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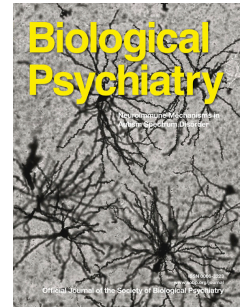
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Genetic architecture and risk of suicide attempt across neurodevelopmental and psychiatric conditions

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Genetic architecture and risk of suicide attempt across neurodevelopmental and psychiatric conditions

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Running Title

Genetic architecture of suicide attempt

Key words

suicide attempt, neurodevelopmental conditions, psychiatric disorders, GWAS, polygenic scores, absolute risk

Abstract

Background: Suicide attempt (SA) is prevalent among individuals with neurodevelopmental and psychiatric conditions, yet similarities and differences in the genetic architecture of SA across these conditions remain unclear.

Methods: In the iPSYCH cohort (N=98,069), SA was identified using ICD-10 codes among individuals diagnosed with attention-deficit hyperactivity disorder (ADHD) (N=22,962), autism (N=17,670), schizophrenia (N=5,974), bipolar disorder (N=3,028), depression (N=28,844), and controls (N=34,049). We evaluated 21 polygenic scores (PGSs) in individuals with and without SA within each diagnosis, stratified individuals into PGS quantiles, estimated absolute SA risk, and conducted sex-stratified analyses.

Results: SA was 1% among controls but ranged from 5% in autism to 31% in schizophrenia. Several PGSs were increased in individuals with SA across diagnoses, including PGS for ADHD, depression, and substance use disorders (SUD). SA-PGS stratification showed marked SA absolute risk differences, e.g., 40% in the top PGS tertile vs 29% in the lowest tertile in schizophrenia. PGS-loads did not differ between females and males with SA across diagnoses. However, absolute SA risk differed substantially. In the highest SA-PGS tertile in ADHD, the absolute SA risk reached 36% for females and 22% for males and was further increased to 48% in those with comorbid SUD.

Conclusions: SA genetic architecture is similar across neurodevelopmental and psychiatric conditions and individuals can be stratified into SA risk groups based on PGSs, and co-occurring SUD. Being a female or having comorbid SUD are strong risk factors for SA, however SA common variants, still affect SA risk in the presence of those factors.

Introduction

Suicide attempt (SA) refers to a range of behaviors that involve self-harm or self-injuries with the intent to die(1) and is estimated to account for ~34 million disability-adjusted life years globally in 2019.(2)

SA has a considerable genetic risk component; a large Swedish register study estimated the overall twin-based heritability to 41-50%.(3) Common genetic risk variants for SA have been identified in the largest genome-wide association study (GWAS) of SA(4) to date, which included 43,871 individuals with SA and 915,025 controls. This study identified 12 genome-wide significant loci(4) and established that common genetic variants contribute substantially to SA risk, with an estimated single nucleotide polymorphism (SNP)-based heritability of 7.0% (SE=0.4%) in the European population.

It is well established that SA rates are significantly higher among individuals diagnosed with neurodevelopmental and psychiatric conditions, including major depressive disorder (MDD), schizophrenia (SCZ), bipolar disorder (BPD), substance use disorders (SUD), eating disorders, and personality disorders, in comparison to the general population.(5,6) Studies based on Danish individuals have reported increased risk of SA among individuals with depression,(7,8) and a large Danish register study based on more than 7 million people demonstrated death by suicide to be significantly increased across all examined major neurodevelopmental and psychiatric diagnoses.(9)

SA and some neurodevelopmental and psychiatric conditions might have a shared genetic component. For example, a study using structural equation modeling incorporating genetics found a strong loading of SA, MDD, attention-deficit hyperactivity disorder (ADHD), and alcohol use disorder (AUD) on a shared latent genetic factor.(10) Furthermore, a high genetic liability for MDD, captured by

polygenic scores (PGS), was associated with an increased risk of SA in individuals severely affected by psychiatric conditions.(11,12) The role of depression in SA risk was also reinforced by drug target enrichment analyses that have revealed a significant overlap between SA risk loci and molecular targets of antipsychotic and antidepressant drug classes, underscoring that treatment of depression could decrease suicidal behavior.(4)

In this study we evaluate potential variation in the genetic architecture of SA across neurodevelopmental and psychiatric conditions. This information is highly needed for understanding if the biological factors underlying SA risk in one diagnosis are similar to the biological factors underlying SA in other diagnoses.

Methods

Cohort description and phenotype definition

This study was performed in the Danish case-control cohort iPSYCH.(13) Individuals diagnosed with one or more of the five common neurodevelopmental and psychiatric diagnoses (ADHD, ASD, MDD, BPD, and SCZ) and individuals with at least one SA were identified using ICD-10 codes obtained from the Danish registries (See Supplementary Information for information about cohort design and ICD10 codes). Additionally, a random sample of population-based controls was included. Information on genotyping of the included individuals, quality control, and imputation is available in the Supplementary Information.

Polygenicity of SA and genetic correlations with neurodevelopmental and psychiatric conditions

To evaluate the polygenicity of the genetic risk component of SA, the number of common variants influencing SA was estimated using univariate mixture modeling implemented in MiXeR.(14) Genetic correlations between SA and the five neurodevelopmental and psychiatric conditions were estimated with LDSC(15) using summary statistics from the largest available GWAS of ADHD,(16) ASD,(17) MDD,(18) BPD,(19) and SCZ(20) (Supplementary Information).

GWAS of SA corrected for neurodevelopmental and psychiatric conditions and SNP heritability

We performed a GWAS of SA in the iPSYCH cohort and accounted for neurodevelopmental and psychiatric diagnoses among the individuals. The GWAS was performed using additive logistic regression, with SA as the outcome variable, imputed dosage genotypes as predictive variable, and covarying for the five neurodevelopmental and psychiatric diagnoses (ADHD, MDD, ASD, BPD, and SCZ), the first ten ancestral principal components, age, and sex. The genome-wide significant locus was linked to potentially affected genes using the OPERA(21) and FLAMES(22) (Supplementary Information, Supplementary Table 1).

We also estimated the proportion of phenotypic variance explained by the genotyped common variants, referred to as the single nucleotide polymorphism heritability (h^2_{SNP}). SA h^2_{SNP} within each of the five neurodevelopmental and psychiatric conditions was estimated using GREML(23) (Supplementary Information).

PGS analyses

We performed PGS analyses to identify potential similarities or differences in the genetic architecture underlying SA across the five neurodevelopmental and psychiatric

conditions. Using LDpred2-auto(24) we generated PGSs that represent an individual's genetic predisposition to 21 phenotypes grouped into five domains **(1)** suicide-related phenotypes (SA,(4) suicidal thoughts and behaviors [SITB](25)), **(2)** neurodevelopmental and psychiatric conditions (ADHD,(16) ASD,(17) BPD,(19) MDD,(18) and SCZ(20)), **(3)** personality characteristics or behaviors (fed up feelings(26) [Fed], guilty feelings(26) [Guil], risk taking(27) [Risk], nervous feelings(26) [Nerv], loneliness(28) [Lone], miserableness(26) [Mise], sociability(29) [Socia], subjective well-being(30) [SWB]), **(4)** life outcomes and adverse life experience (educational attainment(31) [EA], childhood maltreatment(32) [CM]), and **(5)** substance- use and use disorders (smoking initiation(33) [SmoIni], alcohol-(34) [AUD], cannabis-(35) [CUD], opioid use disorder(36) [OUD]), details in Supplementary Information. For phenotypes for which the published GWAS included iPSYCH data, we used GWAS summary statistics for SA, CUD, BPD, MDD, and SCZ without iPSYCH data as the basis for generating PGSs. See the Supplementary Information for details on the partly internally derived PGSs for ADHD and ASD.

We applied multivariate multivariable regression to evaluate the PGS load in individuals with and without SA within each subgroup (Supplementary Information), benchmarked against a population-based control group from which individuals with a diagnosis of any of the five conditions or a history of SA were excluded. A sensitivity analysis was conducted for the MDD PGS to determine if the observed effects across neurodevelopmental and psychiatric conditions were still present after removing individuals with comorbid MDD from each subgroup. Individuals with MDD were retained in the sensitivity analysis for comparative purposes. It should be noted that excluding individuals with an MDD diagnosis from the BPD group does not eliminate depressive symptoms associated with BPD.

Sex-specific PGS analyses

We performed sex-specific analyses to test for PGS differences between females and males with a history of SA within each diagnosis (SCZ+SA [females vs males], BPD+SA [females vs males], ASD+SA [females vs males], ADHD+SA [females vs males], MDD+SA [females vs males]), following the same approach and using the same covariates as described above.

