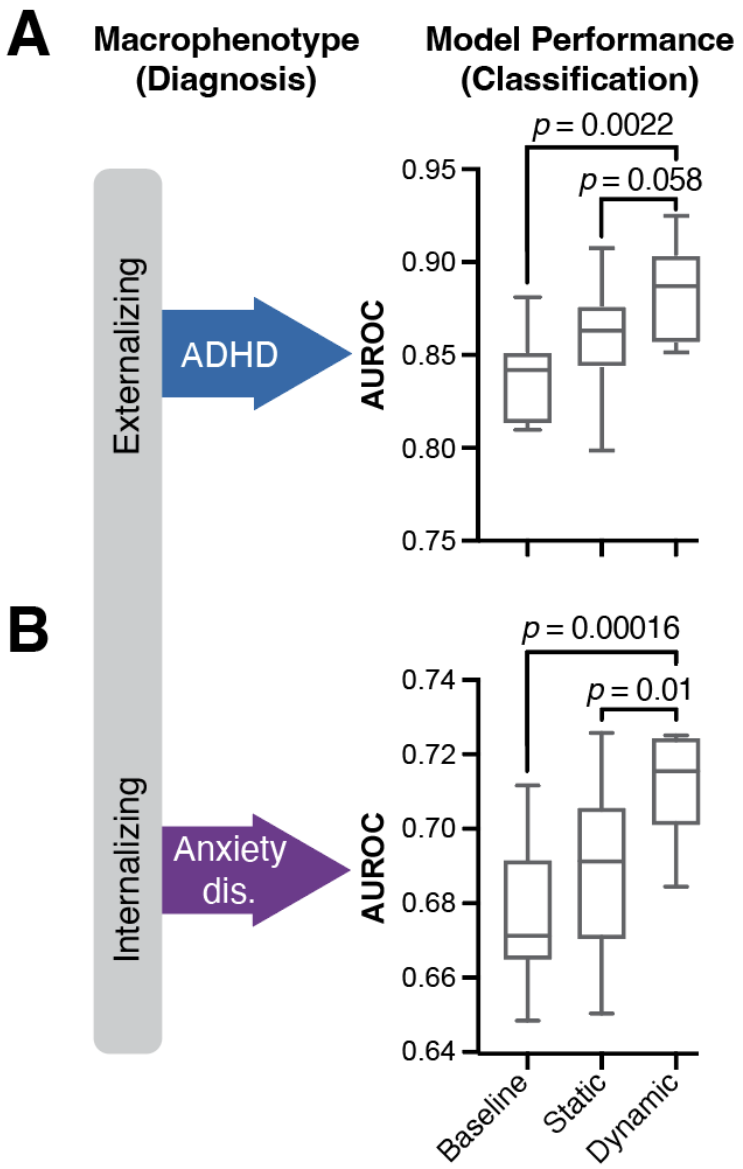
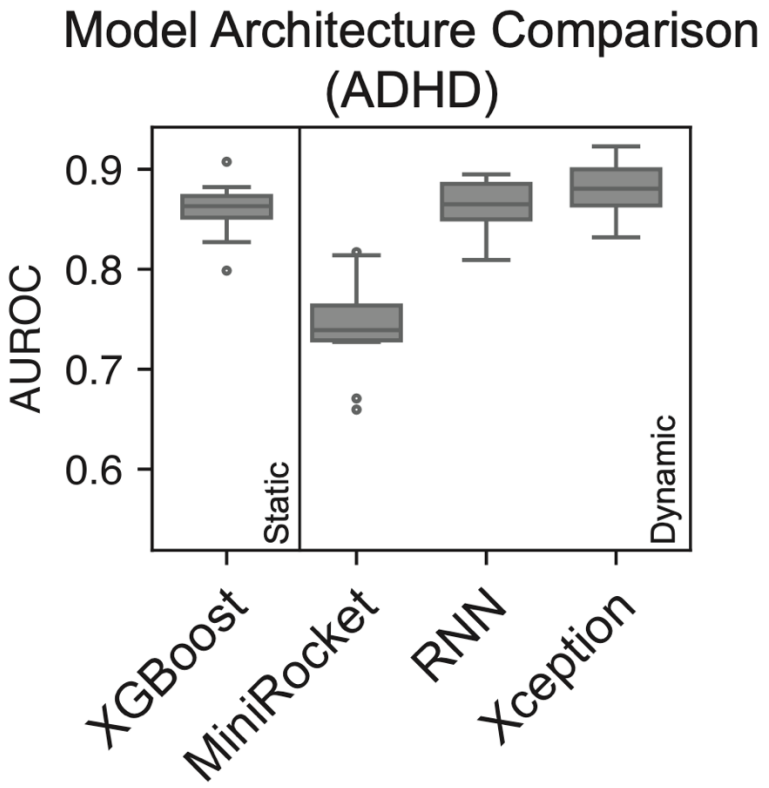
Digital Phenotypes Improve Classification and Provide Clinical Insights





