Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Study Measures and Analysis

Genetic Data

Genetic data were acquired using the Illumina HumanHap550 quad genome-wide single nucleotide polymorphism (SNP) genotyping platform from 9912 participants. Individuals were excluded from further analysis on the basis of gender mismatches, minimal or excessive heterozygosity, disproportionate levels of individual missingness (>3%), evidence of cryptic relatedness (>10% of alleles identical by descent), and being of non-European ancestry (assessed by multidimensional scaling analysis including HapMap 2 individuals). SNPs with a minor allele frequency (MAF) of < 1%, Impute2 information quality metric of < 0.8, a call rate of < 95% or evidence for violations of Hardy-Weinberg equilibrium (p value < 5×10^{-7}) were removed. Imputation of the target data was performed using Impute V2.2.2 against the 1000 genomes reference panel (Phase 1, Version 3; all polymorphic SNPs excluding singletons), using 2186 reference haplotypes (including non-Europeans). Following quality control assessment and imputation and restricting to 1 young person per family, genetic data was available for 8230 ALSPAC individuals.

Measures

Psychotic experiences

The semi-structured Psychosis-Like Symptom Interview (PLIKSi),[1,2] which draws on principles of standardized clinical examination developed for the Schedule for Clinical Assessment in Neuropsychiatry (SCAN), was used to assess psychotic experiences at ages 12 and 18 years. The PLIKSi allows rating of 12 psychotic experiences including hallucinations (visual and auditory), delusions (spied on, persecution, thoughts read, reference, control, grandiosity, other) and experiences of thought interference (broadcasting, insertion and withdrawal). Any unspecified delusions elicited are also rated. Structured stem questions (e.g. “have you ever seen something or someone that other people could not see?”; “have you ever thought you were being followed or spied on?”; “Have you ever felt that thoughts are put into your mind that are not your own?”) are followed up by cross-questioning to allow the interviewer to make a decision as to whether experiences described meet SCAN criteria for a psychotic experience.

The interviewers were psychology graduates trained in assessment using the SCAN psychosis section and using the PLIKSi. Psychotic experiences were rated as not present, suspected or definitely psychotic. Unclear responses were always ‘rated down’ and symptoms were rated as definite only when a clear example was provided. At regular intervals samples of recorded interviews were also rated by a psychiatrist to ensure interviewers were rating experiences correctly. The PLIKSi shows very good inter-rater and test-retest reliability.[3]

To maximise the numbers within our sample, individuals were deemed as having a psychotic experience if rated as having 1 or more definite psychotic experiences at either age 12 or 18 years, compared to no or only suspected psychotic experiences at age 12 or 18 years.

To assess the sensitivity of results analyses were repeated using data from age 12 and age 18 years separately and from the psychosis-like symptoms questionnaire (PLIKS-Q)[4] at ages 11, 13, 14 and 16 years. Individuals answered questions relating to presence and frequency of experiencing hallucinations, delusions and thought interference. Participants were classed as having had a psychotic-like experience if they rated hallucinations as definitely present, or delusions or thought interference as definitely present and that these occurred at least monthly over the previous year.

Negative Symptoms

The presence of negative symptoms was assessed using 10 questions based on items from the Community Assessment of Psychic Experiences (CAPE) self-report questionnaire[5] at age 16.5 years (*eTable 1*). These questions covered a range of negative symptom domains including apathy, anergia, shyness, asociality and attention to appearance. The questions measured the frequency of occurrence of negative symptoms using a 4-point scale (0: never, 1: sometimes, 2: often, 3: always).

A negative symptom total score was constructed for each individual based on the sum of their responses to the 10 questions (minimum score: 0, maximum score: 30). A binary variable was created using a total score of 14 as a cut-off, chosen to approximately define the top decile (9.18%) of the sample. To assess whether using this cut-

off affected results, analyses were repeated using binary variables generated from all possible negative symptom score cut-offs.