Hazard rate ratio and absolute risk of SA across neurodevelopmental and psychiatric conditions

We estimated the relative hazard rate ratio (HRR) and the absolute risk of SA among individuals with neurodevelopmental and psychiatric diagnoses (SCZ, BPD, ADHD, ASD, and MDD) stratified into tertiles based on their PGS for SA, MDD, and ADHD using Cox regression (Supplementary Information). For the two phenotypes with the largest sample size of individuals with SA (ADHD and MDD), we also explored the absolute risk among individuals with particularly high and low PGSs, i.e., those in the 10% highest and 10% lowest PGS groups, respectively.

For comparison, we assessed the relative and absolute risk of SA in the general population stratified into PGS tertiles by running a Cox model on the population-based controls. This analysis was also conducted separately for males and females to match the sex-stratified analyses.

Impact of sex and comorbid substance use disorder on absolute SA risk

Since sex and substance use are well-established risk factors for SA, we estimated the relative and absolute risk of SA within ADHD and MDD for males and females separately, and for individuals with comorbid SUD (ICD-10: F10-F19).

Results

After QC 98,069 unrelated individuals of European ancestry in the iPSYCH cohort were available for further analyses. Among these we identified 9,854 individuals with a history of SA (Supplementary Table 2). SA was overrepresented among individuals with neurodevelopmental and psychiatric diagnoses and especially among those with SCZ (30.9%) and BPD (24.9%). For all diagnoses SA was more prevalent among females than males (Supplementary Table 2), e.g. SA was over four times more prevalent among females (12.10%) than among males (2.87%) with ASD and nearly twice as prevalent among females (39.70%) than males with SCZ (23.18%).

We found SA to be highly polygenic, with an estimated 6,359 (s.e. = 469) common variants explaining 90% of the SNP-heritability (Supplementary Table 3). The genetic overlap of SA and the five neurodevelopmental and psychiatric conditions was substantial with significant positive genetic correlations (r_g) (Supplementary Table 4) ranging from $r_g=0.28$ (s.e.=0.055, $P=3.47\times10^{-7}$) for SA vs ASD to $r_g=0.73$ (s.e.=0.025, $P=7.03\times10^{-190}$) for SA vs MDD in line with what has been reported previously.¹

To identify common genetic variants associated with SA independent of neurodevelopmental and psychiatric conditions we conducted GWAS of SA adjusted for the five diagnoses. We identified one genome-wide significant locus, on chromosome 4, with the index variant rs11728027 demonstrating an odds ratio=1.099,

P-value= 1.4×10^{-8} (Supplementary Figure 1.A and 1.B, Supplementary Table 5). The locus is located downstream *PDGFRA* and in the long non-coding RNA *LINC02283* (Supplementary Figure 1).

Using OPERA, we found that variants in the genome-wide significant locus influenced both DNA methylation and gene expression in blood and brain tissues (Supplementary Table 6). The results highlighted also genotype-driven changes in *LINC02283* expression in several brain regions, including cerebral and prefrontal cortex, hypothalamus, hippocampus and fetal brain, as well as DNA methylation changes in blood and brain (frontal cortex and bulk brain) affecting both *LINC02283* and *PDGFRA* expression (Supplementary Table 6, Supplementary Figure 2).

When using FLAMES to link credible variants in the SA risk locus to genes, *PDGFRA* was highlighted as risk gene (estimated cumulative precision = 0.84; Supplementary Table 7).

Common genetic variants did explain a small, but significant part of SA risk within ADHD, ASD and MDD in iPSYCH, with h^2_{SNP} estimates on the liability scale ranging from 0.09 (s.e.=0.02; P-value= 3.81×10^{-6}) in MDD to 0.18 (s.e.=0.04; P-value= 3.04×10^{-8}) in ADHD (Supplementary Table 8). The h^2_{SNP} of SA within SCZ was practically zero.

When evaluating the polygenic architecture of SA across the five neurodevelopmental and psychiatric conditions we identified significantly increased SA- and SITB-PGS in all groups both with and without SA compared to the population-based controls reflecting the genetic overlap between SA and neurodevelopmental and psychiatric

conditions in general (Figure 1.A). We identified a further and significant increase of these PGSs in individuals with SA compared to those without SA within all diagnoses (although only nominally significant within BPD; Figure 1.A) suggesting that the SA- and SITB PGSs contribute to SA risk in individuals with neurodevelopmental and psychiatric conditions beyond their contribution to being diagnosed (Supplementary Table 9).

When evaluating the PGSs for neurodevelopmental and psychiatric conditions, we observed a significantly increased ADHD- and MDD-PGS among individuals with SA compared to those without SA within all diagnoses (Figure 1.B). The MDD-PGS remained significantly increased across all the neurodevelopmental and psychiatric conditions also when individuals with comorbid MDD were removed, solidifying the role of MDD associated variants in SA risk across all five diagnoses (Supplementary Figure 3, Supplementary Table 10). The PGSs for BPD and SCZ were not associated with SA except from among individuals diagnosed with ADHD (Figure 1.B; Supplementary Table 9). Overall, these results indicate that genetics of ADHD and MDD associates with SA not only in individuals with ADHD and MDD but across all the analyzed neurodevelopmental and psychiatric conditions.

Regarding adverse life experiences and life outcomes, the CM-PGS, representing genetics associated with exposure to CM, was significantly higher in individuals with SA compared to individuals without SA within ASD, ADHD and MDD. Conversely, the EA-PGS was lower in individuals with SA than in those without SA across all neurodevelopmental and psychiatric conditions (however only nominally significant in ASD) (Figure 1.C; Supplementary Table 9). These findings suggest that genetics associated with decreased EA/cognitive ability and increased risk of maltreatment in

childhood are associated with SA across all analyzed neurodevelopmental and psychiatric conditions.

Seven PGSs representing personality and behavioral phenotypes (fed up, guilty feelings, loneliness, miserableness, risk taking behavior, sociability, and subjective well-being) were significantly increased in individuals with ADHD and SA compared to ADHD without SA (Supplementary Figure 4, Supplementary Table 9). Four of them (feeling fed up, loneliness, miserableness, and risk-taking) were significantly increased in individuals with MDD and SA compared to MDD without SA (Supplementary Figure 4, Supplementary Table 9). None of the personality-related PGSs were associated with SA in SCZ, BPD and ASD suggesting that genetics related to general emotions and personality contributes more to SA risk in ADHD and MDD than in SCZ, BPD and ASD.

We further explored the absolute risk of SA within individuals with the five neurodevelopmental and psychiatric diagnoses stratified into SA, MDD- and ADHD-PGS tertiles. In general, SA risk increased across all neurodevelopmental and psychiatric diagnoses with increasing PGS-loads and the PGSs could be used to stratify individuals into different risk groups (Supplementary Figure 6, Supplementary Table 11). The SA-PGS demonstrated the highest HRR for SA among individuals with neurodevelopmental and psychiatric conditions. When comparing individuals in the 3rd SA-PGS tertile to those in tertile one, risk was similar across the neurodevelopmental and psychiatric conditions and ranged from HRR=1.42 (s.e.=0.032, P-value= 1.67×10^{-28}) in MDD to 1.65 (s.e.=0.05, P-value= 1.19×10^{-24}) in ADHD (Supplementary Table 11). The highest absolute risk for SA at age 30 was 40% for individuals diagnosed with SCZ in the highest SA-PGS tertile while it was 29% in the lowest SA-PGS tertile. The

lowest risks were observed for ASD with an absolute risk of 12% in the highest PGS-tertile (Figure 2, Supplementary Table 11). The SA-, MDD-, and ADHD-PGSs were also able to stratify population-based controls into SA risk groups (Figure 2, Supplementary Figure 6), with the highest absolute risk for SA at age 30 reaching 5.3-5.4% in the highest PGS tertile (Supplementary Table 11). In the two phenotypes (ADHD and MDD) with sufficient sample sizes to stratify individuals into smaller groups, the absolute risk of SA at age 30 increased only slightly when restricting the analysis to those with the 10% highest SA-PGS, reaching 0.31 in MDD and 0.28 in ADHD (Supplementary Figure 7, Supplementary Table 11).

In the sex-specific analyses no significant differences in the loads of the 21 PGSs were observed between males and females with SA within each of the conditions, except for a significant decreased EA-PGS within ADHD for males with SA compared to females with SA ($P\text{-value}=1.76\times 10^{-5}$; Supplementary Figure 8, Supplementary Table 12). However, when investigating the relative and absolute risk of SA within ADHD and MDD separately for males and females, striking differences were observed.