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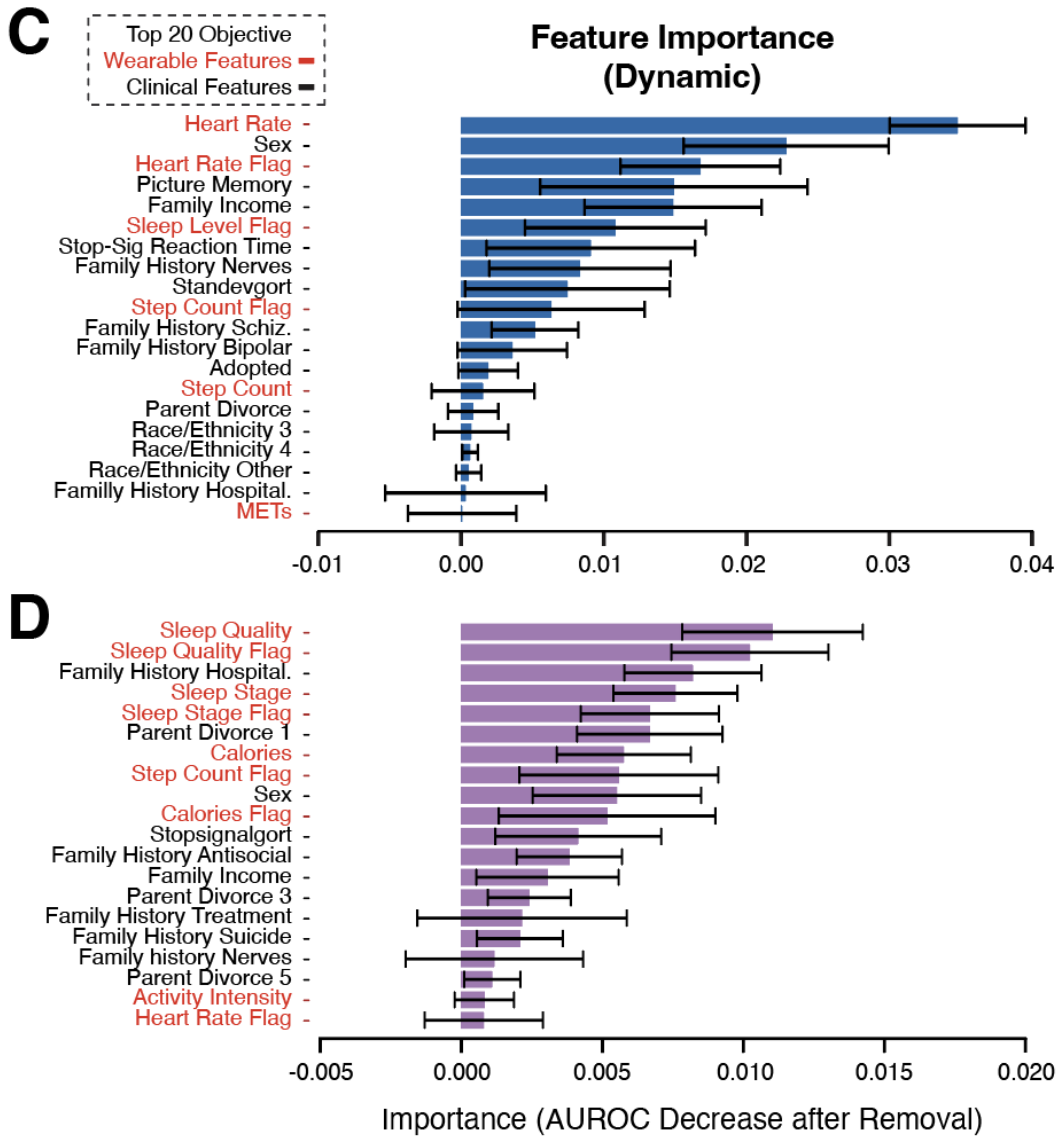
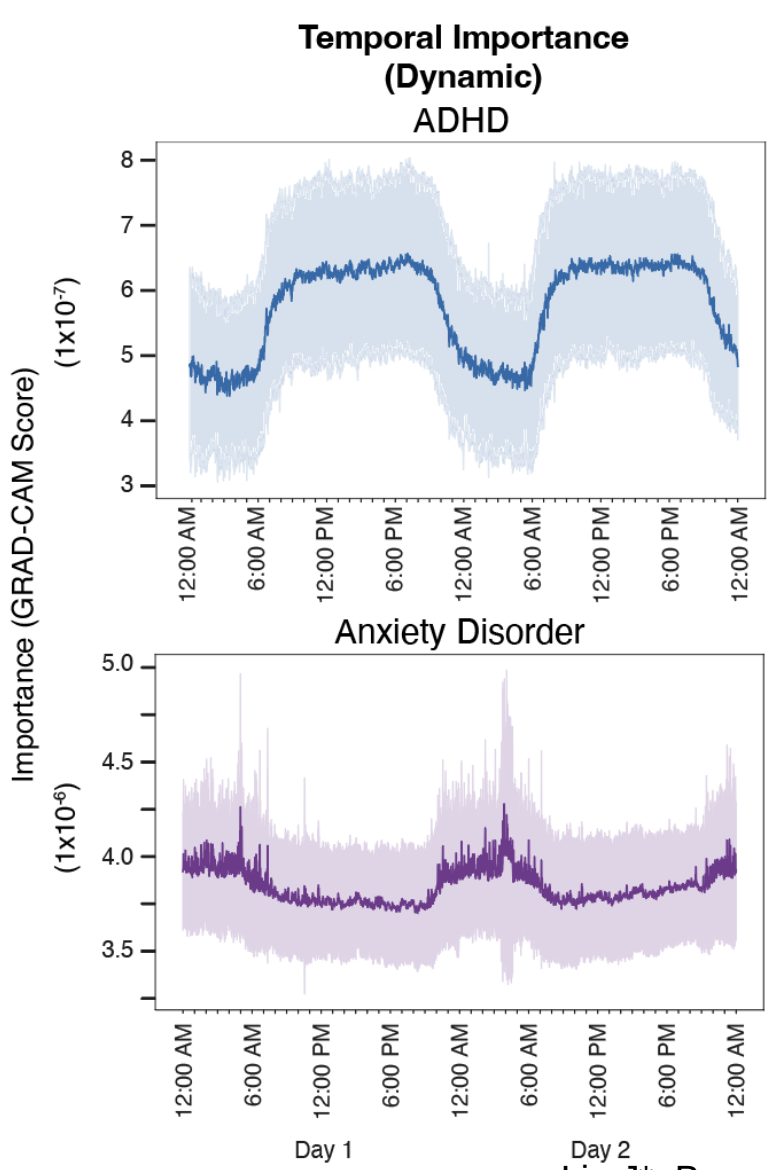
Digital Phenotypes Enable Clinical Interpretability





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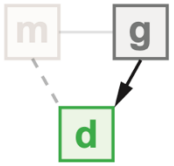
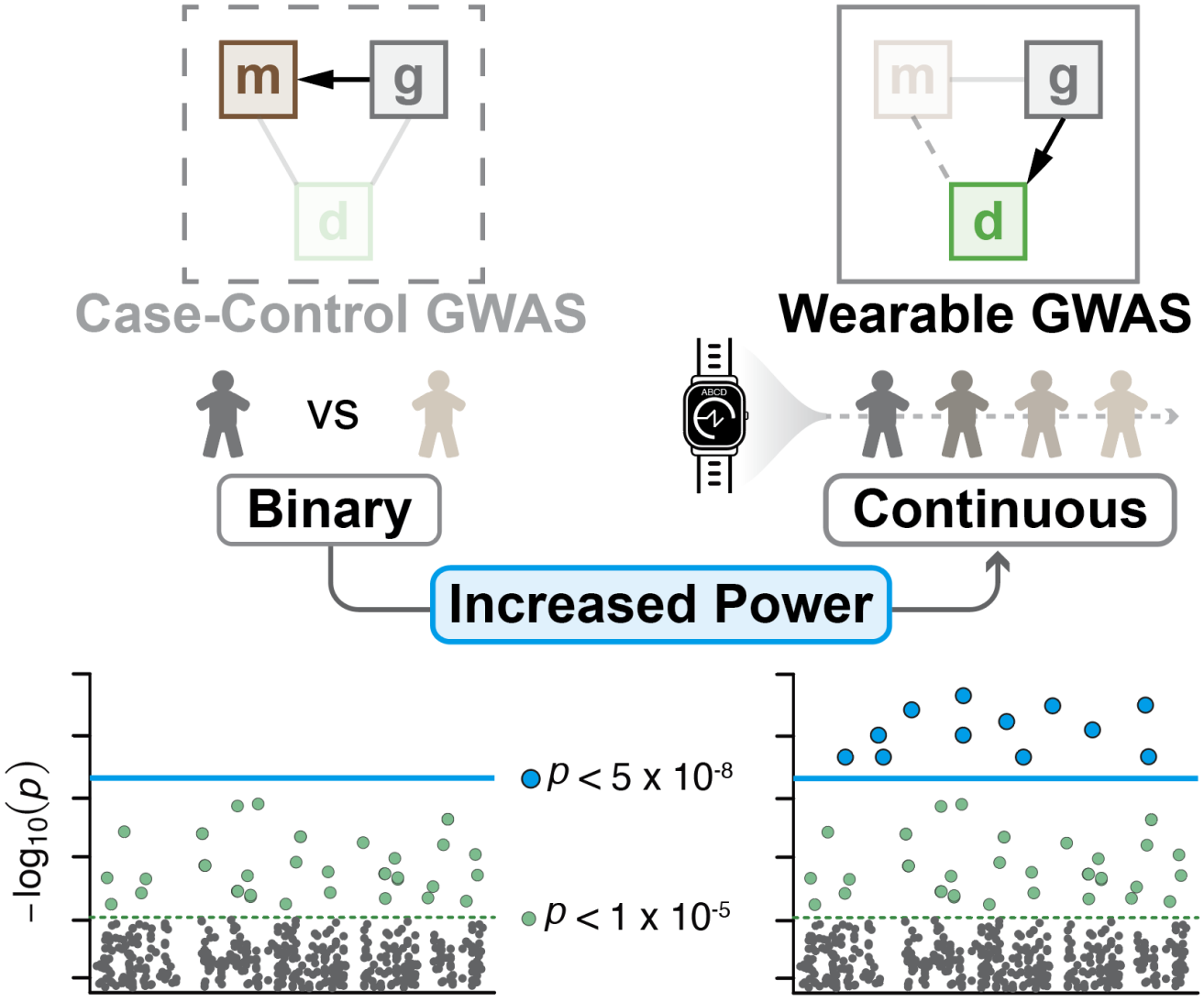


Can we use "digital phenotype" to improve genetic studies?



