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Supplementary information

Differences in the genetic architecture of common and rare variants in childhood, persistent and late-diagnosed attention-deficit hyperactivity disorder

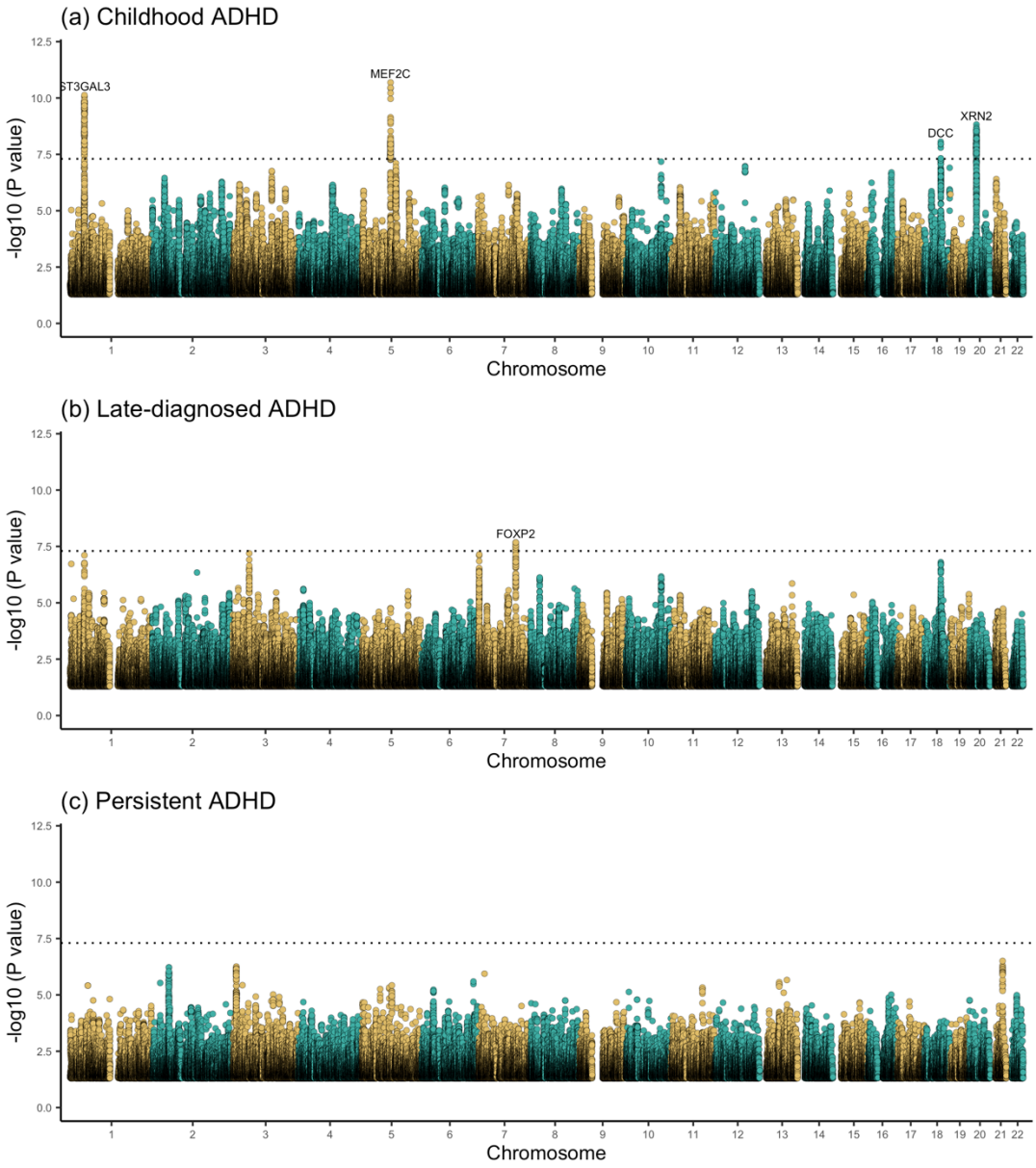
In the format provided by the authors and unedited