The absolute SA risk for females with ADHD in the highest SA-PGS tertile reached 36% at age 30, which was considerably higher than the absolute risk observed for males in the highest SA-PGS tertile which reached 22% (Figure 3; Supplementary Table 13). In fact, the highest absolute risk observed for the males corresponded to what was observed for females with ADHD in the lowest SA-PGS tertile, where the absolute risk reached 25% at the age of 30. The same pattern was observed for MDD, where absolute risk of SA at age 30 for females in the highest tertial reached 32% while it was 24% for males (Figure 3, Supplementary Table 13).

Finally, we explored the impact of SUD associated genetics on SA risk. The PGSs for substance use (smoking initiation) and SUD (alcohol-, cannabis-, opioid use disorder) were all significantly increased in individuals with SA compared to those without SA across all the neurodevelopmental and psychiatric diagnoses (Figure 4.A, Supplementary Table 9), except from the OUD-PGS among individuals with ASD. These results suggest a general association of SUD related genetics with SA risk.

Moreover, when exploring the impact of comorbid SUD in individuals with ADHD (N=3,488) or MDD (N= 4,408) on SA risk we identified a large impact on the absolute risk, which reached 49% for individuals with MDD+SUD the highest SA-PGS tertile at age 30, and 48% for individuals with ADHD+SUD (Figure 4, B-C, Supplementary Table 14). This was strikingly higher in comparison to the general risk of 3.7% at age 30, observed for the population-based controls in the middle SA-PGS tertile.

Discussion

Suicidal behaviors, including SA, represent a serious public health problem, rooted in a complex interplay of genetic and environmental factors. SA is particularly prevalent among individuals with neurodevelopmental and psychiatric conditions,(5,6) underscoring the urgent need for a better understanding of the biological mechanisms involved in SA in people with these diagnoses. In this study we performed comprehensive analyses of the polygenic architecture underlying SA across five neurodevelopmental and psychiatric conditions.

First, we identified a novel genome-wide significant locus associated with SA independent of neurodevelopmental and psychiatric diagnoses.(4,26) Linking credible variants to functional genomics data suggested risk variants to impact regulation of *LINC02283* and *PDGFRA*. This finding is consistent with recent evidence implicating

dysregulation of the PDGF-PDGFR signalling, which regulates a range of functions in the central nervous system, at both receptor and ligand levels in suicide vulnerability.(37)

We further provide evidence that SA is a highly polygenic condition, with around 6.3K common influencing variants, comparable in magnitude to estimates reported for ADHD (7.3K variants), SCZ (8.3K variants), and BPD (6.4K variants)^{16,14}, and that it has a substantial genetic overlap with neurodevelopmental and psychiatric conditions in line with previous findings.(4,10) We found that the h^2_{SNP} of SA within the neurodevelopmental and psychiatric conditions was significantly different from zero within ADHD, ASD, and MDD, supporting that genetic variance explain a part of the liability to SA within these diagnoses. The h^2_{SNP} of SA within SCZ was zero, despite 30.9% of individuals with SCZ having SA in our cohort. Although this contradicts with PGS results showing significant differences between individuals with and without SA, it may reflect heterogeneity in SA, with individuals reaching SA through different causal pathways.

We demonstrated that the PGSs for SA and SIBT are associated with SA in individuals with neurodevelopmental and psychiatric conditions, suggesting that SA within those conditions is influenced by genetics beyond what is associated with the diagnosis. When evaluating the PGSs for neurodevelopmental and psychiatric conditions, the ADHD- and MDD-PGSs showed significant and consistent associations with SA risk across all five diagnostic groups, which was not observed for the SCZ-, BPD-, ASD-PGSs. In other words, the polygenic risk for SA within e.g. SCZ seems to be driven, not by an additional load of SCZ associated variants but by increased load of variants more strongly associated with ADHD and MDD. The association between MDD-PGS and SA was not driven by comorbid MDD, as it remained significant after excluding

individuals with MDD. It could be speculated that increased ADHD- and MDD-related genetic load may elevate SA risk by affecting behaviors or mood states related to impulsivity/self-control(38–40) and depressive symptoms(41) across conditions.

Within each of the five neurodevelopmental and psychiatric conditions, we were able to stratify individuals into SA risk groups based on their SA, ADHD, and MDD PGSs. Individuals in the highest PGS tertiles had markedly increased relative and absolute SA risk at age 30 compared with those in the lowest tertiles and population-based controls. These findings may inform clinical practice by helping identify patients at elevated SA risk through inclusion of PGSs in risk assessment.

Besides neurodevelopmental and psychiatric diagnoses, exposure to maltreatment in childhood, level of educational attainment and substance use, have also been reported to modulate risk of suicidal behaviors.(42–45) Our study suggests that genetics associated with these factors also contributes significantly to SA risk within conditions, observed as an association of the CM-, EA-, and SUD-PGSs with SA across the five diagnostic groups. Higher EA-PGS was associated with lower SA risk across all five conditions, consistent with previous reports showing educational attainment, but not cognitive performance, protective against SA.(44,46) Among individuals with ADHD and SA, males had lower EA-PGS than females, aligning with reports of sex-specific protective effects of high EA on SA risk in males.(43)

No sex-specific genetic differences in SA were observed across the remaining 20 PGSs. However, females with MDD or ADHD showed ~8-14% higher absolute SA risk than males by age 30. The absolute SA risk for females in the lowest SA-PGS tertile, was at the same level as observed for males in the highest SA-PGS tertile. The fact that we observed substantially different absolute SA risks for males and females with MDD or ADHD, coupled with the absence of strong genetic differences between males and

females with SA, suggests strong contribution of other genetic factors or female specific risk factors, such as being victim of dating violence and previous abortion, to SA in females.(47)

We also report a consistent association of of SUD-related PGSs with SA risk across all diagnoses in one homogenous large cohort suggesting a general role of SUD genetics in SA independent of diagnosis. The absolute risk of SA was high among individuals with comorbid SUD in line with other studies finding increased SA rates within SUD.(48) The risk decreased 8-10% from the highest SA-PGS tertile to the lowest, suggesting that genetics do modulate the risk slightly.

These findings altogether shed light on the genetic architecture of SA across neurodevelopmental and psychiatric conditions and demonstrate how the polygenic profile of an individual can modulate SA risk even in the presence of known strong risk factors, such as being a female or comorbid SUD. As larger and better-powered GWASs of suicide-related phenotypes are on the way, the variance in SA explained by common variants, and consequently the discriminative power of PGSs, is expected to keep improving.(49) This brings further promise for refining our understanding of the genetic architecture underlying SA risk in the context of neurodevelopmental and psychiatric disorders.

While this study provides valuable insights into the genetic architecture of SA, it is important to acknowledge both strengths and possible limitations. The iPSYCH cohort, which is a population-based case-cohort, provided a unique opportunity to investigate the genetic architecture of SA in a large and representative sample.(13,50) SA data were obtained from national registers, providing objective ascertainment and reducing reporting bias, and longitudinal data enabled estimation of absolute SA risk across conditions. However, some SA events may not be captured in the registers, potentially

underestimating its true prevalence. Additionally, the iPSYCH cohort is drawn from a relatively genetically homogeneous Danish population, which may limit generalizability of our findings to populations with different ancestral backgrounds.

In summary, we conducted a comprehensive investigation of the genetic architecture of SA across five major neurodevelopmental and psychiatric conditions and identified similarities in the genetic architecture of SA across the conditions. We also demonstrated how PGSs can be used to stratify individuals with these conditions, or even population-based controls, into different SA risk groups. We also elucidated the impact of sex and comorbid SUD on SA risk and how the risk is modulated by genetics. Our findings highlight how genetics can contribute to identifying high-risk individuals and informing personalized approaches for SA prevention and intervention, thereby advancing efforts to lower SA rates globally.

Patients' consent and permission to publish

The iPSYCH study was approved by the Scientific Ethics Committee in the Central Denmark Region (Case No 1-10-72-287-12) and the Danish Data Protection Agency. In accordance with Danish legislation, the Ethics Committee waived the need for specific informed consent in biomedical research based on existing biobanks, and was approved by the Ethics Committee in 2012, with subsequent amendments in 2013, 2015, and 2018. New Danish legislation (effective from January 2024) introduced the possibility for participants to opt out of studies that are exempted from active informed consent. After consulting with the Ethics Committees and patient organizations, iPSYCH contacted all ~140,000 participants in the iPSYCH cohort in June 2025 and offered the possibility to opt out of new genetic studies initiated henceforth. Overall, 1.8% of the iPSYCH participants chose to opt out, and their data will be deleted from

the active research database. Data included in finalized and ongoing studies, like the present, will not be removed.

