Data supplement for Brikell et al., Interplay of ADHD Polygenic Liability With Birth-Related, Somatic, and Psychosocial Factors in ADHD: A Nationwide Study. Am J Psychiatry (doi: 10.1176/appi.ajp.21111105)

Contents

Methods: Targeted literature review of ADHD associated birth-related, somatic and psychosocial risk-factors

To identify birth-related, somatic and psychosocial factors associated with ADHD and to put our research in context, we conducted a non-systematic, targeted review of the current phenotypic, familial and common genetic variant literature of birth-related, somatic and psychosocial factors linked to ADHD. We searched PubMed until May 2021 to identify the most recent meta-analyses, umbrella reviews, systematic reviews and consensus statements of ADHD risk-factors and correlates and snowballed from these. Based on this review, we kept risk-factor showing phenotypic and/or familial associations in ≥ 2 independent samples. We then selected 24 risk-factors that were available in Danish national registers with sufficient coverage. For example, we did not include risk-factors with limited follow-up time in the registers (e.g., smoking during pregnancy which is only available from 1997 onwards) or where the N exposed was low to report according to Danmark Statistics regulations (e.g. certain rare somatic diseases in the mother or the index person). For phenotypic and familial associations, we preferentially present pooled (and when available, adjusted) risk-estimates from the largest available meta-analysis, followed by evidence from published systematic reviews. If such estimates were not available, we present estimates from large-scale population studies, prioritized based on sample size and the inclusion of clinically diagnosed cases. For gene-environment correlation and interactions, we present results of the largest available genetic correlation analyses based on linkage disequilibrium score regression (LDSC) (PMID: 25642630) and summarize the available ADHD-PRS literature, guided by a recently published systematic review (PMID: 33548493). We did not identify any genome-wide by environment interaction studies on ADHD to include in the review. To limit the scope of our targeted literature review, we did not include twin studies or molecular genetic studies using other methods than LDSC or PRS. Results of the literature review are presented in Table 1 in the main text.

TABLE S1. International classification of disease (ICD) and Anatomical Therapeutic Chemical (ATC) codes and definitions of included ADHD risk-factors

Domain	Risk-factor	ICD-codes /ATC-codes	Definition	Reference
	Birth weight (BW)	n/a	Low BW <2500 g Average BW 2500–3999 g (ref) High BW ≥ 4000 g	PMID: 25726514
	Small for gestational age (SGA)	n/a	SGA defined as being in the 10th percentile of the birthweight distribution in the iPSYCH2012 subcohort, within each birth year and sex	PMID: 23026073
	Apgar score at 5 minutes	n/a	10 (ref), < 10	PMID: 25726514
Somatic	Maternal hypertension during pregnancy	**ICD-8:** 637.00, 637.03, 637.09,637.99, 637.04, 637.19, 762.19, 762.29, 762.39 **ICD-10:** O13, O14.0, O14.1, O14.2, O14.9, O16, O15.0–15.9	≥1 discharge diagnoses 20 weeks after gestation until birth of index child	PMID: 30785920
	Maternal infection during pregnancy	**ICD-8:** 038, 070, 000-009, 540, 680-686, 050-057, 110, 111, 035, 460-486, 580, 590, 59500, 59501, 612, 620, 622, 381-382, 04000-04399, 013, 320, 322, 392, 474, 04509-04699, 32300, 07199, 07202, 07501, 07929, 09049, 05201, 05302, 05403, 05501, 05601, 03609, 02701, 06209-06599, 09490-09499 **ICD-10:** A40, A41, B15-B19, A00-A09, K35, L00-L08, B00-B09, A46, J00-J18, N00, N10, N300, N390, N518B, N70, N71, N72, N76, N770D, N771B, N771L, H65-67, I02, G00-G07, A17, A80-89, B003, B004, B010, B011, B020, B021, B050, B051, B060, B261, B262, B375, B451, B582, B602, A022C, A548A, A548D, A521A, A521B, A229C, A321, A504, A390, E236A	≥1 discharge diagnoses within 40 weeks prior to birth of index child	PMID: 30446204
	Maternal and paternal autoimmune disease	**ICD-8:** 242, 245.03, 249, 255.10, 255.11, 255.12, 255.18, 255.19,269, 281.00, 281.01, 281.08, 281.09, 283.90, 283.91, 446.49, 340, 354, 364, 446.29, 563.01, 563.19, 571.9, 571.93, 694, 696.09, 696.10, 696.19, 704, 709.01, 712.19, 712.39, 712.59 712.09, 716,	≥1 discharge diagnoses by child's 5th birthday	PMID: 28219489