Supplementary Information

Differences in the genetic architecture of common and rare variants in childhood, persistent and late-diagnosed attention deficit hyperactivity disorder

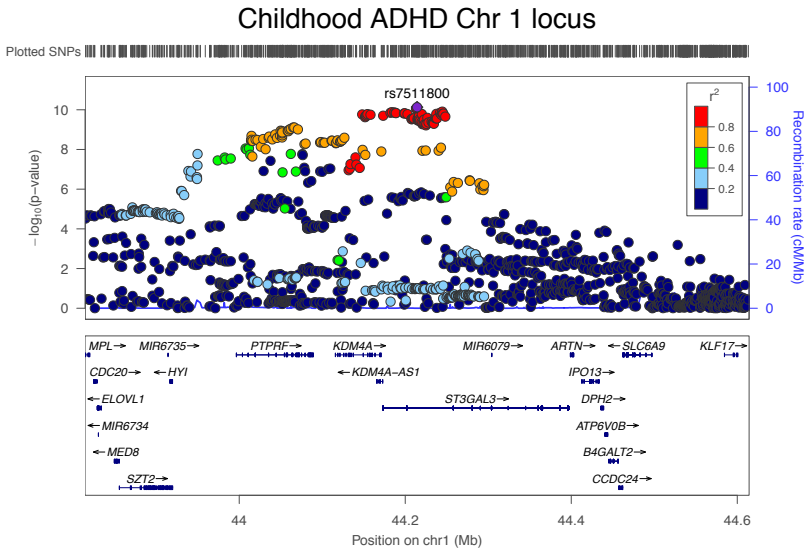
Supplementary figures 1-7 and supplementary notes 1-3

Supplementary Figure 1. Manhattan plots from GWAS of ADHD subgroups
Results from logistic regression corrected for sex and ancestry principal components 1-10. Y-axes represent two-sided -log(P-values) and x-axes represent location on autosomal chromosomes. The red horizontal line represents the threshold for genome-wide significant association ($P = 5x10^{-8}$) **(a)** GWAS of childhood ADHD (14,878 cases; 38,303 controls) **(b)** GWAS of late-diagnosed ADHD (6,961 cases; 38,303 controls) **(c)** GWAS of persistent ADHD (1,473 cases; 38,303 controls).

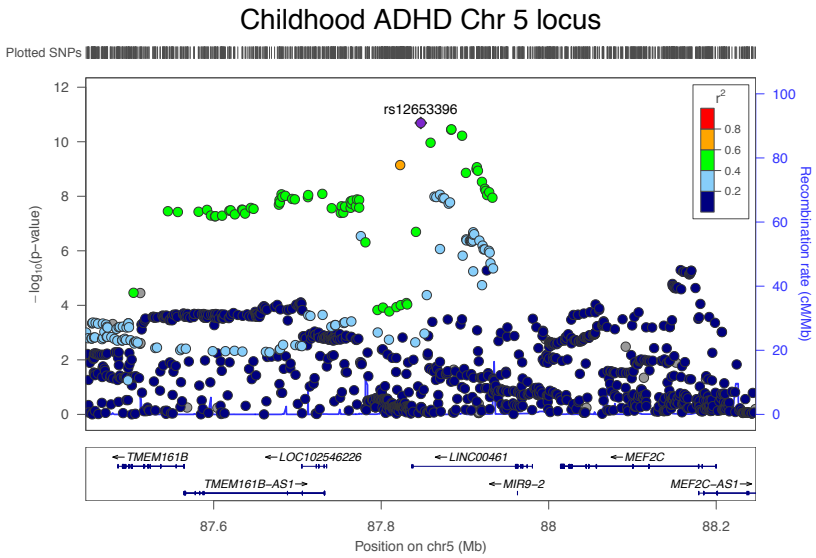


Supplementary Figure 2. Regional association plots of genome-wide significant loci
Regional association plots of the local association results from the GWAS of ADHD sub-groups **(a-d)** the four genome-wide significant loci identified in the GWAS of childhood ADHD (14,878 cases; 38,303 controls) **(e)** the genome-wide significant locus identified in the GWAS of late-diagnosed ADHD. The y-axis represents –log(P-values) of variant association; the P-values are two-sided from logistic regression corrected using relevant covariates. Location and orientation of the genes in the regions are indicated on the X-axis, LD estimates of surrounding SNPs with the index SNP (r^2 values estimated based on 1KGP3) is indicated by colour (colour bar in upper left corner indicates r^2 values). Additionally, the local estimation of recombination rate is indicated in blue (legend on vertical axis at right).