Depressive Disorder and Anxiety Disorder

Evidence of depression and anxiety disorders were derived from the semi-structured Development and Well Being Assessment (DAWBA) interview at age 15.5 years which has been shown to be a valid instrument in both community and clinical samples.[6] Children were interviewed using the DAWBA and DSM-IV and ICD-10 diagnoses of depressive or any anxiety disorder were generated using a computerised diagnostic algorithm that predicts the likelihood of a clinical rater assigning a diagnosis to each child.[7]

Questions used to assess presence of depressive disorder within the previous four weeks included "have there been times when you have been very sad, miserable, unhappy or tearful?", "have there been times when you have been grumpy or irritable in a way that was out of character for you?" and "have there been times when you have lost interest in everything, or nearly everything, that you normally enjoy doing?". Questions used to assess presence of anxiety disorder included "do you ever worry?" and "do you particularly fear or avoid social situations that involve a lot of people, meeting new people, or doing things in front of other people?". For further information please see http://www.DAWBA.com.

Within the current study, individuals were assessed as having suffered with a depressive disorder or an anxiety disorder if they fell into the DAWBA band predicting a ≥ 15% probability of being diagnosed. These band cut-offs were again chosen to approximately define the top deciles of the sample.

To assess the sensitivity of using a ≥ 15% probability DAWBA band threshold to represent prevalence of depressive and anxiety disorders in ALSPAC, analyses were repeated and compared using the more stringent ≥ 50% probability band cut-off, and also using ICD-10 diagnoses of depression and anxiety disorders (generalised anxiety, panic disorder, agoraphobia, social phobia or specific phobia) at age 18 years using the Clinical Interview Schedule-Revised (CIS-R).[8] The sensitivity of using a ≥ 15% probability DAWBA band threshold to represent prevalence of depressive disorder was further assessed using the short (13 item) Mood and Feelings Questionnaire (MFQ) age 16.5 years.[9,10] MFQ scores were dichotomised at the ≥80th and ≥90th percentile, generating two binary variables representing the top two and top deciles of the sample, respectively.

Polygenic Risk Score

Construction of PRSs within the current study follows the methodology described by the International Schizophrenia Consortium (ISC).[11] PRSs were constructed using results from the second Psychiatric Genomics Consortium (PGC) Schizophrenia GWAS[12] as a training set. The PGC study enabled the identification of risk alleles and their corresponding effect sizes, to be used to generate PRSs for each ALSPAC individual within the study.

Prior to construction of scores, SNPs were removed from the analysis if they had a minor allele frequency less than 0.01, an imputation quality less than 0.8 or if there was allelic mismatch between samples (the alleles reported by the PGC study did not match the alleles present in the ALSPAC sample). Due to the high linkage disequilibrium (LD) within the extended major histocompatibility complex (MHC; chromosome 6: 25-34Mb) only a single SNP (rs116137698) was included to represent this region within the analysis. Remaining SNPs were then further pruned for LD using the PLINK (v1.90)[13] 'clump' command to retain SNPs with a schizophrenia association p value ≤ 0.5 and $r^2 < 0.25$ within 500kb windows.

Polygenic scores were calculated for each ALSPAC individual using the PLINK (v1.07) 'score' command. Scores are calculated by summing the number of reference alleles present for each SNP (0, 1 or 2) weighted by the logarithm of its odds ratio for schizophrenia.

Our primary analysis used scores generated using a list of SNPs meeting a training set p value threshold of ≤ 0.05 as this threshold explains approximately 7% of schizophrenia case-control variation on the liability scale.[12] As the composition of a PRS is a balance between true and null effects,[14] scores generated using lists of SNPs meeting a series of p value thresholds and using all independent SNPs meeting genome-wide significance as reported by the PGC Schizophrenia GWAS[12] were used in a secondary analysis to investigate the distribution of effect sizes when using high to low PRS p value thresholds.