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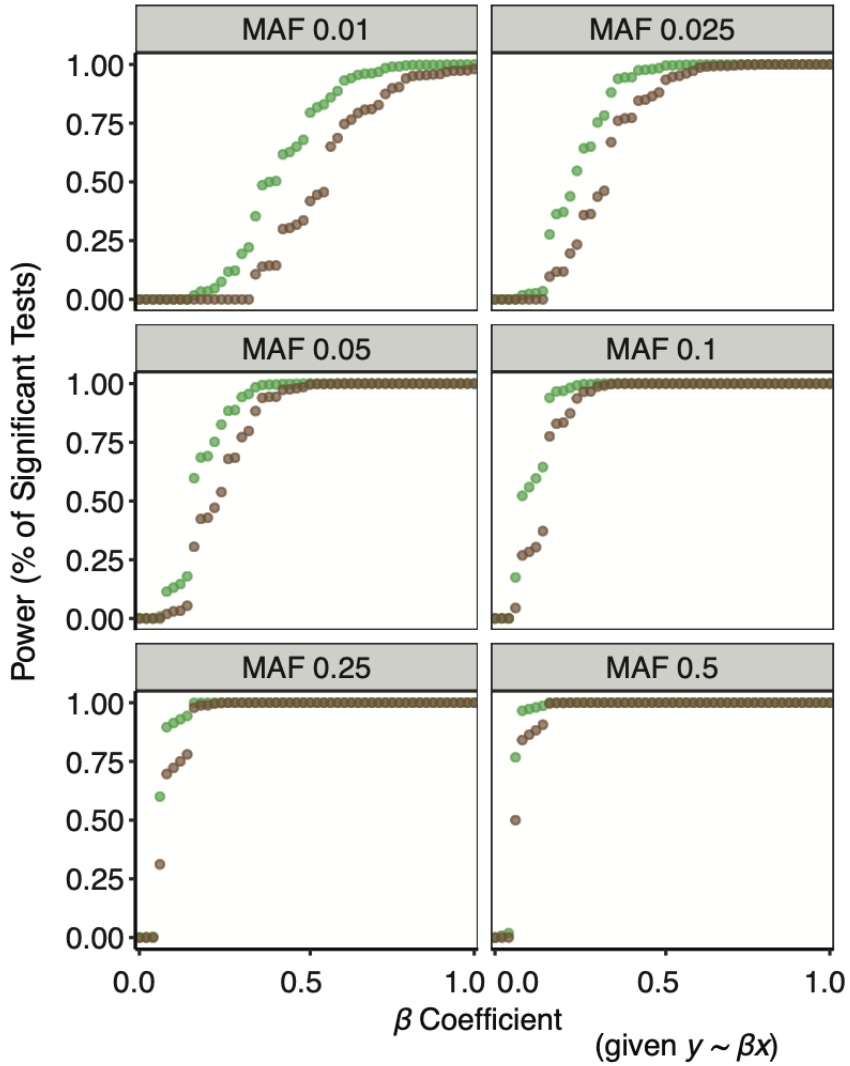
Detection Power in Binary vs Continuous GWAS Simulation

Binary Continuous

$$y \sim \beta x$$

$$y \sim \beta x$$



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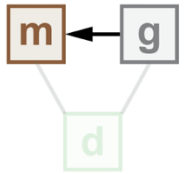
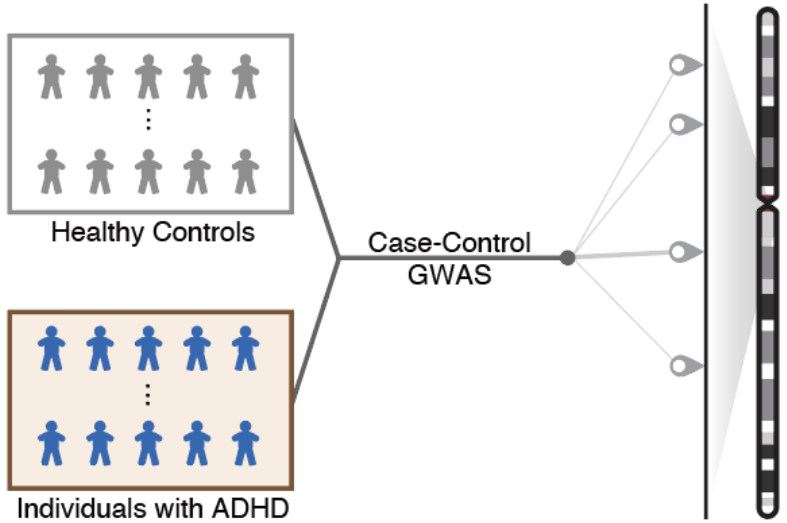