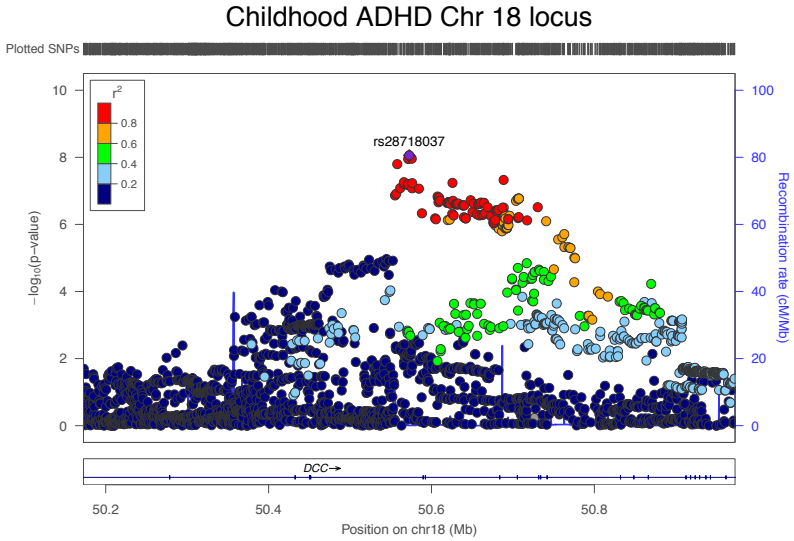
a.



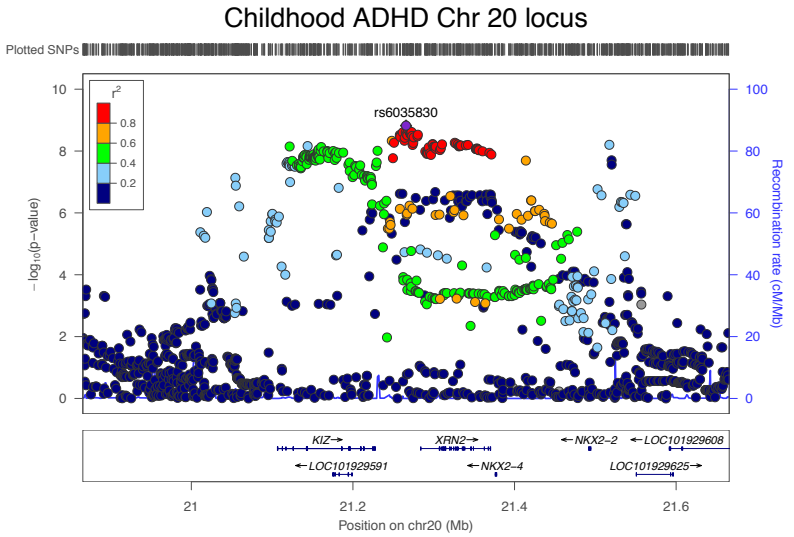
b.