Statistical analysis

Logistic regression was used to test for association between psychopathology outcomes and schizophrenia PRS. Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs) per standard deviation (SD) increase in PRS. Nonlinear associations between PRSs and outcomes were examined by inclusion of quadratic terms in the regression models. We examined whether associations with different phenotypes were independent by inclusion of other phenotypes within a multivariable model. We also examined the association for each decile of PRS compared to the lowest decile.

Correcting for multiple testing

To correct *p* values for potential type I errors arising from using 13 different p_T within our sensitivity analyses, permutation-adjusted *p* values were computed (coin package for R[15]). This method was chosen as the association tests carried out were not independent. The trait positive/negative status was permuted 10,000 times and associations between psychopathology outcomes and schizophrenia PRS were re-calculated. The permutation-adjusted, empirical *p* value was calculated as the number of simulations with *p* value smaller than the un-adjusted *p* value divided by the number of permutations.

Bivariate probit regression & converting probit estimates to odds ratios

To test whether associations of schizophrenia PRS with different phenotypes were the same, or different, across phenotypes, we used bivariate probit regression to jointly model pairs of outcomes. We tested equality of regression parameters expressing the effect of schizophrenia PRS (p_T of 0.05) on each outcome using a likelihood ratio test to compare a model that allows effect estimates to differ with a model where the PRS effect was constrained to be equal for both outcomes. To aid interpretation, probit estimates were converted to ORs by taking the exponent of the approximate logit parameters which were derived by multiplying the probit parameters by a factor of 1.6 (See eq. 2.7 in Amemiya, 1981[16] and Kounali et al., 2014[17] for an example of previous use).

eReferences

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eTable 1. Items Used to Create the Negative Symptoms Measure in ALSPAC

Item*
Have you felt that you are not much of a talker when you are chatting with other people?
Have you felt that you experience few or no emotions at important events, such as on your birthday?
Have you felt that you are lacking in motivation when you have to do things?
Have you felt that you are spending all your days doing nothing?
Have you felt that you are lacking 'get up and go'?
Have you felt that you have only a few hobbies or interests?
Have you felt that you have no interest to be with other people?
Have you felt that you are not a very lively person?
Have you felt that you are neglecting your appearance or personal hygiene?
Have you felt that you can never get things done?

* Based on items from the Community Assessment of Psychic Experiences (CAPE) self-report questionnaire

eTable 2. Association Between Schizophrenia Polygenic Score per SD and Psychopathology in Adolescence

P value cut off in discovery sample	OR	LCI	UCI	P	Empirical P*
Psychotic experiences at age 12/18					
0.5	1.086	0.984	1.200	0.101	0.1036
0.3	1.084	0.982	1.197	0.111	0.1121
0.1	1.079	0.977	1.191	0.133	0.1369
0.05	1.079	0.977	1.191	0.134	0.1417
1e-03	0.979	0.886	1.082	0.682	0.6768
1e-05	**0.904**	**0.817**	**0.999**	**0.048**	**0.0493**
1e-07	**0.899**	**0.814**	**0.994**	**0.038**	**0.0371**
5e-08 †	**0.903**	**0.817**	**0.998**	**0.046**	**0.0484**
Negative symptoms (score ≥14) at age 16.5					
0.5	**1.220**	**1.090**	**1.366**	**0.001**	**0.0004**
0.3	**1.212**	**1.083**	**1.357**	**0.001**	**0.0007**
0.1	**1.225**	**1.094**	**1.370**	**0.000**	**0.0003**
0.05	**1.211**	**1.082**	**1.355**	**0.001**	**0.0006**
1e-03	**1.136**	**1.016**	**1.270**	**0.025**	**0.0260**
1e-05	1.059	0.946	1.186	0.319	0.3160
1e-07	1.044	0.933	1.167	0.454	0.4461
5e-08 †	1.104	0.985	1.238	0.088	0.0874
Depressive disorder (≥15% probability) at age 15.5					
0.5	1.010	0.908	1.123	0.854	0.8538
0.3	1.016	0.914	1.130	0.763	0.7649
0.1	1.037	0.933	1.154	0.498	0.4993
0.05	1.016	0.913	1.131	0.768	0.7700
1e-03	1.023	0.919	1.139	0.677	0.6763
1e-05	1.040	0.934	1.159	0.474	0.4775
1e-07	1.023	0.919	1.139	0.680	0.6723
5e-08 †	1.017	0.913	1.133	0.755	0.7464
Anxiety disorder (≥15% probability) at age 15.5					
0.5	**1.156**	**1.048**	**1.276**	**0.004**	**0.0037**
0.3	**1.162**	**1.053**	**1.282**	**0.003**	**0.0023**
0.1	**1.167**	**1.058**	**1.289**	**0.002**	**0.0015**
0.05	**1.171**	**1.060**	**1.293**	**0.002**	**0.0017**
1e-03	**1.113**	**1.007**	**1.229**	**0.035**	**0.0347**
1e-05	1.083	0.980	1.196	0.120	0.1234
1e-07	1.055	0.955	1.165	0.294	0.2964
5e-08 †	1.025	0.927	1.133	0.632	0.6331