Traditional Strategy for GWAS



Case-Control GWAS

Binary, Univariate Response Variable

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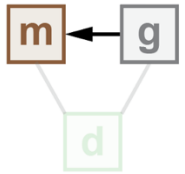
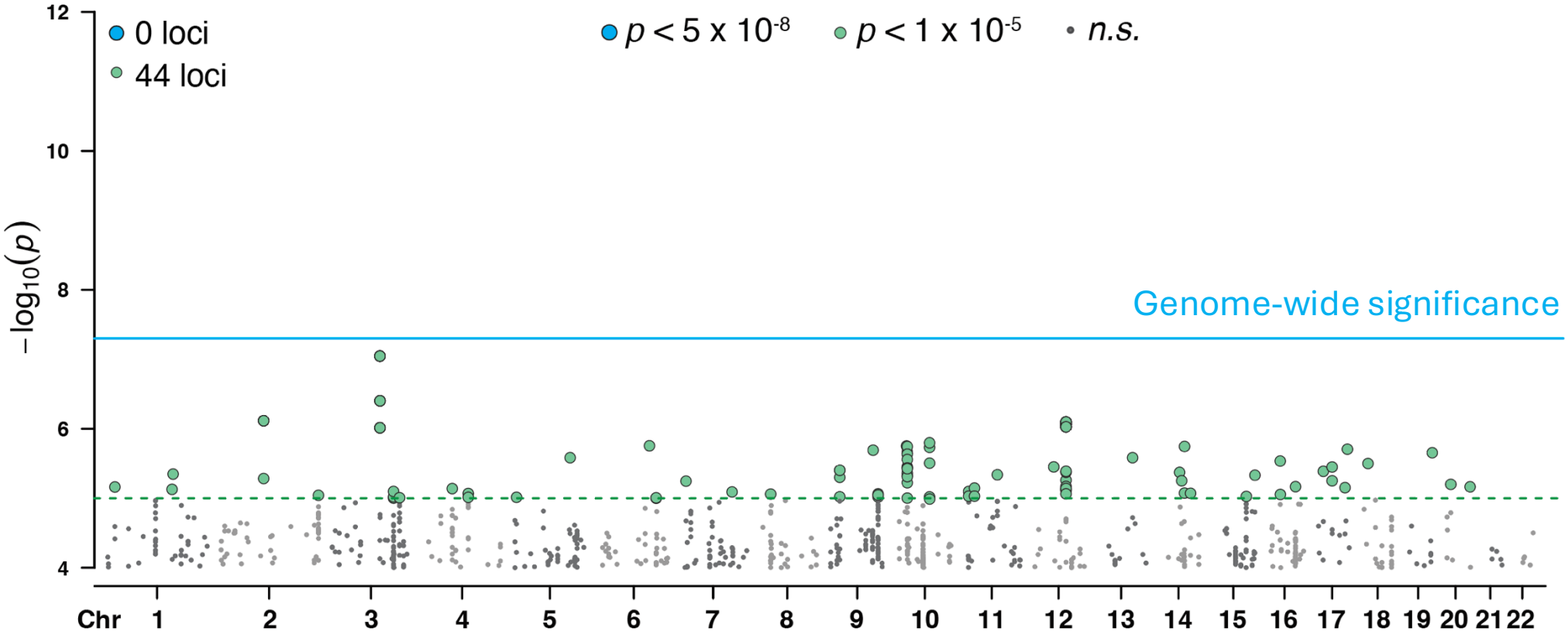


Traditional Strategy for GWAS

n=1191

Univariate, Binary
Case-Control GWAS



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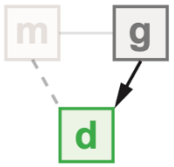
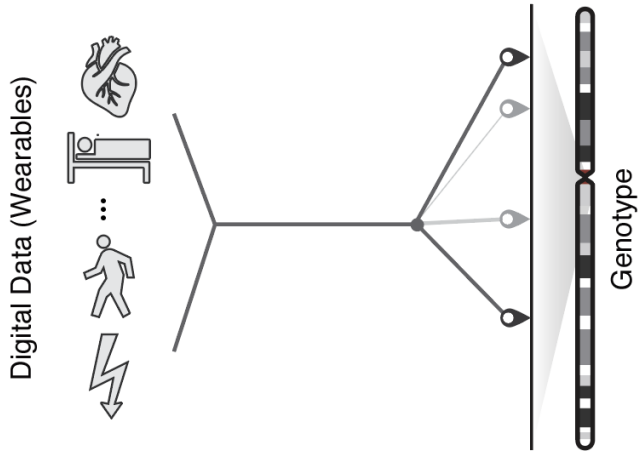
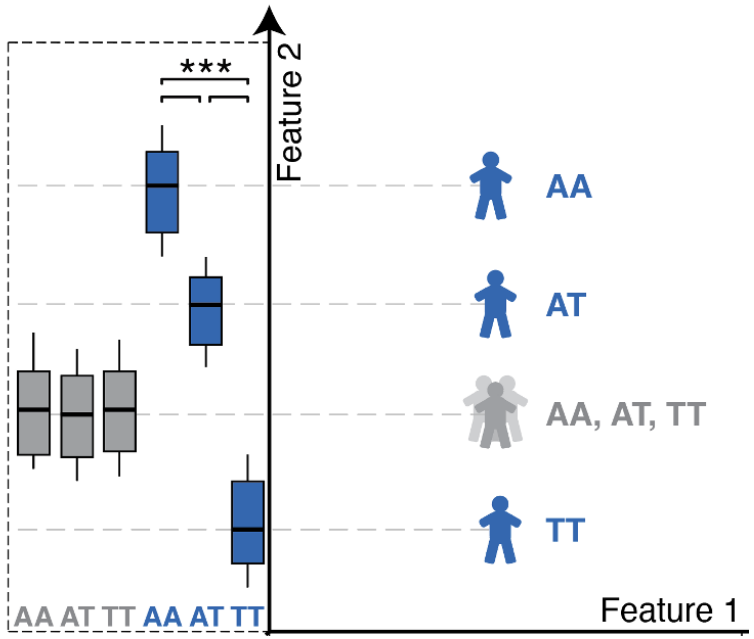


Linking Digital Phenotypes to Genotype





Continuous, Multivariate Response Variable

(with gxm interaction)

$$\vec{d} \sim g + m + g \times m + c$$

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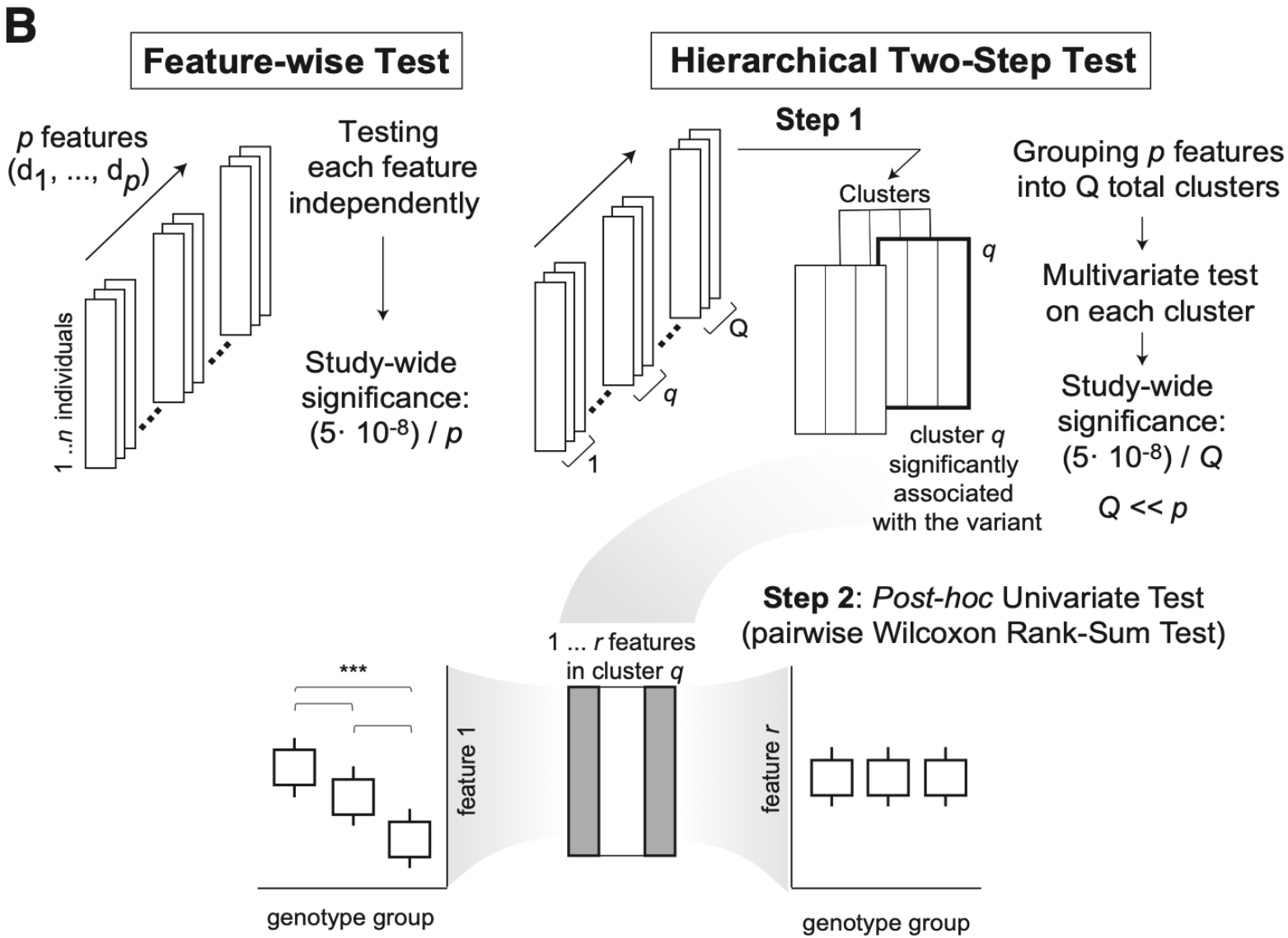
Linking Digital Phenotypes to Genotype