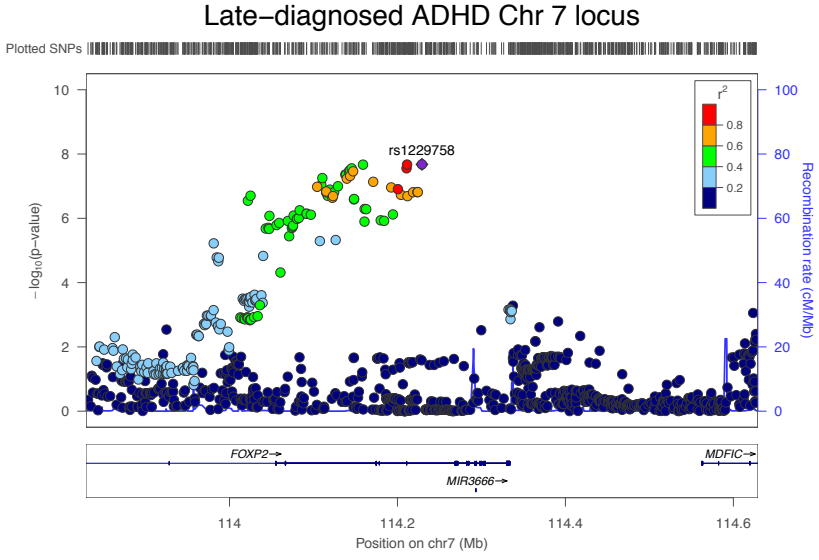
c.


Childhood ADHD Chr 18 locus
Plotted SNPs
rs28718037
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
DCC
50.2
50.4
50.6
50.8
Position on chr18 (Mb)

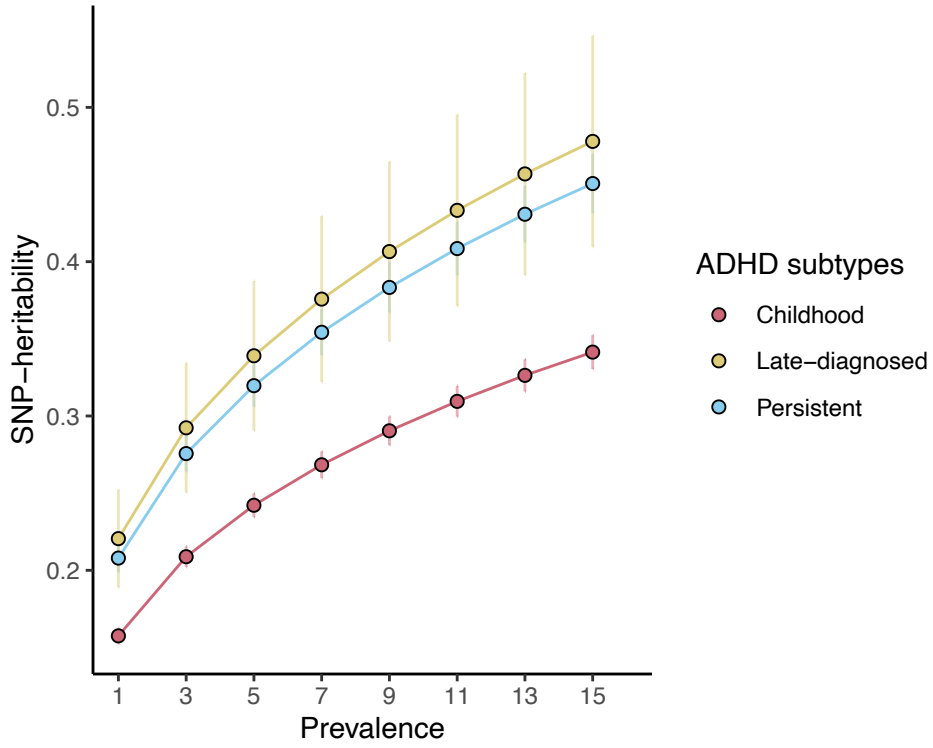
d.


Childhood ADHD Chr 20 locus
Plotted SNPs
rs6035830
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
KIZ
XRN2
NKX2−2
LOC101929608
LOC101929591
NKX2−4
LOC101929625
21
21.2
21.4
21.6
Position on chr20 (Mb)