Note: OR, Odds Ratio; LCI, L95% CI; UCI, U95% CI.

† 111 genome-wide significant SNPs reported by the PGC

* calculated from 10000 permutations

eTable 3. Association Between Schizophrenia Polygenic Risk Score Decile and Psychopathology in Adolescence

	Decile group	OR*	Std. Err	z	P	LCI	UCI
Psychotic experiences	2	1.016	0.245	0.070	0.947	0.634	1.629
	3	1.188	0.271	0.750	0.450	0.760	1.858
	4	1.275	0.290	1.070	0.285	0.817	1.991
	5	1.183	0.273	0.730	0.466	0.753	1.860
	6	1.255	0.285	1.000	0.317	0.804	1.959
	7	1.036	0.246	0.150	0.881	0.650	1.650
	8	1.044	0.252	0.180	0.860	0.651	1.674
	9	1.840	0.397	2.830	0.005	1.205	2.808
	10	1.138	0.269	0.550	0.585	0.716	1.808
Negative symptoms	2	1.067	0.299	0.230	0.816	0.617	1.847
	3	1.213	0.324	0.720	0.469	0.719	2.048
	4	1.392	0.368	1.250	0.211	0.829	2.336
	5	1.165	0.315	0.560	0.573	0.685	1.981
	6	1.442	0.377	1.400	0.161	0.864	2.406
	7	1.620	0.427	1.830	0.067	0.967	2.715
	8	1.565	0.414	1.690	0.091	0.931	2.629
	9	1.770	0.464	2.180	0.030	1.058	2.960
	10	1.856	0.485	2.370	0.018	1.113	3.097
Depressive disorder	2	1.064	0.244	0.270	0.786	0.678	1.670
	3	0.903	0.211	-0.440	0.663	0.572	1.427
	4	0.681	0.174	-1.510	0.132	0.412	1.123
	5	0.902	0.212	-0.440	0.661	0.569	1.430
	6	1.025	0.235	0.110	0.913	0.654	1.608
	7	1.147	0.261	0.600	0.546	0.735	1.791
	8	0.983	0.235	-0.070	0.943	0.615	1.571
	9	0.800	0.199	-0.900	0.370	0.492	1.303
	10	1.123	0.264	0.490	0.621	0.709	1.779
Anxiety disorder	2	1.506	0.351	1.760	0.078	0.955	2.377
	3	1.225	0.291	0.850	0.393	0.769	1.952
	4	1.198	0.291	0.740	0.457	0.744	1.930
	5	1.226	0.293	0.850	0.393	0.768	1.959
	6	1.276	0.304	1.020	0.305	0.801	2.034
	7	1.844	0.417	2.700	0.007	1.183	2.873
	8	1.385	0.334	1.350	0.177	0.863	2.221
	9	1.956	0.442	2.970	0.003	1.256	3.045
	10	1.735	0.405	2.360	0.018	1.098	2.743