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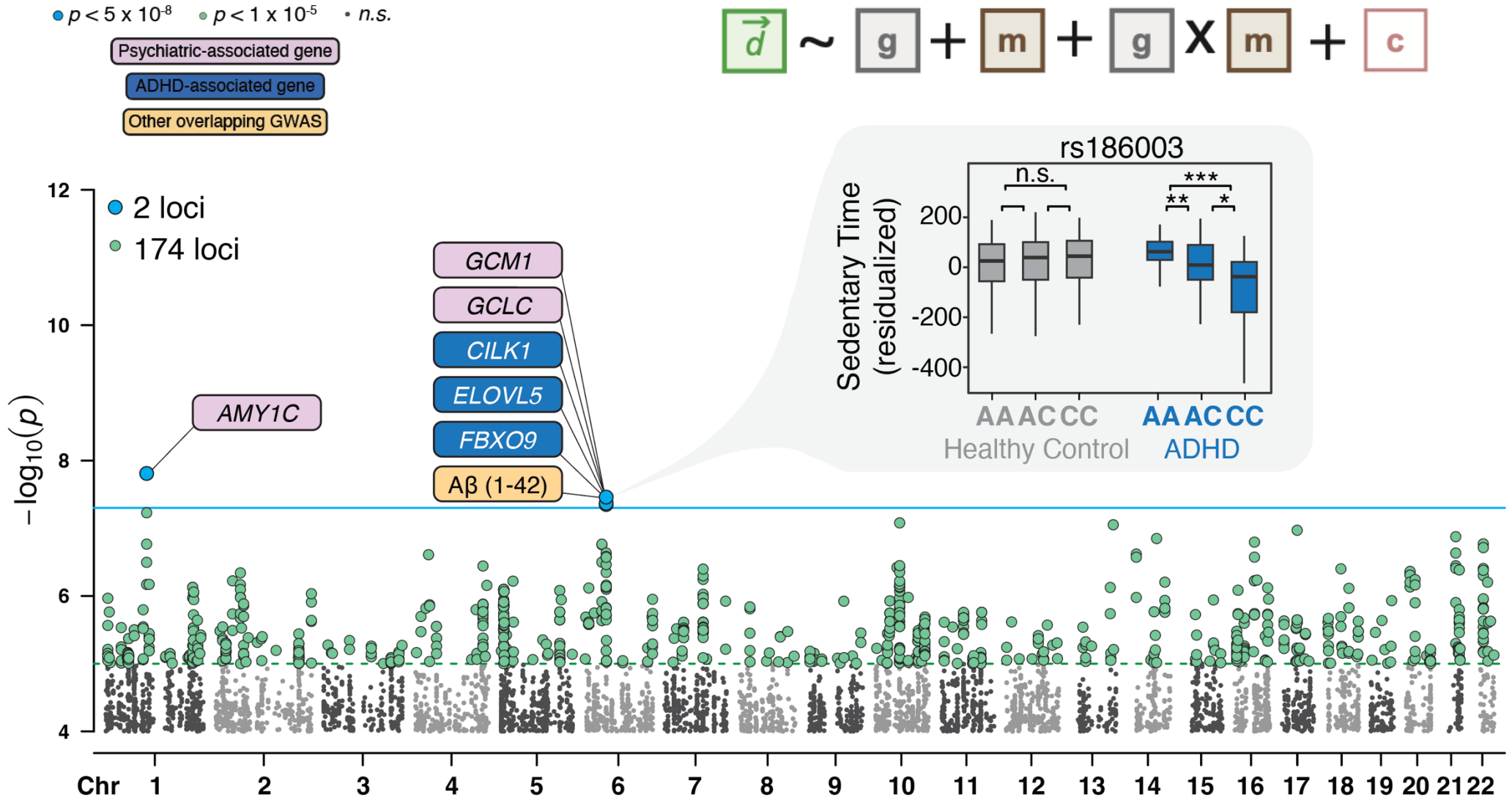
Linking Digital Phenotypes to Genotype

$\vec{d} \sim g + m + g \times m + c$

n=1191

Continuous, Multivariate
(with gxm interaction)
Wearable GWAS



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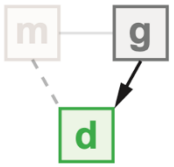
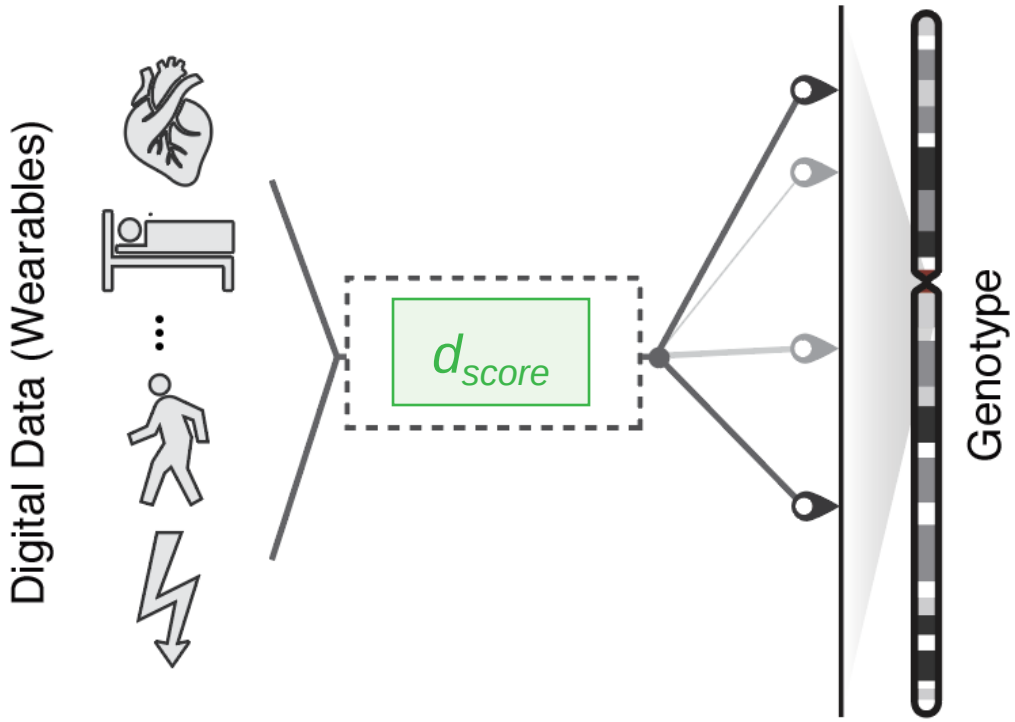