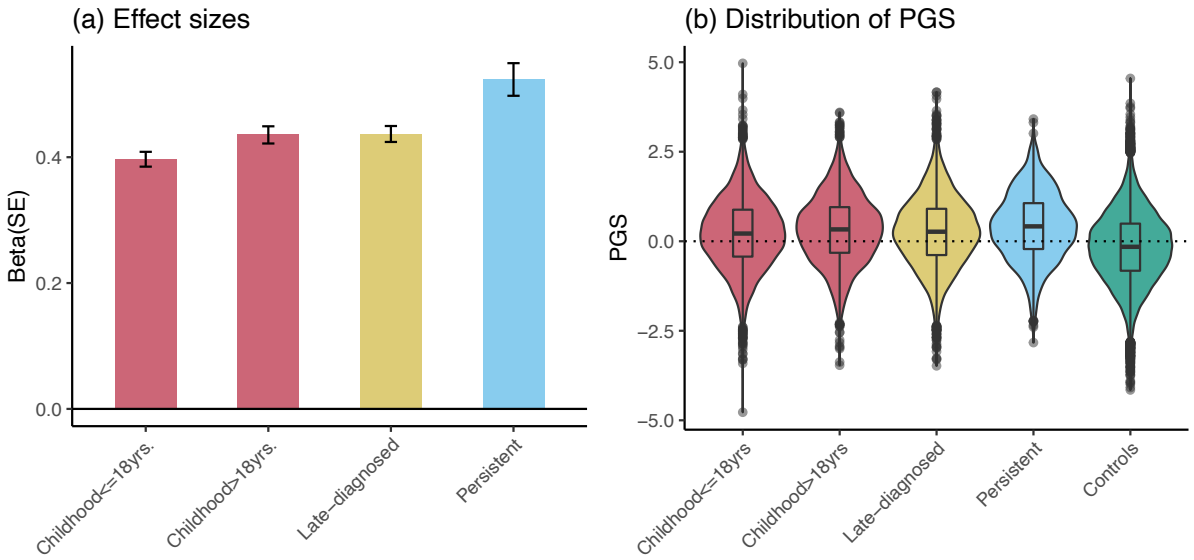
e.


Late−diagnosed ADHD Chr 7 locus
Plotted SNPs
rs1229758
r²
0.8
0.6
0.4
0.2
−log10(p−value)
Recombination rate (cM/Mb)
FOXP2
MDFIC
MIR3666
114
114.2
114.4
114.6
Position on chr7 (Mb)

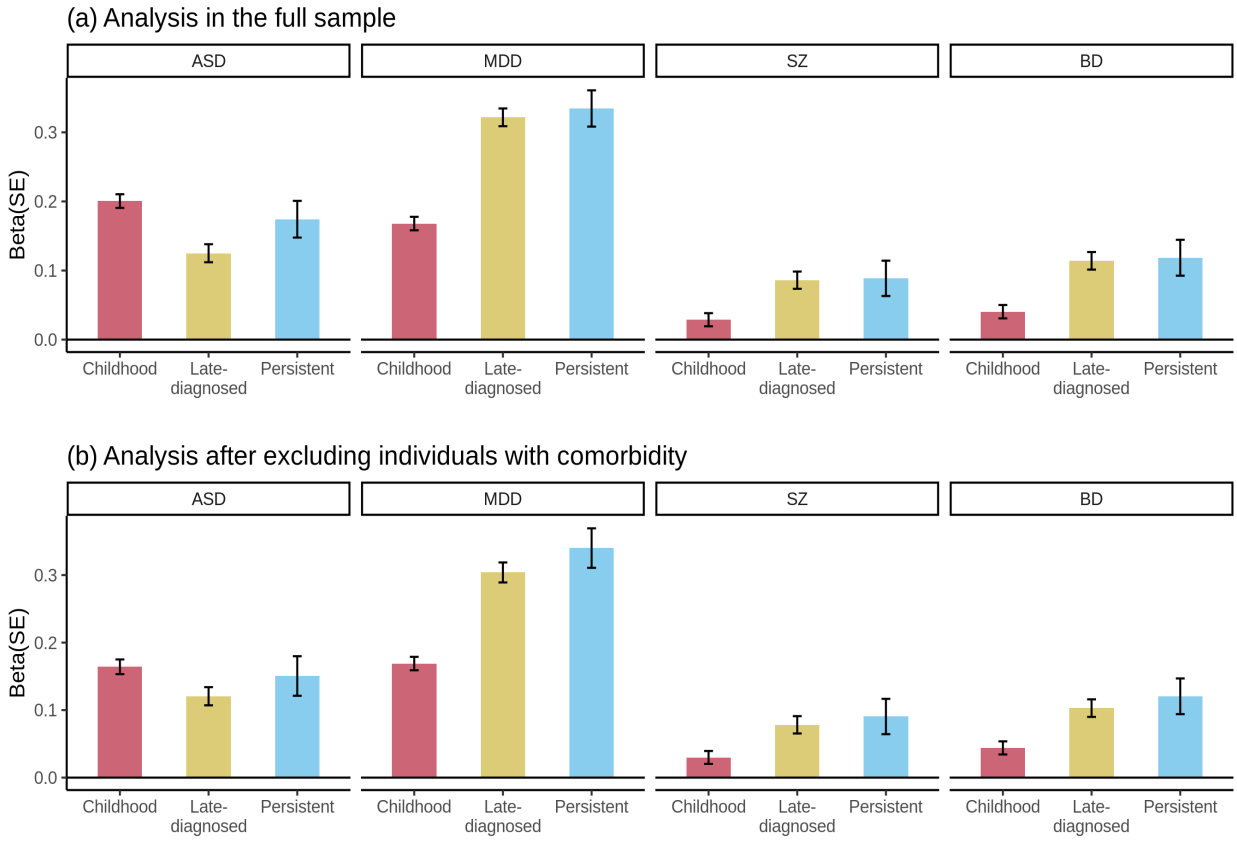
Supplementary Figure 3. SNP-heritability (h2) estimates in childhood (N=14,878), persistent (N=1,473) and late-diagnosed ADHD (N=6,961) compared to controls (N=38,303). The h2 estimates are indicated with dots and are calculated using GCTA. Vertical bars represent standard errors.