Note: *OR, Odds Ratio (decile 1 used as reference); LCI, L95% CI; UCI, U95% CI.

eTable 4. Association Between Schizophrenia Polygenic Risk Score and Psychotic Experiences in Adolescence, Adjusting for Other Psychopathologies

	OR	SE	P>|z|	LCI	UCI
SCZ PRS per SD	1.079	0.055	0.134	0.977	1.191
Adding other psychopathologies as confounders:					
SCZ PRS per SD	1.014	0.076	0.853	0.875	1.175
NegSymp	2.260	0.449	0.000	1.532	3.335
Dep	2.554	0.507	0.000	1.731	3.768
Anx	2.558	0.477	0.000	1.775	3.687

PT = 0.05

eTable 5. Association Between Schizophrenia Polygenic Risk Score and Negative Symptoms in Adolescence, Adjusting for Other Psychopathologies

	OR	SE	P>|z|	LCI	UCI
SCZ PRS per SD	1.211	0.069	0.001	1.082	1.355
Adding other psychopathologies as confounders:					
SCZ PRS per SD	1.183	0.082	0.015	1.033	1.355
PPE	2.254	0.448	0.000	1.527	3.328
Dep	1.993	0.390	0.000	1.358	2.925
Anx	2.448	0.431	0.000	1.733	3.458

PT = 0.05

eTable 6. Association Between Schizophrenia Polygenic Risk Score and Depressive Disorder in Adolescence, Adjusting for Other Psychopathologies

	OR	SE	P>|z|	LCI	UCI
SCZ PRS per SD	1.016	0.055	0.768	0.913	1.131
Adding other psychopathologies as confounders:					
SCZ PRS per SD	0.929	0.067	0.304	0.806	1.070
PPE	2.558	0.508	0.000	1.733	3.775
NegSymp	1.991	0.390	0.000	1.356	2.922
Anx	5.327	0.854	0.000	3.891	7.295

PT = 0.05

eTable 7. Association Between Schizophrenia Polygenic Risk Score and Anxiety Disorder in Adolescence, Adjusting for Other Psychopathologies