Role of the funding source

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Data sharing

iPSYCH data can be accessed after approval by the iPSYCH Data Access Committee and can only be accessed on the secured Danish server (GenomeDK [<https://genome.au.dk>]) as the data are protected by Danish legislation. For data access and correspondence please contact: Ditte Demontis (ditte@biomed.au.dk) or Anders D. Børghlum (anders@biomed.au.dk).

Author contributions

Ditte Demontis and Trine Tollerup Nielsen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ditte, Trine, Anna S

Acquisition, analysis, or interpretation of data: Ditte, Trine, Anna S, Juan, Jakob, Anders, Anna D

Drafting of the manuscript: Anna S, Ditte, Trine

Critical review of the manuscript for important intellectual content: all authors

Statistical analysis: Trine, Juan, Anna S, Jakob, Ditte

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If you are contemplating suicide, please reach out for help; resources are available at <https://www.iasp.info/suicidalthoughts/>.

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Supplement Description (2 files):

Supplement Methods, Figures S1-S8

Tables S1-S14

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Figure 1. PGS load across individuals with and without SA with neurodevelopmental and psychiatric conditions. PGS loads across the five neurodevelopmental and psychiatric conditions with a history of SA and no SA (on the x-axis). On the y-axis the beta-coefficient from the multivariate regression (and the corresponding 95% confidence intervals shown as vertical lines) indicating differences from the population-based controls. Significant difference between the betas observed for individuals with SA compared to the betas observed for individuals with no SA within each neurodevelopmental and psychiatric condition is indicated with a horizontal line with the P-value above (result from the Wald test of equal group effect). Results shown the following PGSs (listed above each plot) (A) suicide attempt (SA), Suicidal thoughts and behavior (SITB) (B) attention deficit hyperactivity disorder (ADHD), autism spectrum diagnosis (ASD), bipolar disorder (BPD), major depressive disorder (MDD), schizophrenia (SCZ) (C) childhood maltreatment (CM), educational attainment (EA). See also Supplementary Table 9.

Figure 2. Absolute SA risk in individuals stratified by their SA-PGS within neurodevelopmental and psychiatric conditions. Absolute risk (with 95% CI) for SA (y-axis) over time (x-axis) in individuals stratified into tertiles by their SA-PGS and diagnosed with MDD (A), ADHD (B), ASD (C), BPD (D), SCZ (E). Curve colors indicate PGS strata: 1st tertile in yellow, 2nd in orange, and 3rd in dark red. Absolute risk (95% CI) of SA in the population-based controls stratified into tertials based on their SA-PGS is shown in light blue. The number at the right indicate the absolute SA risk at 30 years of age. See also Supplementary Table 11.

Figure 3. Absolute SA risk among males and females stratified by their PGS within neurodevelopmental and psychiatric conditions. Absolute risk (with 95% CI) for SA (y-axis) over time (x-axis) in males (A-C) or females (B-D) stratified into tertiles by their SA-PGS and diagnosed with MDD (a-b) or ADHD (c-d). Curve colors indicate PGS strata: 1st tertile in yellow, 2nd in orange, and 3rd in dark red. Absolute risk (95% CI) of SA in the population-based controls stratified into tertials based on their SA-PGS is shown in light blue. The number at the right indicate the absolute SA risk at 30 years of age. See also Supplementary Table 13.

Figure 4. Impact of SUD-PGSs and comorbid SUD on SA risk. (A) PGS load across the five neurodevelopmental and psychiatric conditions with a history of SA and no SA (on the x-axis). On the y-axis the beta-coefficient from the multivariate regression (and the corresponding 95% confidence intervals, vertical lines) against population-based controls. Significant difference between the betas for individuals with SA compared to betas for no SA within each neurodevelopmental and psychiatric condition is indicated with a horizontal line with the P-value above. PGSs (listed above each plot): alcohol use disorder (AUD), cannabis use disorder (CUD), opioid use disorder (OUD), smoking initiation (SmoIni). (B) Absolute risk (with 95% CI) for SA (y-axis) over time (x-axis) in MDD comorbid with SUD or ADHD comorbid with SUD (C) stratified into tertiles by their SA-PGS. Curve colors indicate PGS strata: 1st tertile in yellow, 2nd in orange, and 3rd in dark red. Absolute risk (95% CI) of SA in the population-based controls stratified into tertials based on their SA-PGS is shown in light blue. The number at the right indicate the absolute SA risk at 30 years of age. See also Supplementary Table 9 and 14).