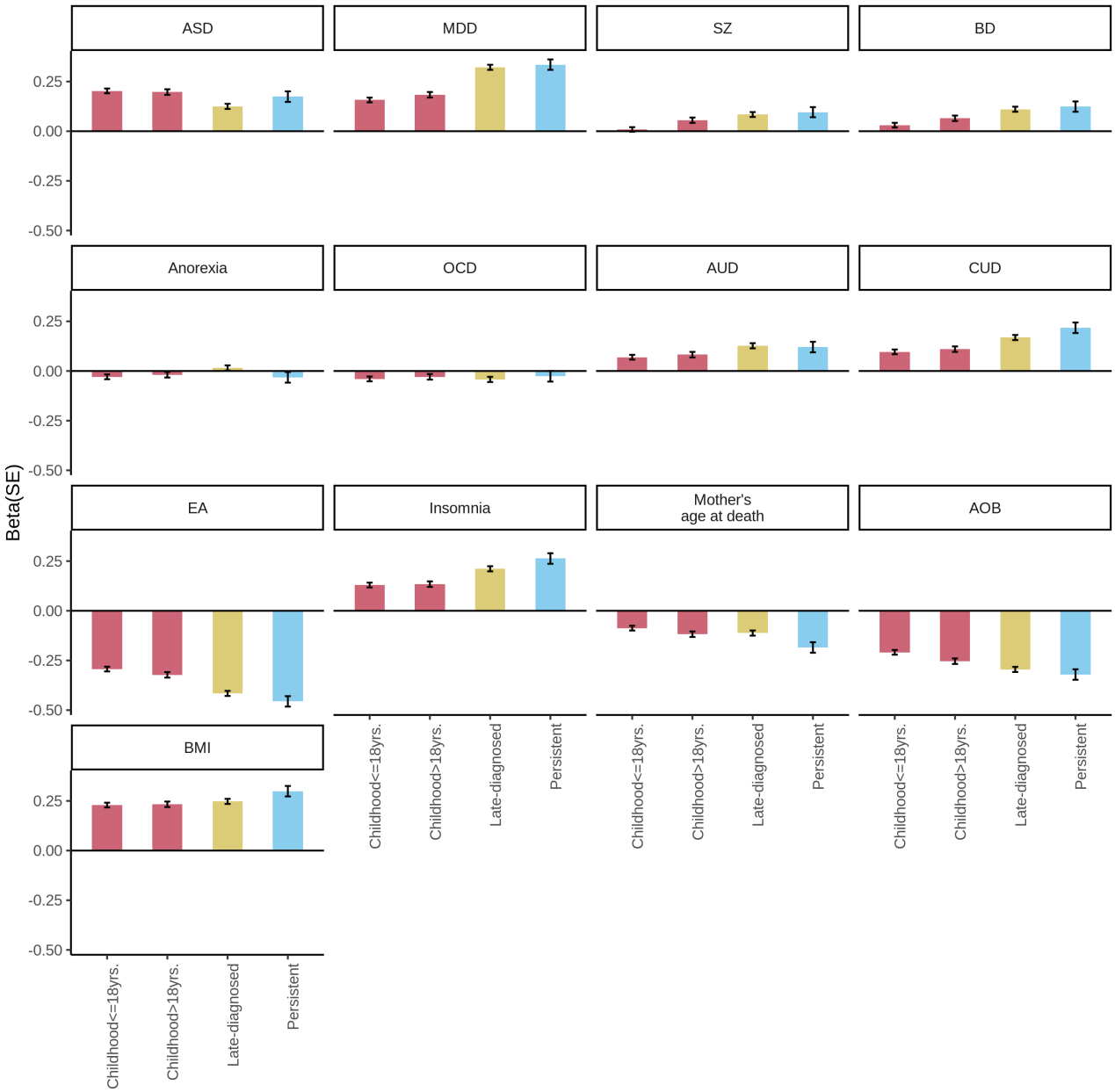
Supplementary Figure 4. ADHD-PGS load in childhood ADHD individuals younger than 18 years of age (N=8,664), childhood ADHD individuals older than 18 years of age (N= 6,214), Persistent ADHD (N=1,473), late diagnosed ADHD (N=6,961) compared to controls (N=38,303) **(a)** The beta from multiple regression is given on the y-axis. Vertical bars represent standard errors **(b)** Distribution of the PGS in the four groups are displayed in the violin plots. The vertical line in the box represents the mean PGS, the box represents the interquartile range, and the thin lines represent the rest of the distribution except for dots determined to be outliers.