		446.30, 446.31, 446.39, 733.09, 734.00, 734.01, 734.02, 734.08, 734.09, 734.19, 734.9, 712.49 **ICD-10:** E05.0, E06.3, E10, E27.1, K90.0, D51.0, D59.1, D69.3, G35, G61.0, H20, M31.3, K50, K51, K74.3, K73, L12, L10, L40 (except L40.4), L63, L80.9, M05, M06, M08, M33, M31.5, M31.6, M35.3, G70.0, M34, M32.1, M32.9, M35.0, M45.9		
	Infections	See maternal infection during pregnancy	Time-varying, first and 5th discharge diagnoses	PMID: 30446204
	Asthma	**ICD-8:** 493 **ICD-10:** J45.0, J45.1, J45.8, J45.9, J46.0, J46.9 **ATC:** R03BA01-R03BA08, R03DC01-R03DC04, R03DC03, R03DB04, R03DA54, R03BB01, R03DX05	Time-varying, first discharge diagnoses and/or ≥1 prescriptions filled within a year and/or ≥1 prescription of D11Ah, S01GX or V01A, and/or ≥2 prescriptions of D07, R01AD01-R01AD60, or R06A filled within a year	PMID: 25828267 PMID: 28632331
	Atopic disease (atopic dermatitis, allergic rhinitis)	**ICD-8:** 691, 507, 502.00 **ICD-10:** L20, L308C, J30, J31.0 **ATC:** ≥1 prescription of D11AH, S01GX, V01A ≥2 prescriptions of D07, R01AD01 – R01AD60, R06A	Time-varying, first discharge diagnosis	PMID: 25828267 PMID: 28632331
	Type 1 diabetes	**ICD-8:** 250.00–250.09 diagnosed before age 18 **ICD-10:** E10 diagnosed before age 18	Time-varying, first discharge diagnosis	PMID: 33824142
	Epilepsy	**ICD-8:** 345 (excluding 345.29) **ICD-10:** G40	Time-varying, first discharge diagnosis	PMID: 27412639
	Traumatic brain injury (TBI)	**ICD-8:** 850, **ICD-10,** S06.0 (**Mild TBI**) **ICD-8:** 800-804, 851-854 **(Moderate/severe TBI**) **ICD-10:** S02.0-1, S02.3, S02.7-9, S06.1-9, S07.0-S07.1, S07.8-S07.9, S09.0, S09.7-9, S18, T02.0, T04.0, T06.0, T90.2, T90.5, T90.8-9 **(Moderate/severe TBI**)	Time-varying, first discharge diagnosis	PMID: 28301451 PMID: 27552147
Psychosocial	Maternal and paternal income	n/a	Defined by quintiles in the subcohort at index child's year of birth	PMID: 26249301

	Maternal and paternal education	n/a	Highest completed level of education at index child's year of birth (elementary school, high school, or academic degree)	PMID: 26249301
	Maternal and paternal employment	n/a	Defined as outside of the workforce, including retirement and currently in education or employed in index child's birth year	PMID: 26249301
	Living in a single parent household	n/a	Evaluated in the first five years of life (no years=reference category)	PMID: 27355346
	Maternal and paternal age at birth of index child	n/a	Maternal age: <20, 20-24, 25-29 (ref), 30-34, ≥35 years-of-age Paternal age: <20, 20-24, 25-29, 30-34 (ref), 35-39, ≥40 years-of-age	PMID: 24452535
	Parental psychiatric history	**ICD-8:** 290-315 **ICD-10:** F00-F99	≥1 discharge diagnoses for any psychiatric disorder in mother, father, or both by index child's 5th birthday	PMID: 27355346

Note: Diagnoses in the Danish National Patient Register (DNPR) and the Danish Psychiatric Central Research Register (DPCRR) are recorded according to the International classification of disease (ICD) version 8 between 1977 and 1993 and ICD-10 from 1994 onwards. ICD-9 was never implemented in Denmark. The Danish National Prescription Registry (DPR) includes information on all prescriptions redeemed at Danish pharmacies since 1995 coded according to the Anatomical Therapeutic Chemical (ATC) classification system.

Abbreviations: Na, not applicable. Ref, reference category in statistical analyses.