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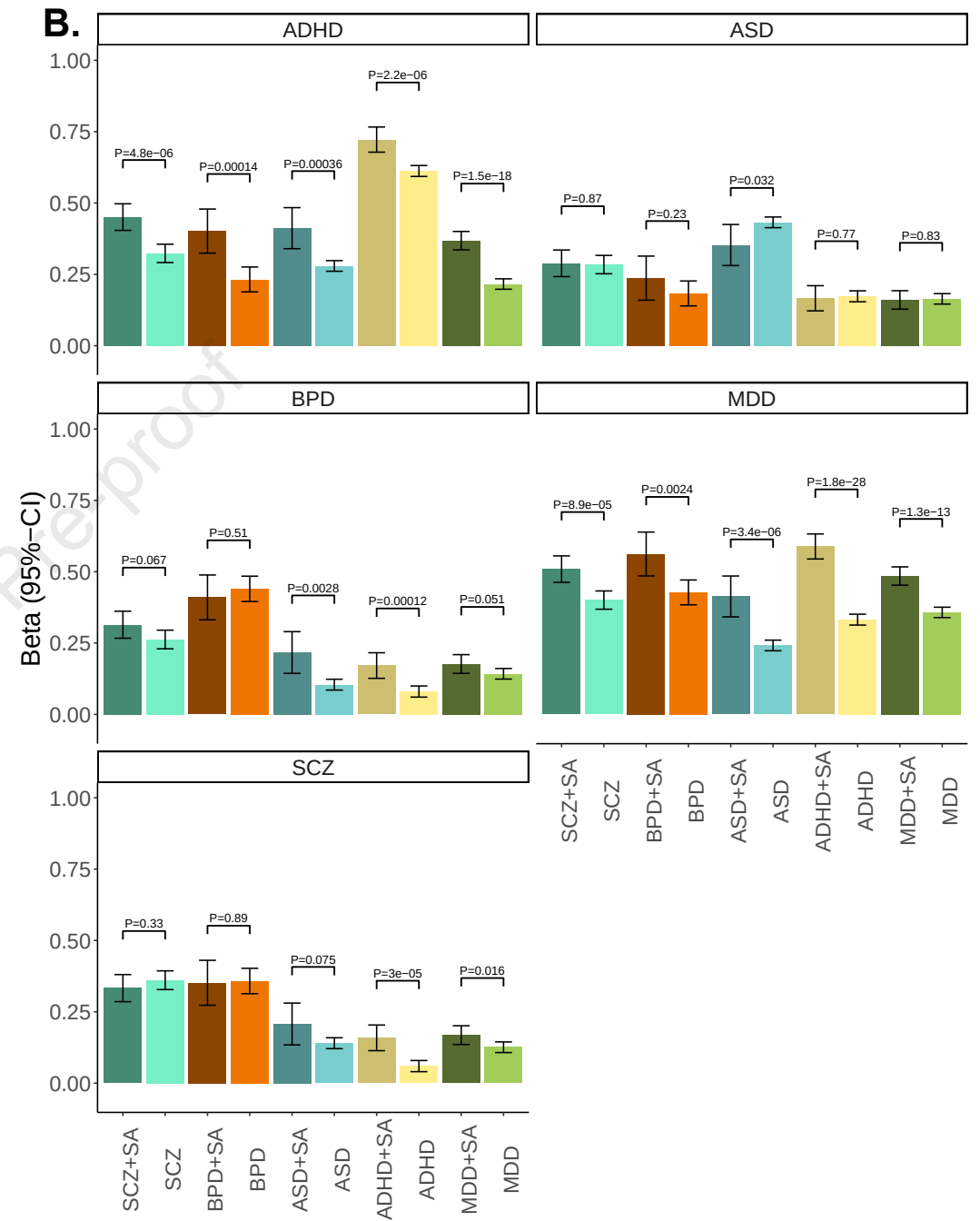
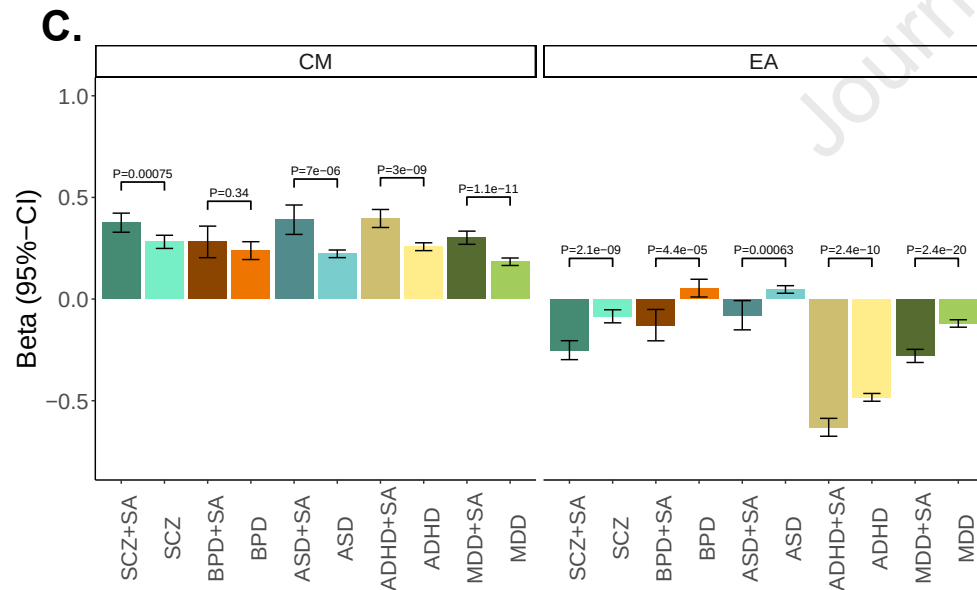
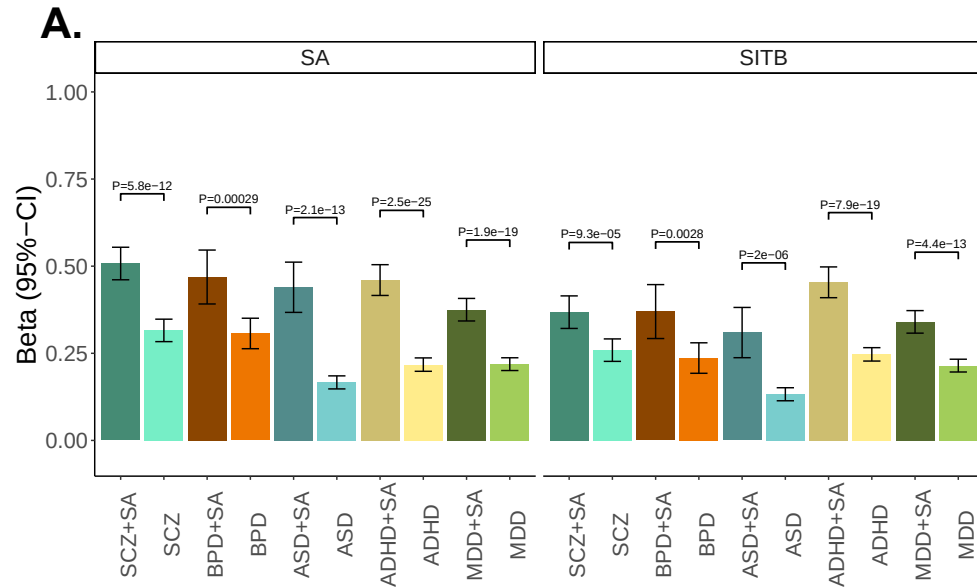
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