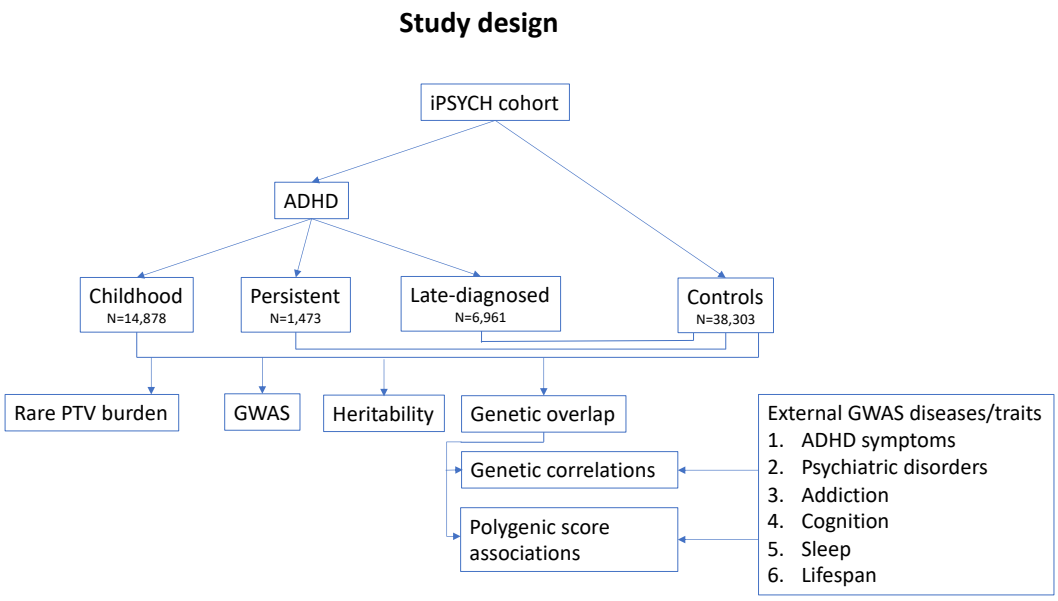
Supplementary Figure 5. Results from PGS analyses, demonstrating the association of PGS for autism (ASD), depression (MDD), schizophrenia (SZ), and bipolar disorder (BD) with childhood, late-diagnosed and persistent ADHD compared to controls in **(a)** the full sample (childhood ADHD N=14,878, late-diagnosed ADHD N=6,961, persistent ADHD N=1,473) and **(b)** in samples where individuals are excluded if they are diagnosed with the disorder of the analyzed PGS (sample sizes can be found in Supplementary Table 10.B).The beta from multiple regression is given on the y-axis. Vertical bars represent standard errors.