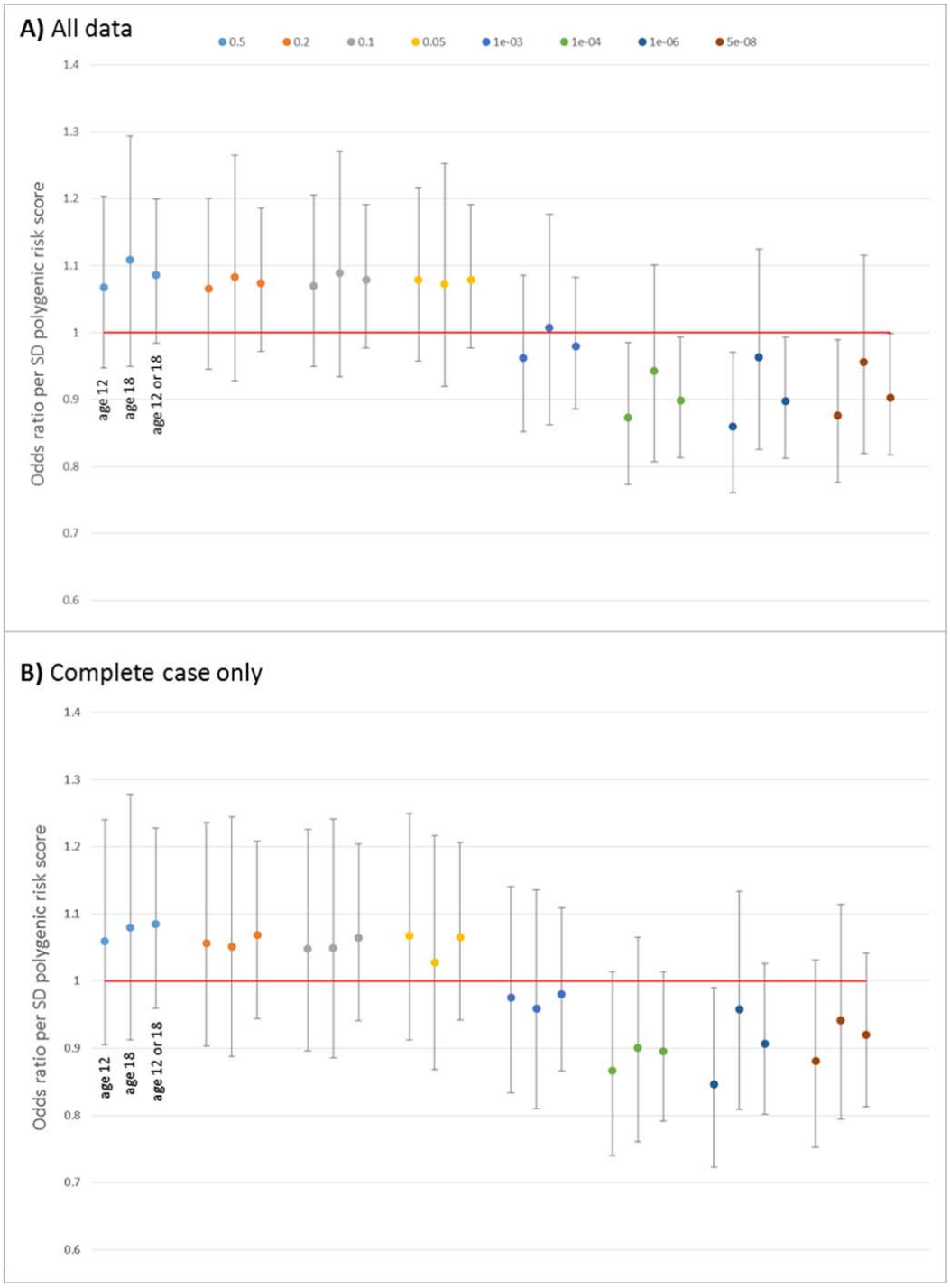
	OR	SE	P>|z|	LCI	UCI
SCZ PRS per SD	1.171	0.059	0.002	1.060	1.293
Adding other psychopathologies as confounders:					
SCZ PRS per SD	1.223	0.080	0.002	1.076	1.391
PPE	2.553	0.478	0.000	1.768	3.686
NegSymp	2.454	0.433	0.000	1.737	3.466
Dep	5.341	0.856	0.000	3.900	7.313