TABLE S2. Associations of ADHD-PRS with evaluated risk-factors in the iPSYCH2012 subcohort (N=21,578), expressed as odds ratios (OR) with 95% confidence intervals (CIs)

				OR per PRS			
Domain	**Risk factor**	**Level**	**N**	**SD**	**LCI**	**LCI**	p_{adj}
Birth-related	Birth weight	<2500 g	698	1.02	0.95	1.10	
		2500-3999 g	16865	Ref			
		≥ 4000 g	3932	0.99	0.95	1.02	1.00
	Small for gestational age	No	19564	Ref			
		Yes	1931	**1.08**	**1.03**	**1.13**	**<.05**
	Apgar score at 5 minutes	10	19892	Ref			
		<10	1487	1.01	0.95	1.06	1.00
Somatic	Maternal hypertensive disorders during pregnancy	No	21264	Ref			
		Yes	314	1.01	0.90	1.12	1.00
	Maternal infection during pregnancy	No	20952	Ref			
		Yes	626	1.06	0.98	1.15	1.00
	Maternal autoimmune disorder by child's 5th birthday	No	21012	Ref			
		Yes	566	**1.14**	**1.04**	**1.24**	**<.05**
	Paternal autoimmune disorder by child's 5th birthday	No	21193	Ref			
		Yes	385	0.98	0.88	1.08	1.00
	1 infection	No	13245	Ref			
		Yes	8333	**1.07**	**1.05**	**1.10**	**<.001**
	≥ 5 infections	No	20989	Ref			
		Yes	589	**1.14**	**1.05**	**1.24**	**<.05**
	Asthma	No	18688	Ref			
		Yes	2890	1.04	1.00	1.08	0.56
	Atopic diseases	No	19814	Ref			
		Yes	1764	0.97	0.93	1.02	0.88
	Type 1 diabetes	No	21486	Ref			
		Yes	92	0.89	0.72	1.09	0.90
	Epilepsy	No	21137	Ref			
		Yes	441	0.99	0.90	1.09	1.00

	Traumatic brain injury	No	19780	Ref			
		Mild	1558	**1.11**	**1.05**	**1.17**	
		Severe	339	1.09	0.98	1.21	**<.01**
Psychosocial	Maternal income at birth	1st quintile	4302	**1.19**	**1.14**	**1.24**	
		2nd quintile	4318	**1.19**	**1.14**	**1.24**	
		3rd quintile	4315	**1.10**	**1.05**	**1.15**	
		4th quintile	4317	**1.04**	**1.00**	**1.09**	
		5th quintile	4326	Ref			**<.001**
	Paternal income at birth	1st quintile	4277	**1.19**	**1.14**	**1.24**	
		2nd quintile	4293	**1.14**	**1.10**	**1.19**	
		3rd quintile	4294	**1.09**	**1.04**	**1.13**	
		4th quintile	4293	**1.04**	**1.00**	**1.09**	
		5th quintile	4302	Ref			**<.001**
	Maternal education at birth	Elementary	6022	**1.16**	**1.12**	**1.20**	
		High school	9409	Ref			
		Academic degree	5914	**0.89**	**0.86**	**0.92**	
	Paternal education at birth	Elementary	5001	**1.17**	**1.13**	**1.21**	**<.001**
		High school	10926	Ref			
		Academic degree	5002	**0.89**	**0.86**	**0.92**	
	Maternal employment at birth	In	21472	Ref			
		Out of	99	1.22	1.01	1.49	0.52
	Paternal employment at birth	In	21313	Ref			
		Out of	97	1.11	0.91	1.36	1.00
	Living in a single parent household by child's 5th birthday	No	17384	Ref			
		1 year	1240	**1.14**	**1.07**	**1.20**	
		2 years	895	**1.21**	**1.13**	**1.30**	
		3 years	793	**1.28**	**1.19**	**1.38**	
		4 years	616	**1.30**	**1.20**	**1.41**	
		5 years	650	**1.26**	**1.16**	**1.36**	**<.001**
	Maternal age at birth	<20	412	**1.29**	**1.17**	**1.42**	
		20-24	3912	**1.15**	**1.11**	**1.20**	