Linking Digital Phenotypes to Genotype



Continuous, Univariate Response Variable

$$d_{score} \sim g + c$$

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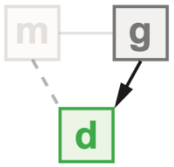
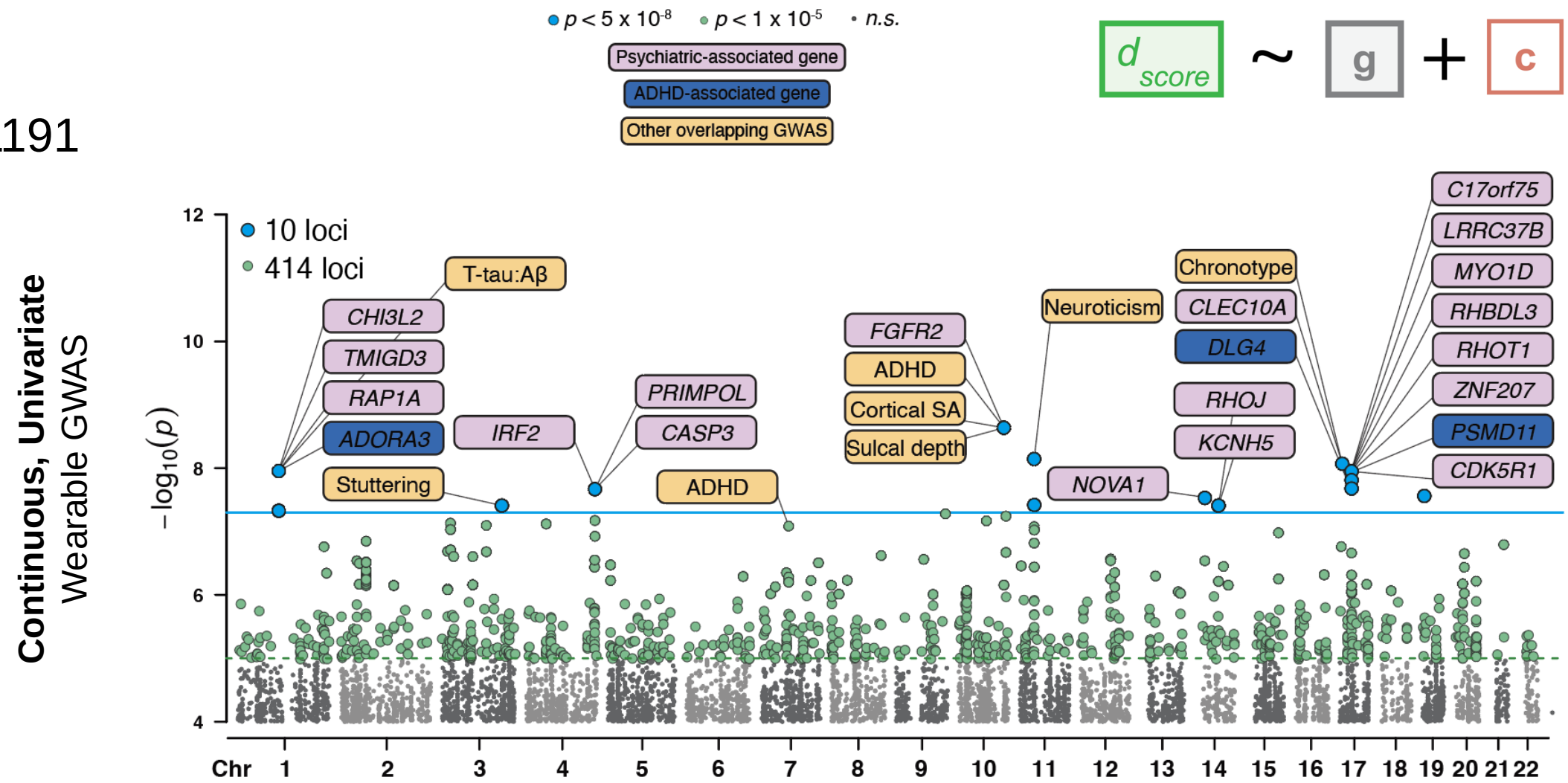


Linking Digital Phenotypes to Genotype

n=1191



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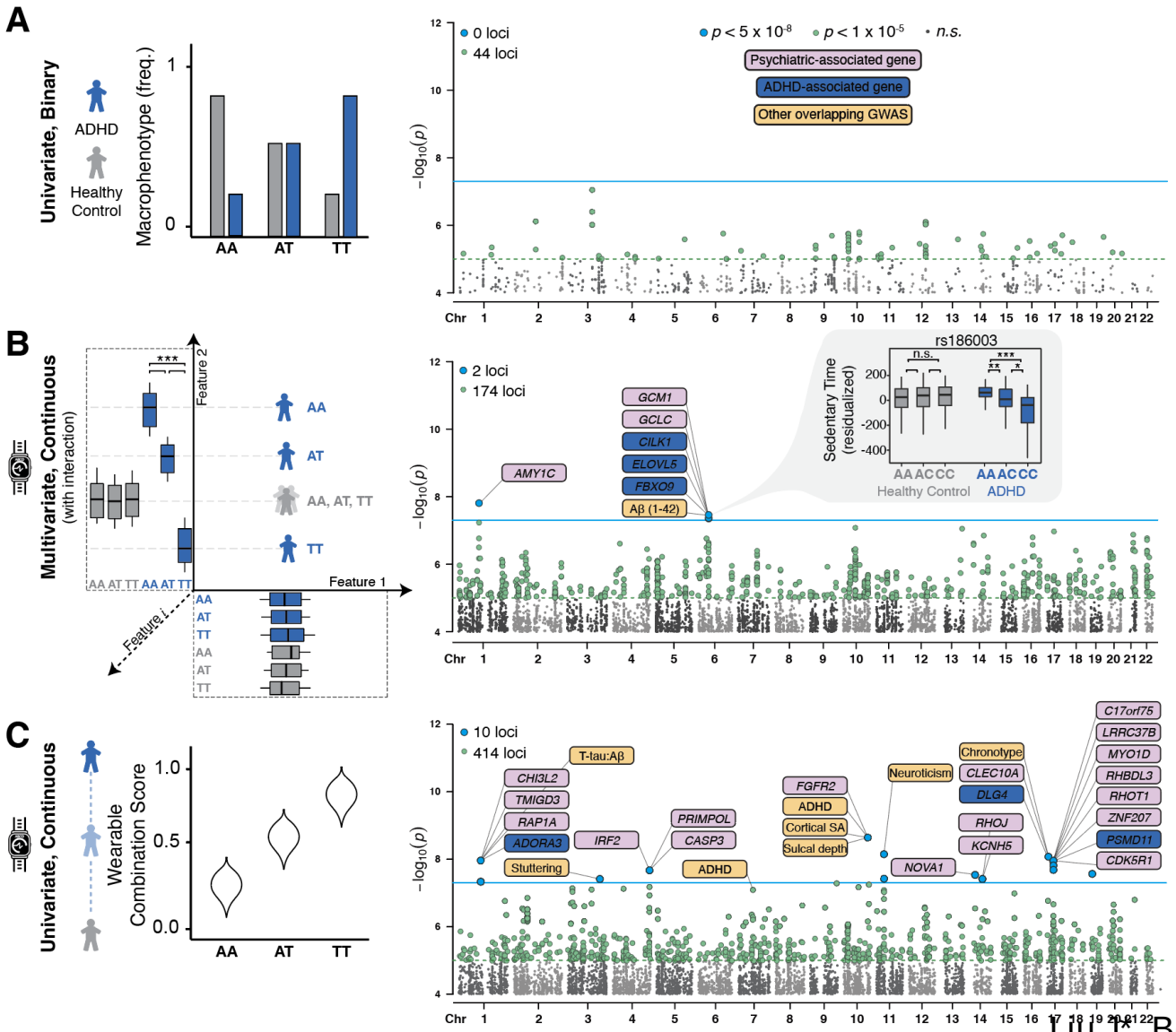
GWAS Results With and Without Digital Phenotypes