PT = 0.05

eTable 8. Tetrachoric Correlations Between Each Psychopathology in Adolescence

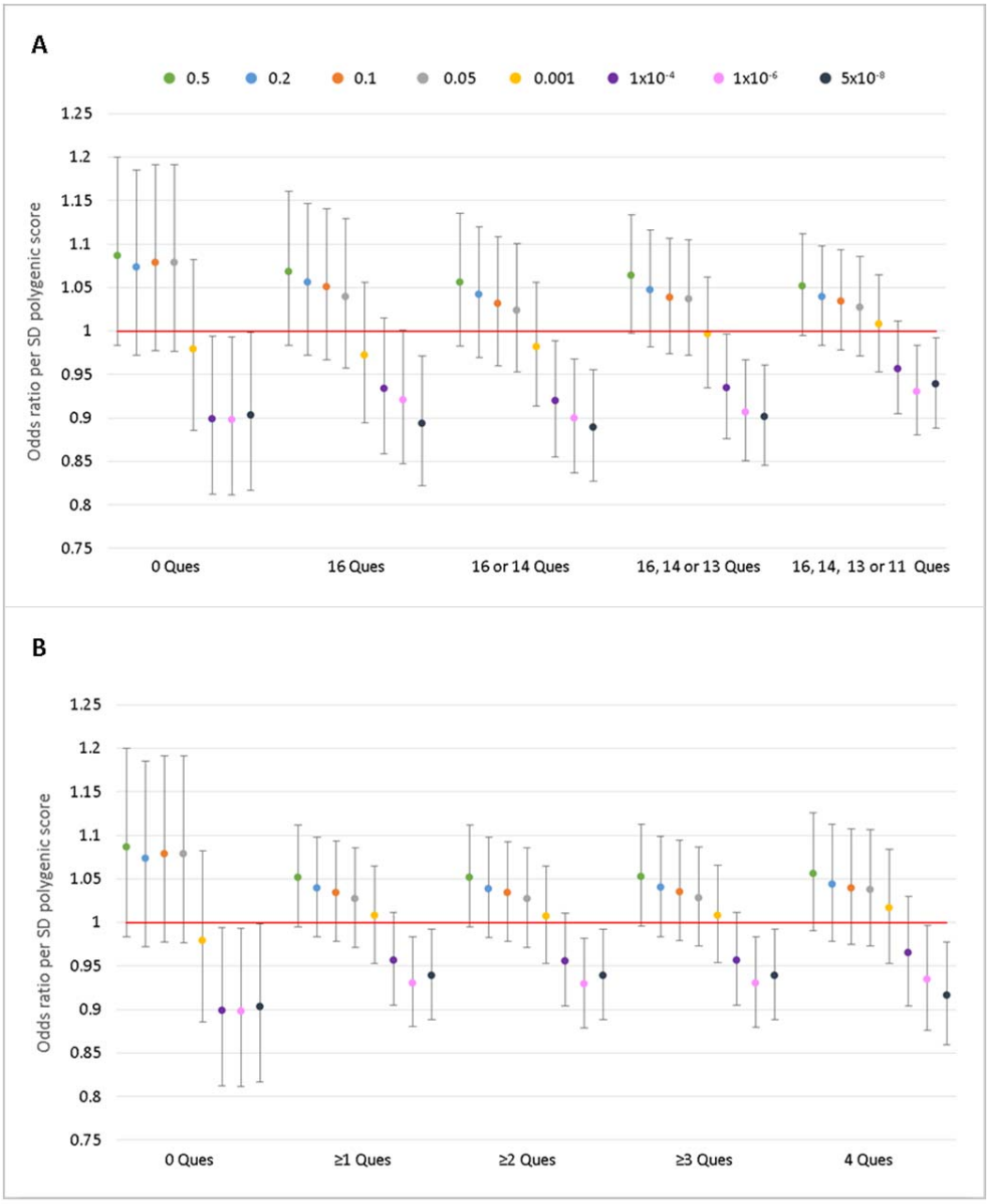
	Psychotic experiences	Negative symptoms	Depressive disorder	Anxiety disorder
Psychotic experiences	1.00			
Negative symptoms	0.30	1.00		
Depressive disorder	0.38	0.31	1.00	
Anxiety disorder	0.37	0.36	0.53	1.00

eFigure 1. Associations Between Psychotic Experiences at Ages 12 and 18 Years Separately and Polygenic Risk Scores for Schizophrenia