	25-29	8543	Ref			
	30-34	6283	0.97	0.94	1.01	
	≥35	2410	**0.95**	**0.90**	**0.99**	**<.001**
Paternal age at birth	<20	112	**1.25**	**1.04**	**1.50**	
	20-24	1972	**1.22**	**1.16**	**1.28**	
	25-29	6880	**1.04**	**1.01**	**1.08**	
	30-34	7380	Ref			
	35-39	3630	1.00	0.96	1.04	
	≥40	1511	0.96	0.91	1.01	**<.001**
Parental history of psychiatric disorder by child's 5th birthday	No	20281	Ref			
	One parent	1211	**1.13**	**1.07**	**1.20**	
	Both parents	86	**1.30**	**1.05**	**1.61**	**<.001**

Note: Odds ratios and 95% CI reflect the increase in risk of exposure by one per standard deviation increase in the ADHD-PRS. $\boldsymbol{p_{adj}}$ represents false discovery rate corrected p-values derived using the Benjamini–Hochberg method. Significant associations (p<.05) after FDR correction are highlighted in bold.

Abbreviations: OR, odds ratio. LCI, lower 95% confidence interval. UCI, upper 95% confidence interval.

TABLE S3. Interaction between each putative risk-factor and ADHD-PRS on ADHD case-controls status in 13,697 individuals with ADHD and 21,290 non-ADHD population controls from the iPSYCH case-cohort, showing the differential (linear) effect of PRS per SD across levels of risk factors for ADHD

Domain	Risk factor	Level	IRR	LCI	LCI	Interaction p-value	p_{adj}
Birth-related	Birth weight	<2500 g	1.77	1.55	2.03		
		2500-3999 g	1.54	1.49	1.58		
		≥ 4000 g	1.49	1.41	1.58	0.07	0.86
	Small for gestational age	No	1.54	1.50	1.58		
		Yes	1.53	1.41	1.65	0.86	0.86
	Apgar score at 5 minutes	10	1.54	1.50	1.58		
		<10	1.46	1.34	1.59	0.24	0.86
Somatic	Maternal hypertensive disorders during pregnancy	No	1.54	1.50	1.57		
		Yes	1.60	1.28	1.98	0.73	0.86
	Maternal infection during pregnancy	No	1.53	1.50	1.57		
		Yes	1.50	1.32	1.70	0.71	0.86
	Maternal autoimmune disorder by child's 5th birthday	No	1.55	1.51	1.59		
		Yes	1.19	1.05	1.35	**<.0001**	**<.01**
	Paternal autoimmune disorder by child's 5th birthday	No	1.53	1.49	1.57		
		Yes	1.77	1.47	2.15	0.13	0.86
	1 infection	No	1.55	1.50	1.60		
		Yes	1.49	1.43	1.55	0.12	0.86
	≥ 5 infections	No	1.53	1.50	1.57		
		Yes	1.49	1.30	1.70	0.66	0.86
	Asthma	No	1.54	1.50	1.58		
		Yes	1.48	1.39	1.58	0.24	0.86
	Atopic diseases	No	1.54	1.50	1.58		
		Yes	1.51	1.30	1.65	0.72	0.86
	Type 1 diabetes	No	1.53	1.50	1.57		
		Yes	2.08	1.42	3.06	0.12	0.86
	Epilepsy	No	1.54	1.50	1.58		

		Yes	1.42	1.22	1.66	0.32	0.86
	Traumatic brain injury	No	1.54	1.50	1.59		
		Mild	1.36	1.26	1.48		
		Severe	1.64	1.35	1.99	**<.01**	0.26
Psychosocial	Maternal income at birth	1st quintile	1.48	1.41	1.56		
		2nd quintile	1.48	1.40	1.55		
		3rd quintile	1.54	1.45	1.63		
		4th quintile	1.57	1.48	1.67		
		5th quintile	1.49	1.39	1.59	0.50	0.86
	Paternal income at birth	1st quintile	1.52	1.45	1.60		
		2nd quintile	1.42	1.35	1.50		
		3rd quintile	1.50	1.42	1.59		
		4th quintile	1.59	1.50	1.68		
		5th quintile	1.56	1.46	1.67	0.07	0.86
	Maternal education at birth	Elementary	1.46	1.40	1.52		
		High school	1.53	1.47	1.59		
		Academic degree	1.41	1.34	1.49	0.06	0.86
	Paternal education at birth	Elementary	1.46	1.40	1.53		
		High school	1.50	1.45	1.55		
		Academic degree	1.48	1.38	1.58	0.67	0.86
	Maternal employment at birth	In	1.54	1.50	1.58		
		Out of	1.32	0.95	1.85	0.38	0.86
	Paternal employment at birth	In	1.53	1.50	1.57		
		Out of	2.44	1.75	3.39	**<.01**	0.14
	Living in a single parent household the first five years of life	No	1.53	1.48	1.58		
		1 year	1.45	1.32	1.59		
		2 years	1.40	1.26	1.56		
		3 years	1.41	1.26	1.57		
		4 years	1.35	1.21	1.51		