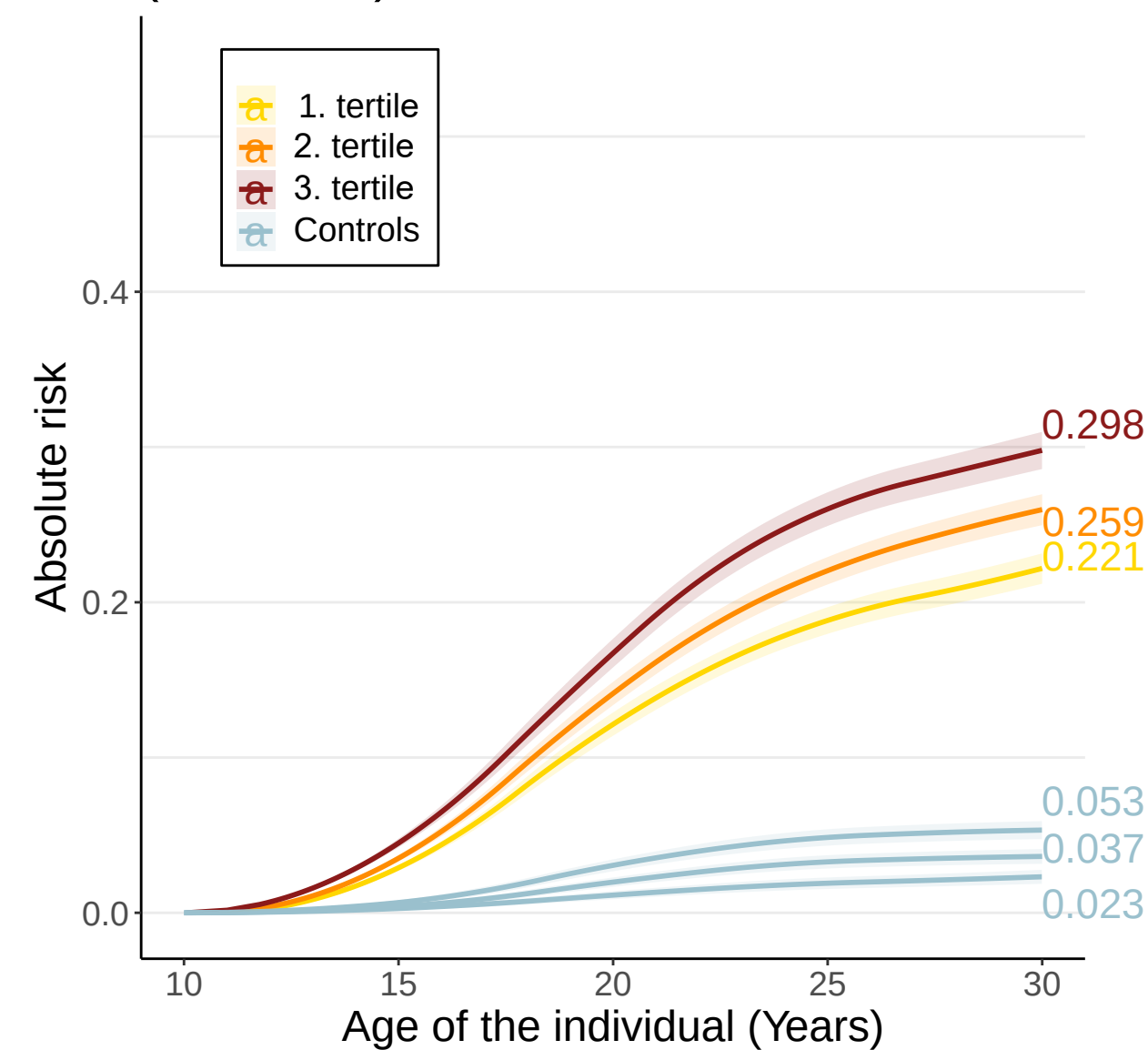
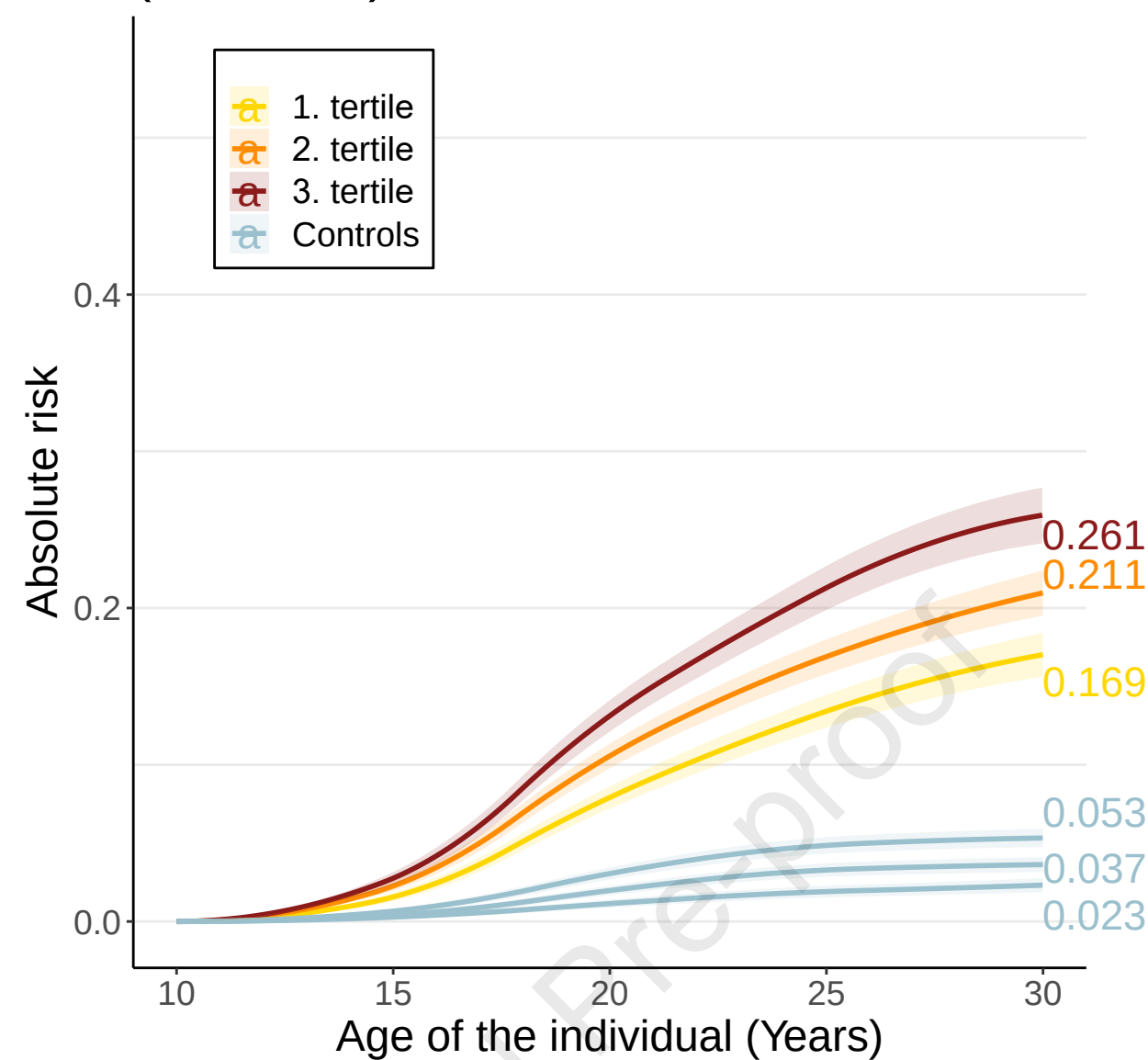
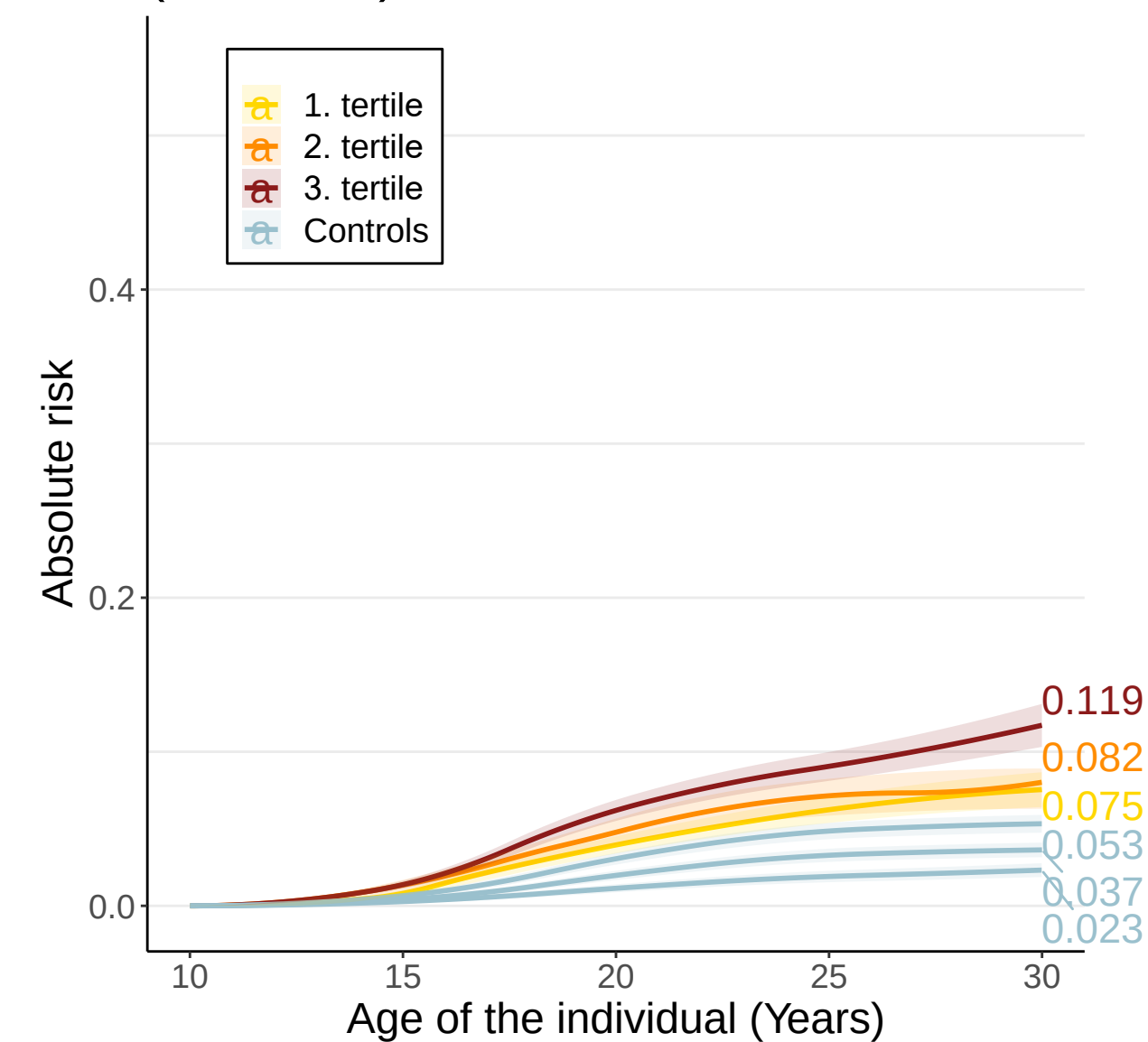
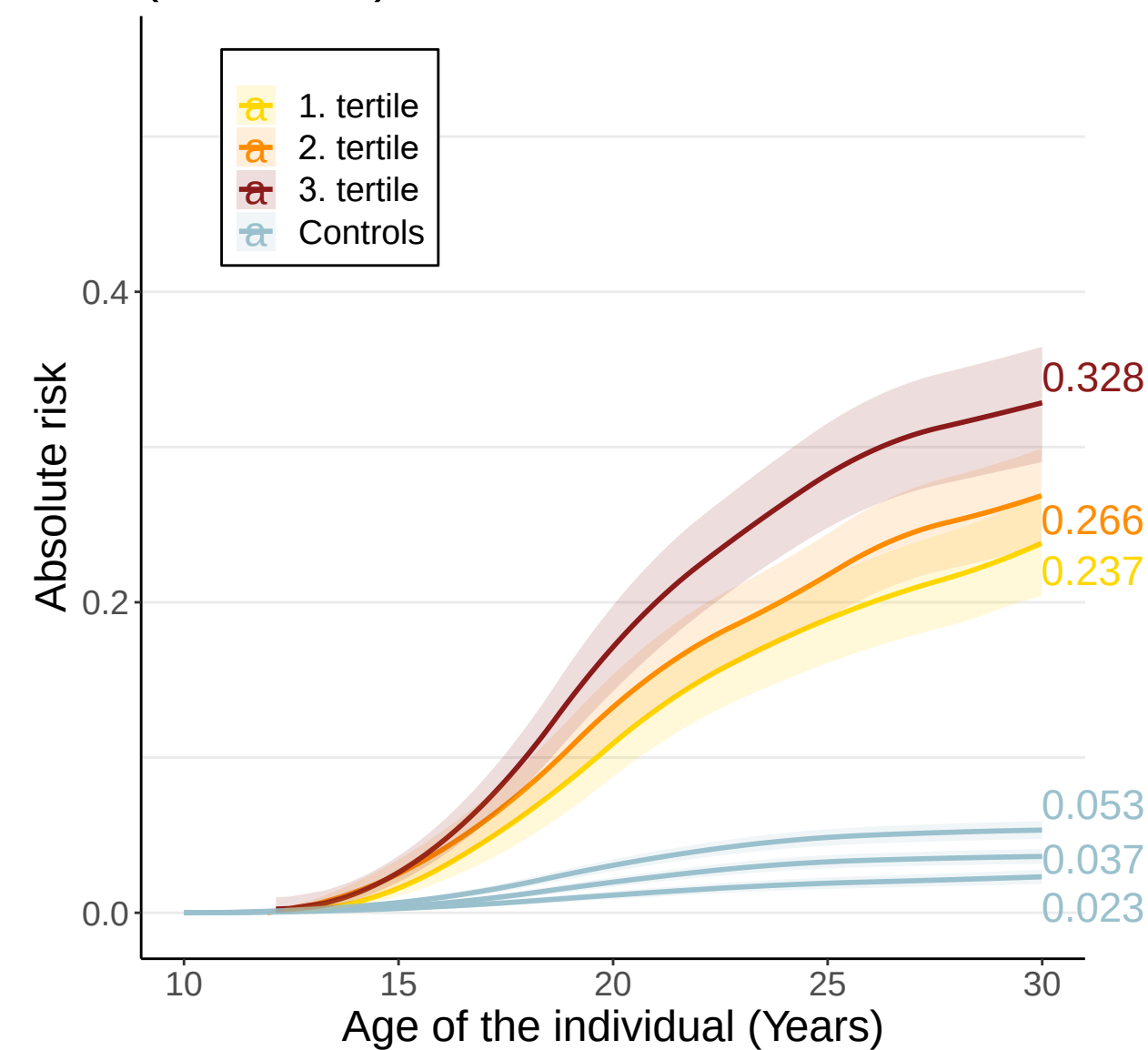
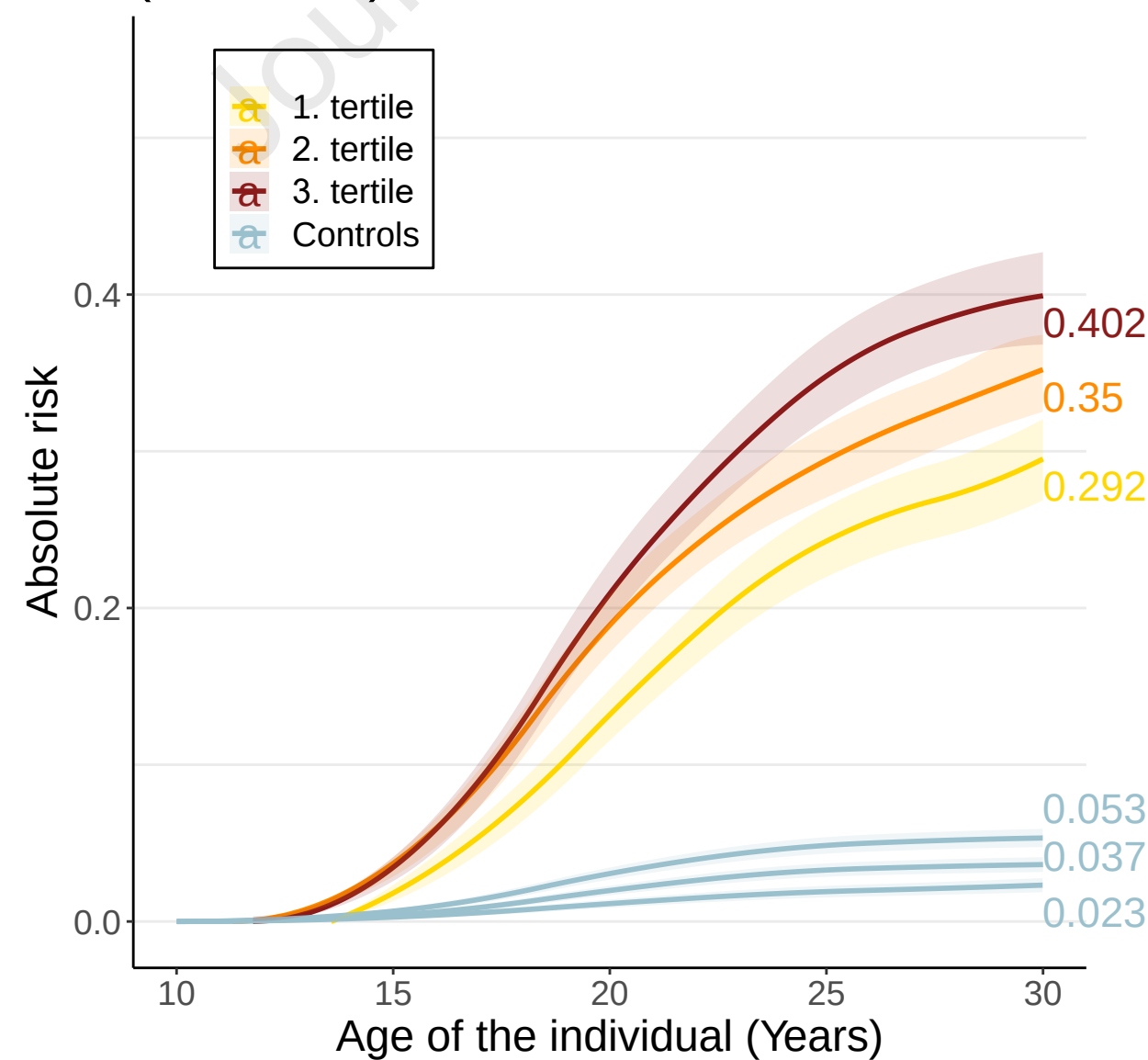