Without Digital Phenotypes

With Digital Phenotypes



n=1191

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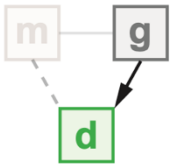
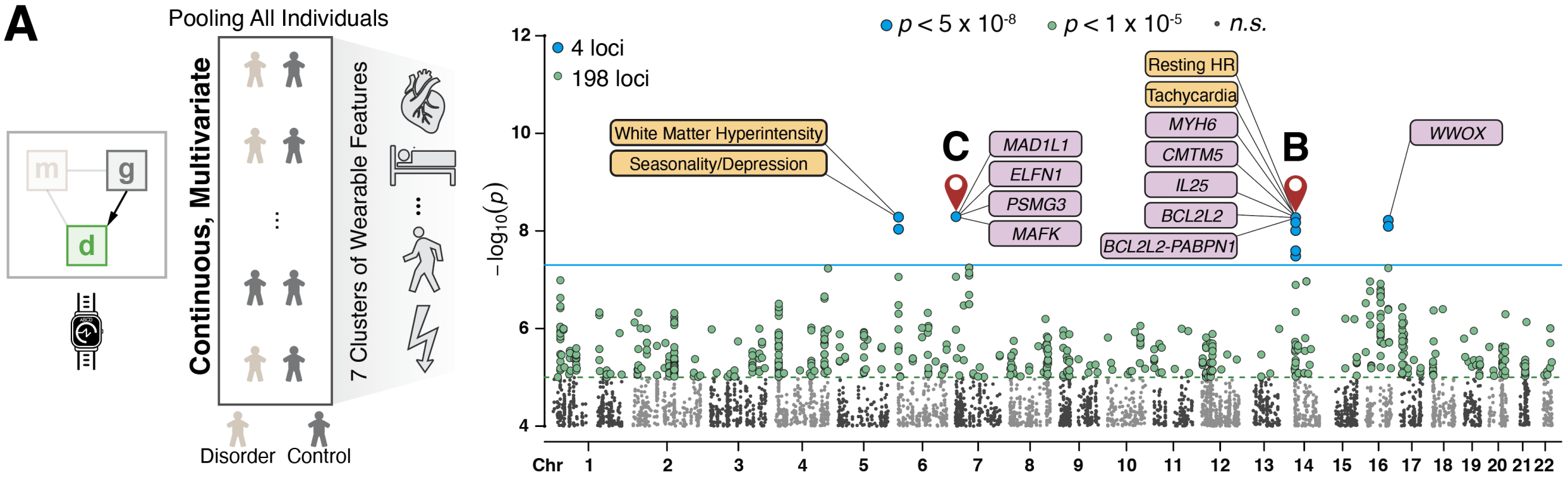


Pooling All Individuals

Pooling all individuals can:

- Increase statistical power
- Rely on digital phenotypes as a proxy for health instead of binary labels



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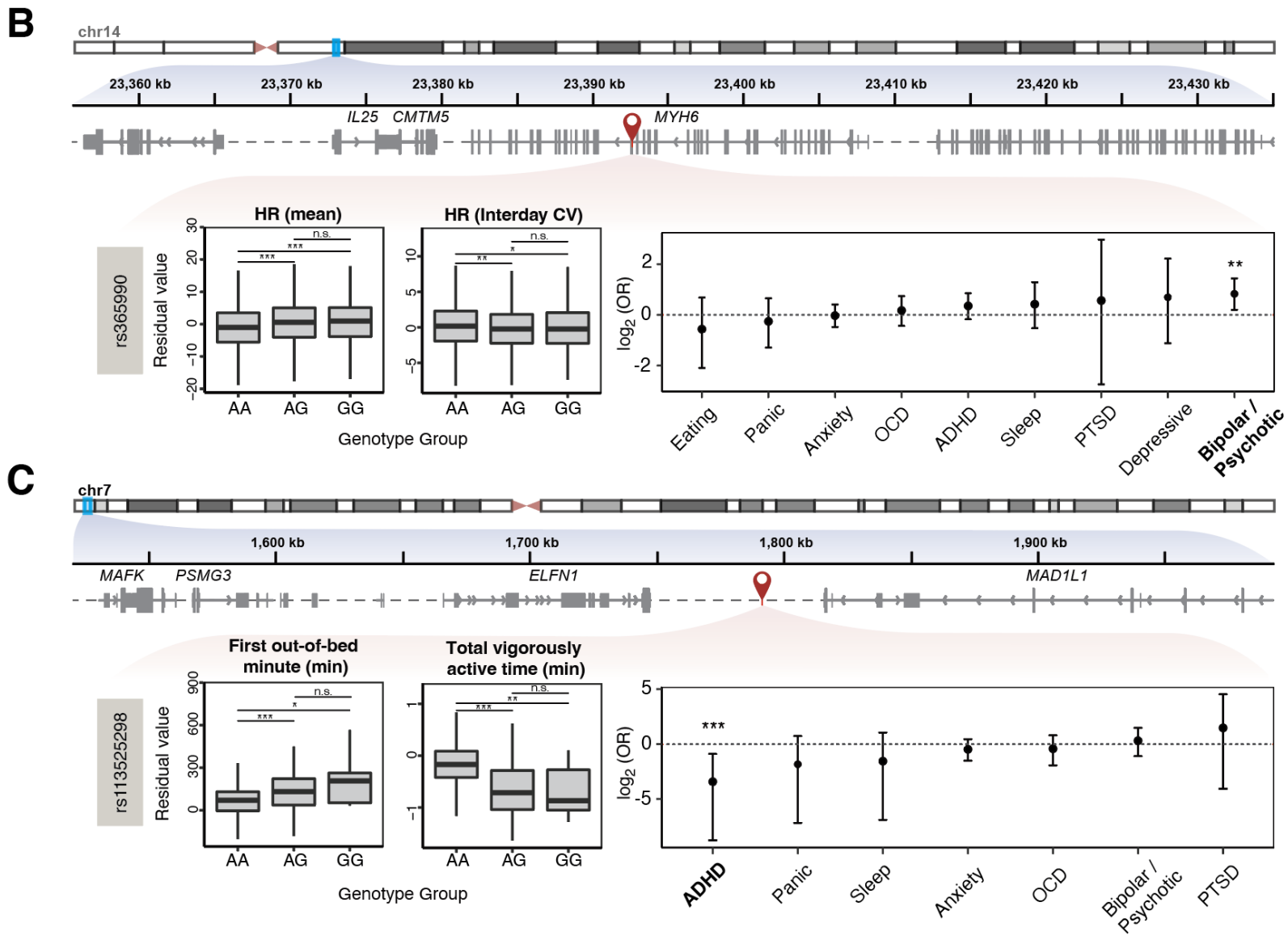
The Interplay of Genetic-Physiological-Psychiatric Factors