	5 years	1.37	1.22	1.54	0.06	0.86
Maternal age at birth	<20	1.54	1.32	1.79		
	20-24	1.43	1.35	1.51		
	25-29	1.53	1.47	1.59		
	30-34	1.50	1.43	1.58		
	≥35	1.60	1.48	1.74	0.15	0.84
Paternal age at birth	<20	1.75	1.30	2.36		
	20-24	1.38	1.28	1.48		
	25-29	1.52	1.45	1.59		
	30-34	1.53	1.46	1.60		
	35-39	1.54	1.44	1.64		
	≥40	1.67	1.51	1.86	**<.05**	0.86
Parental history of psychiatric disorder by child's 5th birthday	No	1.54	1.50	1.58		
	One parent	1.44	1.31	1.57		
	Both parents	1.74	1.18	2.57	0.30	0.86

Note: Incidence rate ratios and 95% confidence intervals reflect the differential linear effect of ADHD-PRS on ADHD case-control status across levels of each risk-factor. p_{adj} represents false discovery rate corrected p-values derived using the Benjamini–Hochberg method. Significant interactions (p<.05) before and after FDR correction are highlighted in bold.

Abbreviations: IRR, incidence rate ratio. LCI, lower 95% confidence interval. UCI, upper 95% confidence interval.