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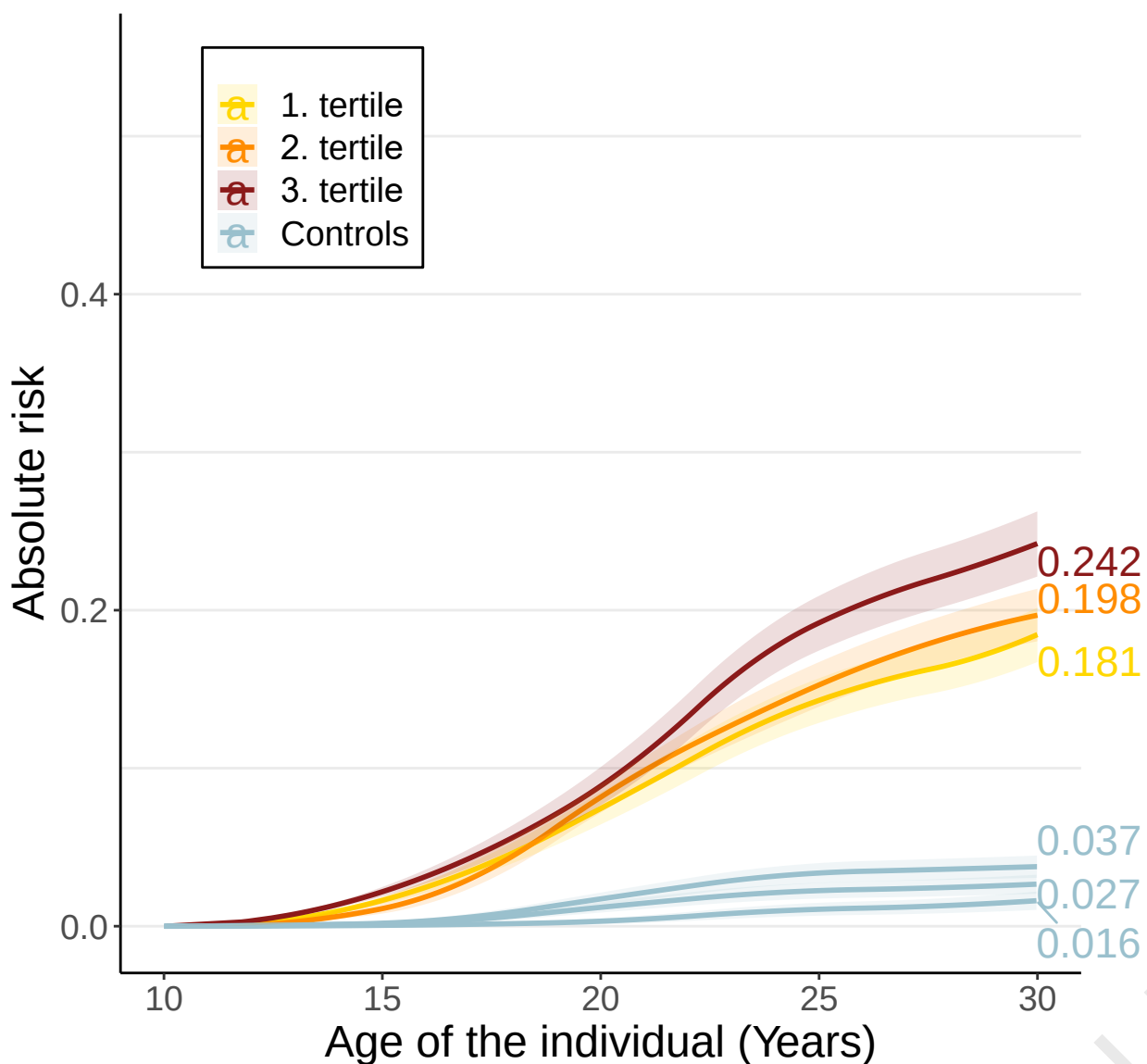
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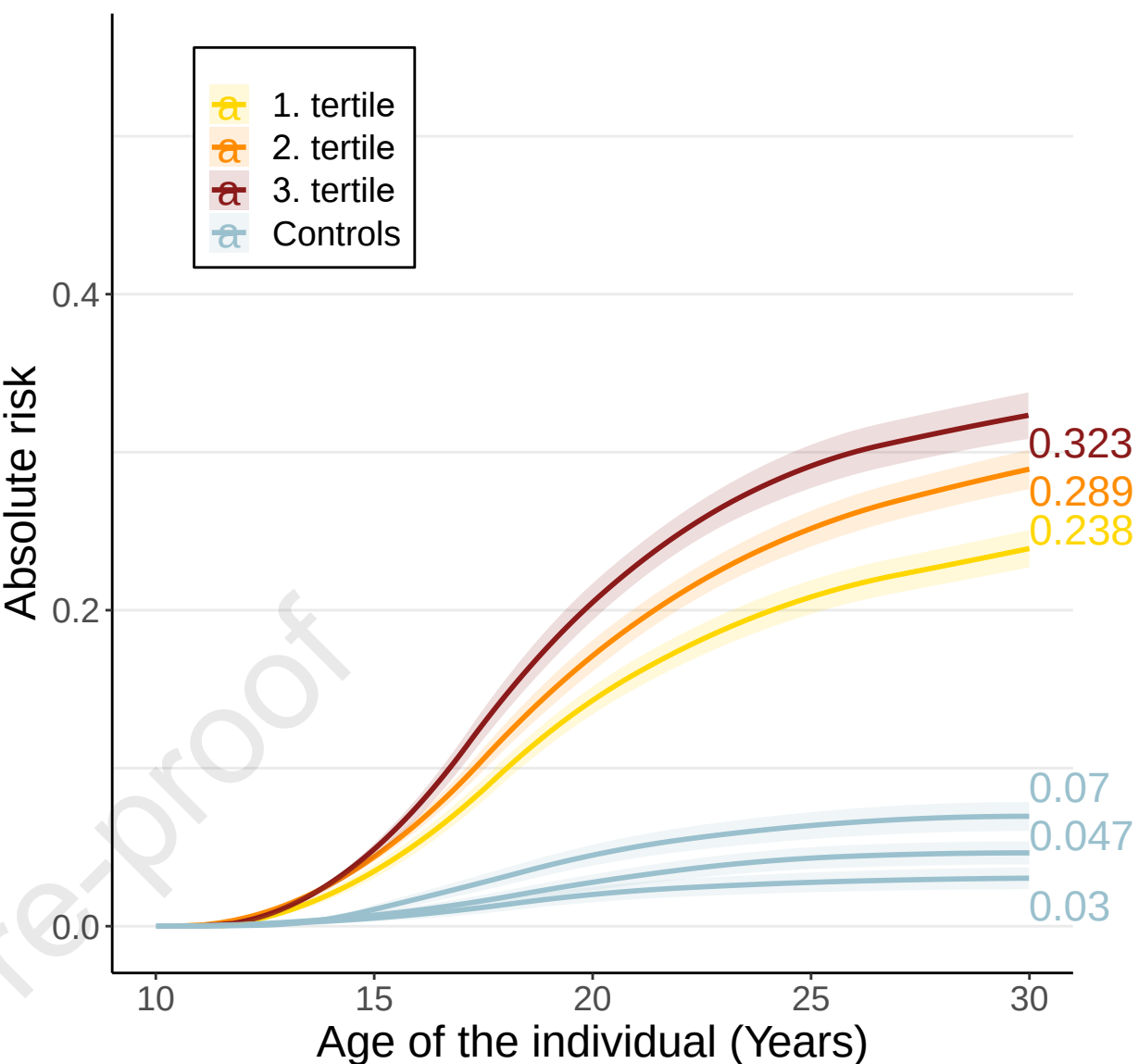