MYH6, previously known to be related to atrial fibrillation and tachycardia, shows enrichment in bipolar and psychotic disorders

ELFN1, related to synaptic function and neuronal activity, previously shown to play a role in other neuropsychiatric disorders[1], shown here related to ADHD and behavioral patterns of activity



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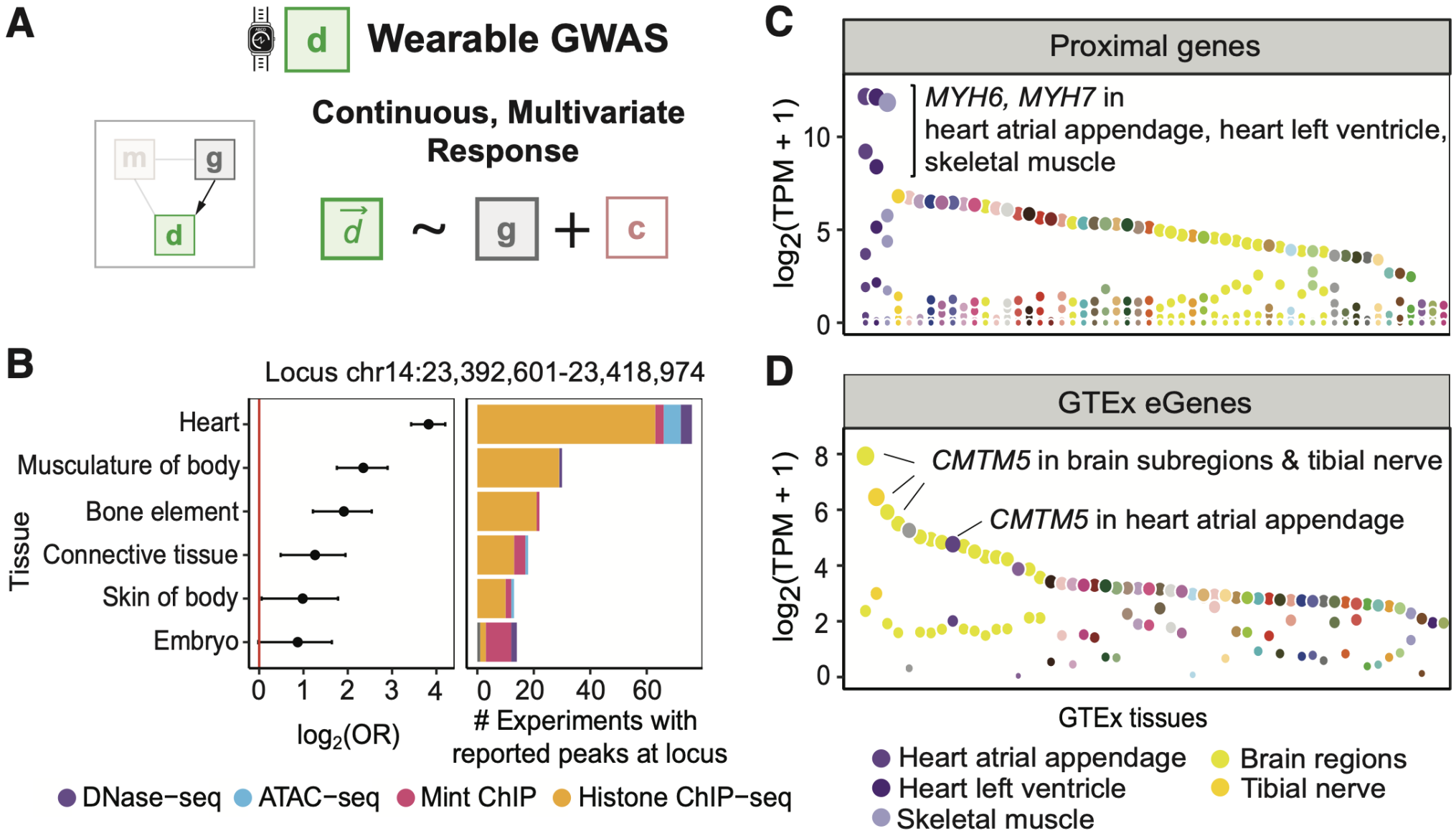
[1]Girgenti MJ et al. Nature Neuroscience ('21)



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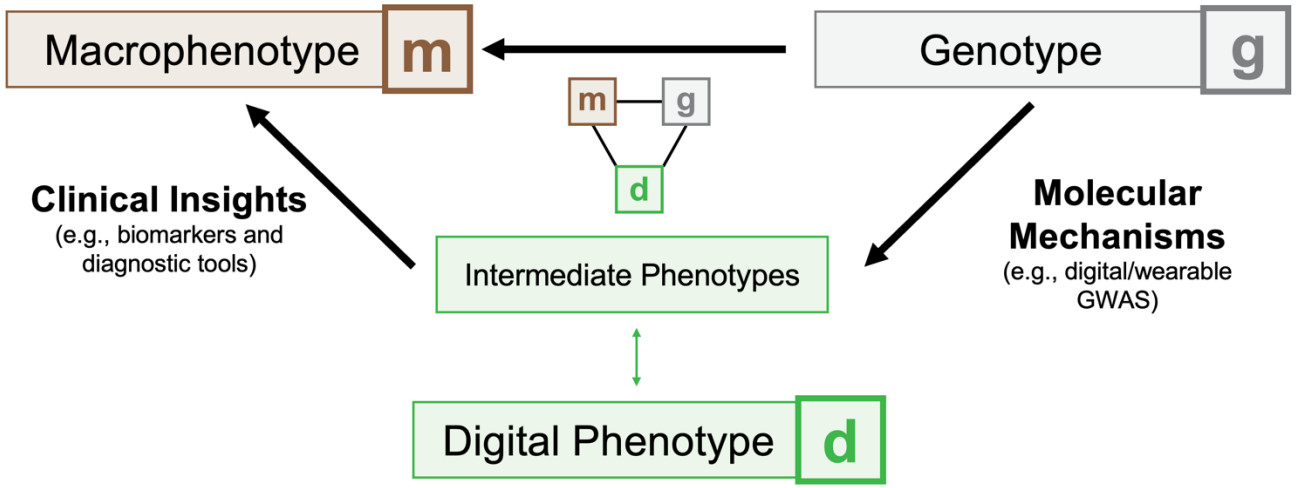
Summary from ABCD Study and Digital Phenotyping

- **Digital phenotypes** can be extracted from digital biosensor data
- AI and digital phenotypes enable potential **diagnostic tools and biomarkers**
- **Linking digital phenotypes to genotype** uncovers SNPs and potential molecular mechanisms otherwise missed by traditional case-control GWAS
- Intersection of **genetic--physiological/behavioral--psychiatric** factors



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