FIGURE S1. Flowchart of study population selection

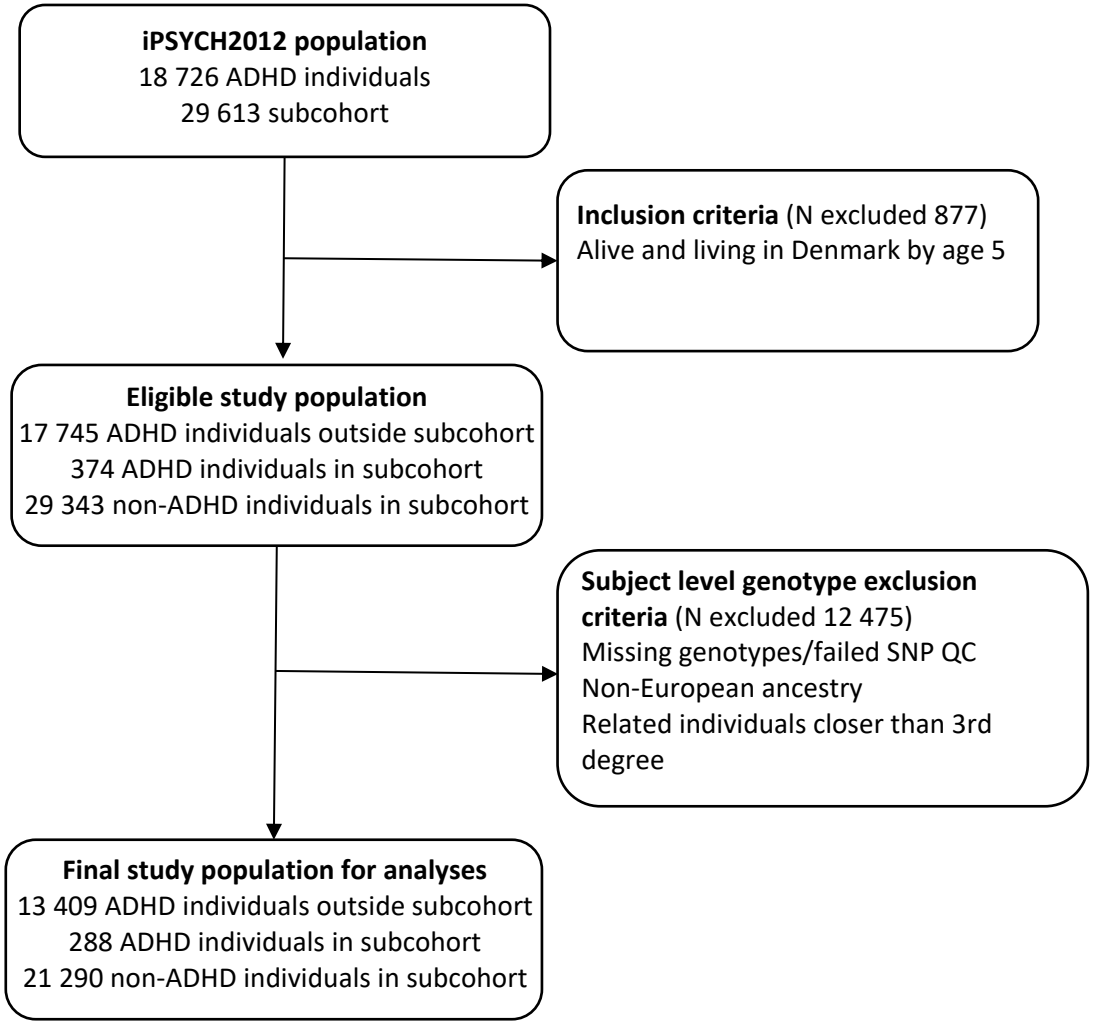
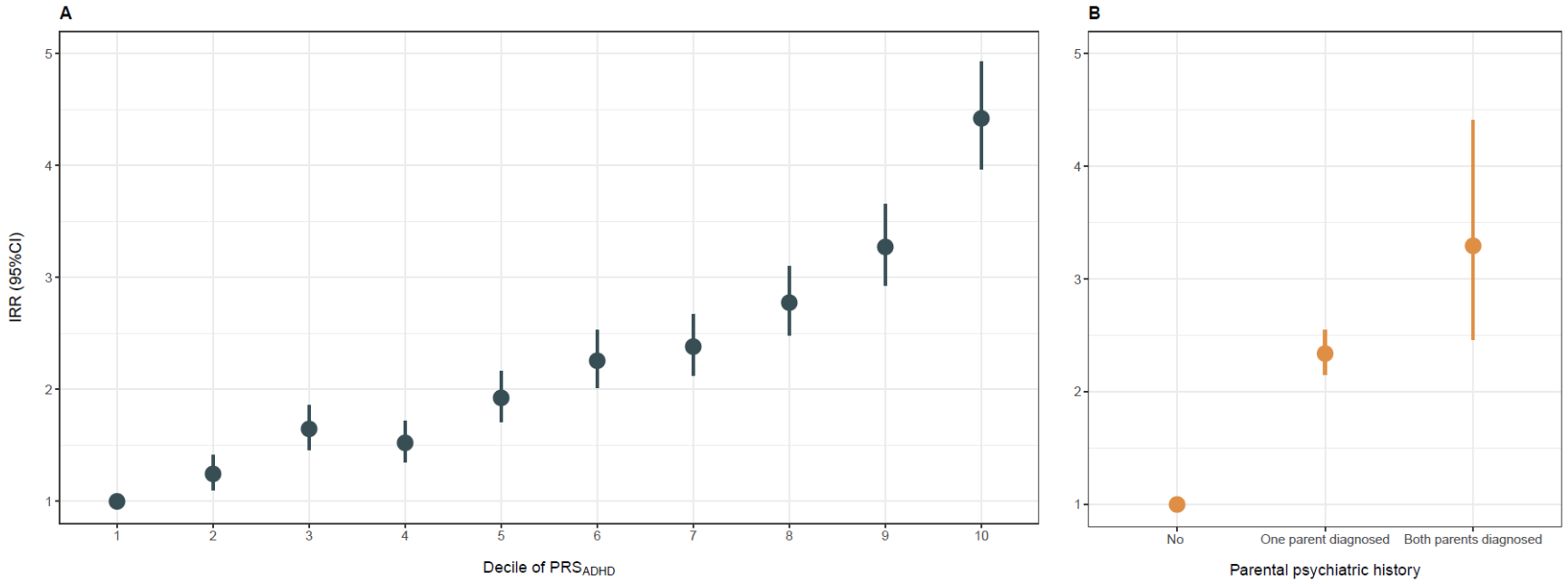


FIGURE S2. Associations of ADHD-PRS (A) and parental psychiatric history (B) with ADHD case-control status, expressed as incidence rate ratios (IRRs) with 95% confidence intervals (CIs)



Note: Incidence ratio ratios and 95% confidence intervals reflect the increase in risk of ADHD by A) deciles of the ADHD-PRS, and B) parental history of any clinically diagnosed psychiatric disorder.

Abbreviations: IRR, incidence rate ratio. LCI, lower 95% confidence interval. UCI, upper 95% confidence interval. PRS, polygenic risk score.