Supplementary Figure 6. Results from PGS analysis demonstrating the association of PGS with childhood ADHD individuals younger than 18 years of age (N=8,664), childhood ADHD individuals older than 18 years of age (N= 6,214), persistent ADHD (N=1,473) and late-diagnosed ADHD. (N=6,961). PGS for psychiatric disorders: autism spectrum disorder (ASD), major depressive disorder (MDD), schizophrenia (SZ), bipolar disorder (BD), anorexia, obsessive compulsive disorder (OCD), alcohol use disorder (AUD), cannabis use disorder (CUD). PGS for five phenotypes representing domains highly correlated with ADHD: educational attainment (EA), insomnia, mother´s age at death and age of first birth (AOB). On the y-axis is the beta from multiple regression against controls (N=38,303), vertical bars represent standard errors (see also Supplementary Table 11).



Supplementary Figure 7. Flow chart demonstrating the genetic analyses that was performed in the study.



Supplementary note 1. Genetic correlation with mother´s age at death

We found a stronger negative genetic correlation of mother's age at death with persistent and late-diagnosed ADHD compared with childhood ADHD. The phenotype mother's age at death captures all variants that affect longevity, for example, variants associated with cardiovascular diseases[1], and our results suggest that ADHD in adulthood is more enriched in variants that decrease longevity than childhood ADHD.

Supplementary note 2. Cases potentially missed by the diagnostic system

We acknowledge that we might have missed cases that never came into contact with the health care system or cases that only briefly interacted with the system and never got diagnosed. This could be due to various reasons such as lack of resources (mentally or physically) to engage with the system, lack of persistency if the diagnostic investigation took too long or unequal access to mental health care. Regarding the latter, we think Denmark, world-wide is one of the countries with least bias caused by unequal access to health care. Denmark is a small welfare

state with health care facilities distributed across the country and citizens have equal access to the health care system that is free of charge.

Additionally, ADHD is considered a childhood-onset disorder and therefore, and according to the current diagnostic criteria, individuals diagnosed with ADHD as adults should be able to describe ADHD symptoms in childhood retrospectively. We would therefore like to note that some adults with ADHD might be missed if they were not able to recall having ADHD symptoms in childhood. In line with this, we also acknowledge that late-diagnosed ADHD probably is more likely to be missed than childhood and persistent ADHD, because the disorder seems to be underdiagnosed among adults[65].

Supplementary note 3. Patient exclusion criteria in the Spanish cohort

Exclusion criteria for patients in the Spanish ADHD cohort were the following: intelligence quotient (IQ) <70, having pervasive developmental disorders, schizophrenia or other psychotic disorders, adoption, sexual or physical abuse, birth weight <1.5 kg, and any significant neurological or systemic disease that might explain ADHD symptoms. Comorbid oppositional defiant disorder, conduct disorder, depression and anxiety disorders were allowed unless determined to be the primary cause of ADHD symptomatology.

1 Pilling, L. C. *et al.* Human longevity is influenced by many genetic variants: evidence from 75,000 UK Biobank participants. *Aging (Albany NY)* **8**, 547-560, doi:10.18632/aging.100930 (2016).