A.**MDD
(SA-PGS)****B.****ADHD
(SA-PGS)****C.****ASD
(SA-PGS)****D.****BPD
(SA-PGS)****E.****SCZ
(SA-PGS)**

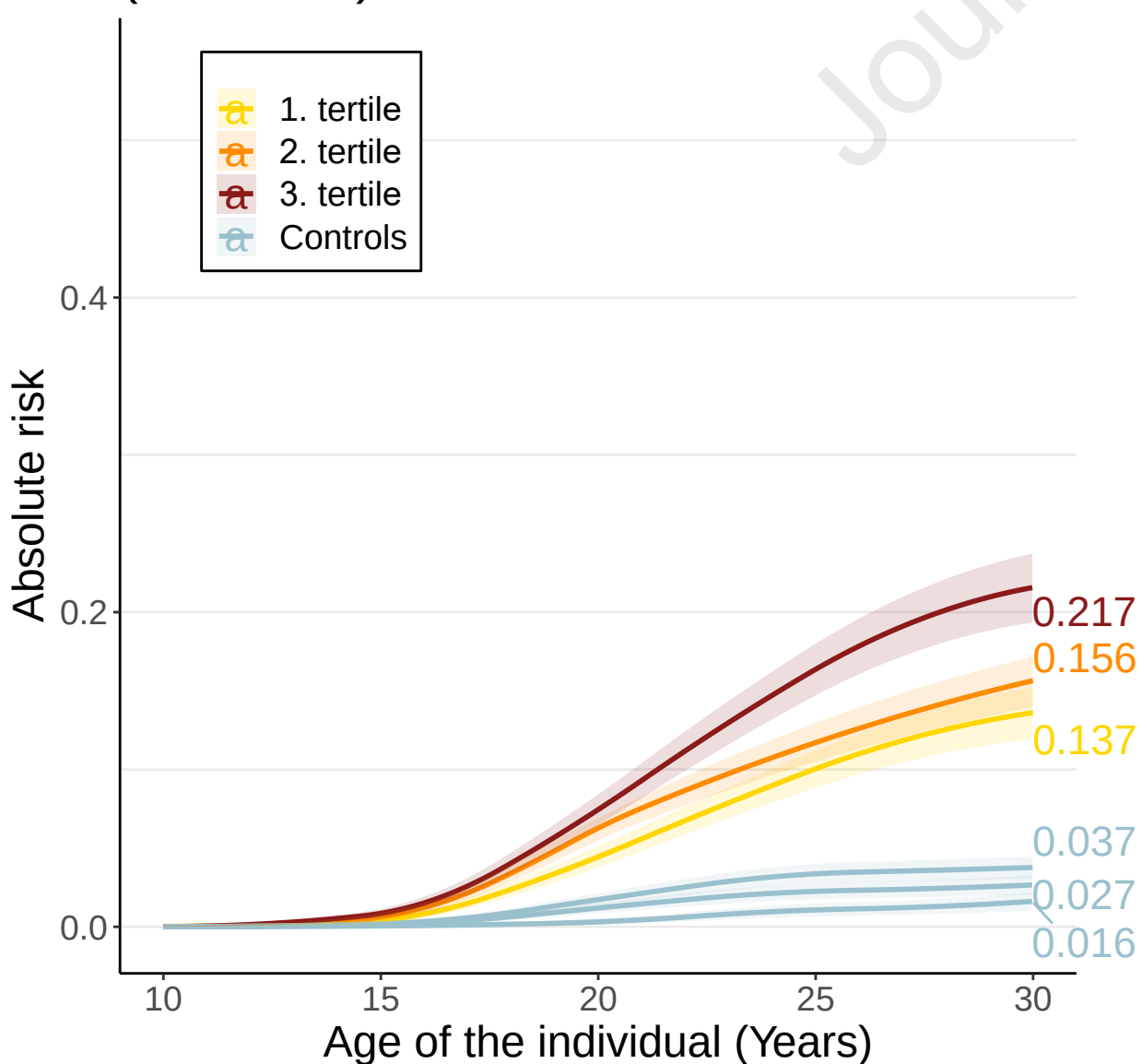
A. MDD (males)
(SA-PGS)



B. MDD (females)
(SA-PGS)



C. ADHD (males)
(SA-PGS)



D. ADHD (females)
(SA-PGS)