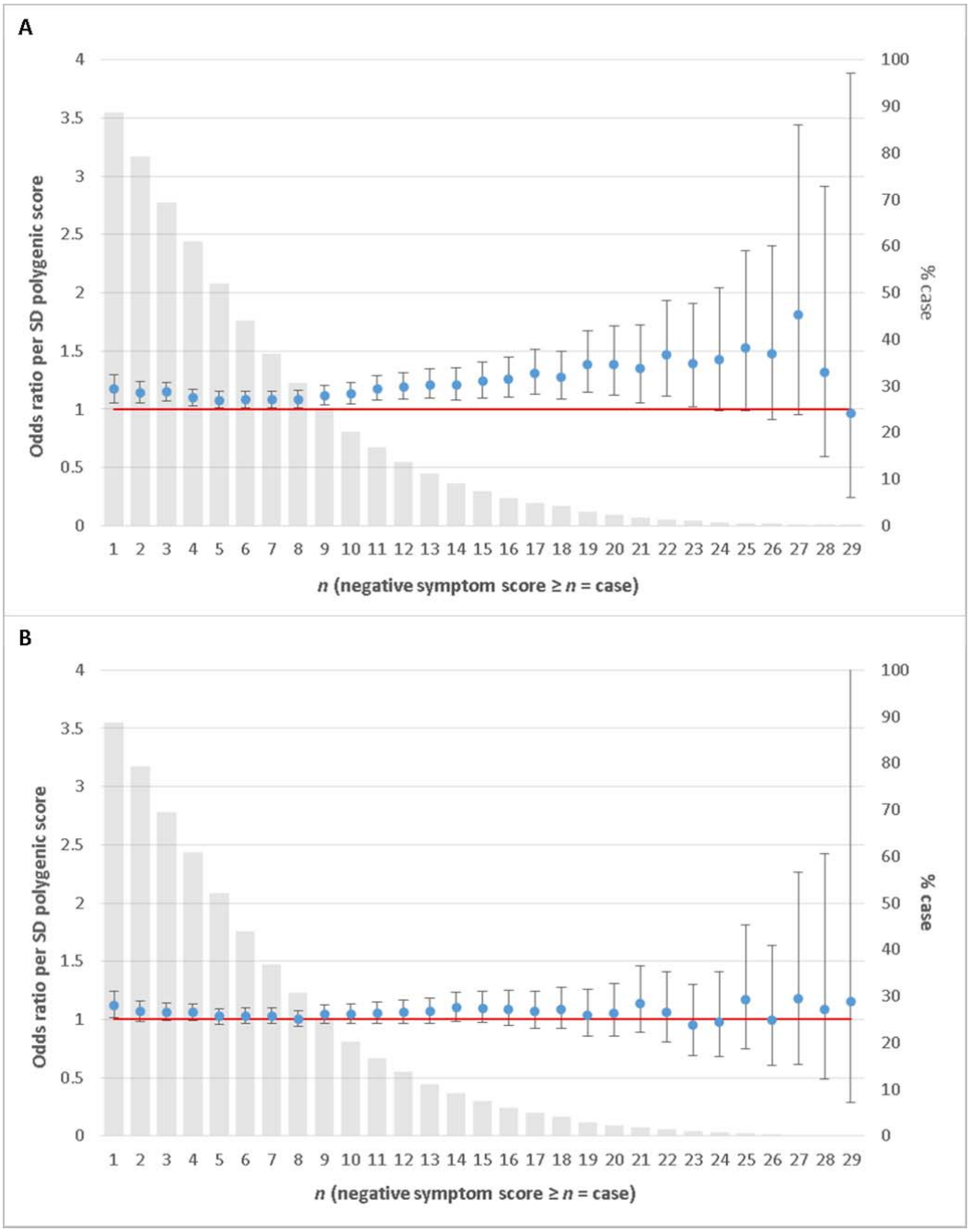
Associations are presented for A) all data and B) complete case data only for age 12 years and age 18 years separately and combined. Odds ratio per standard deviation (SD) change in polygenic risk score are shown with upper and lower 95% confidence intervals. The range of p value thresholds used to create the polygenic risk scores are presented in the legend within the figure. Genome-wide significant polygenic risk score threshold (5×10^{-8}) was created from 111 genome wide significant schizophrenia SNPs as reported by PGC.[12]

eFigure 2. Associations Between Psychotic Experiences, Assessed Using PLIKSI and PLIKS-Q, and Polygenic Risk Scores for Schizophrenia



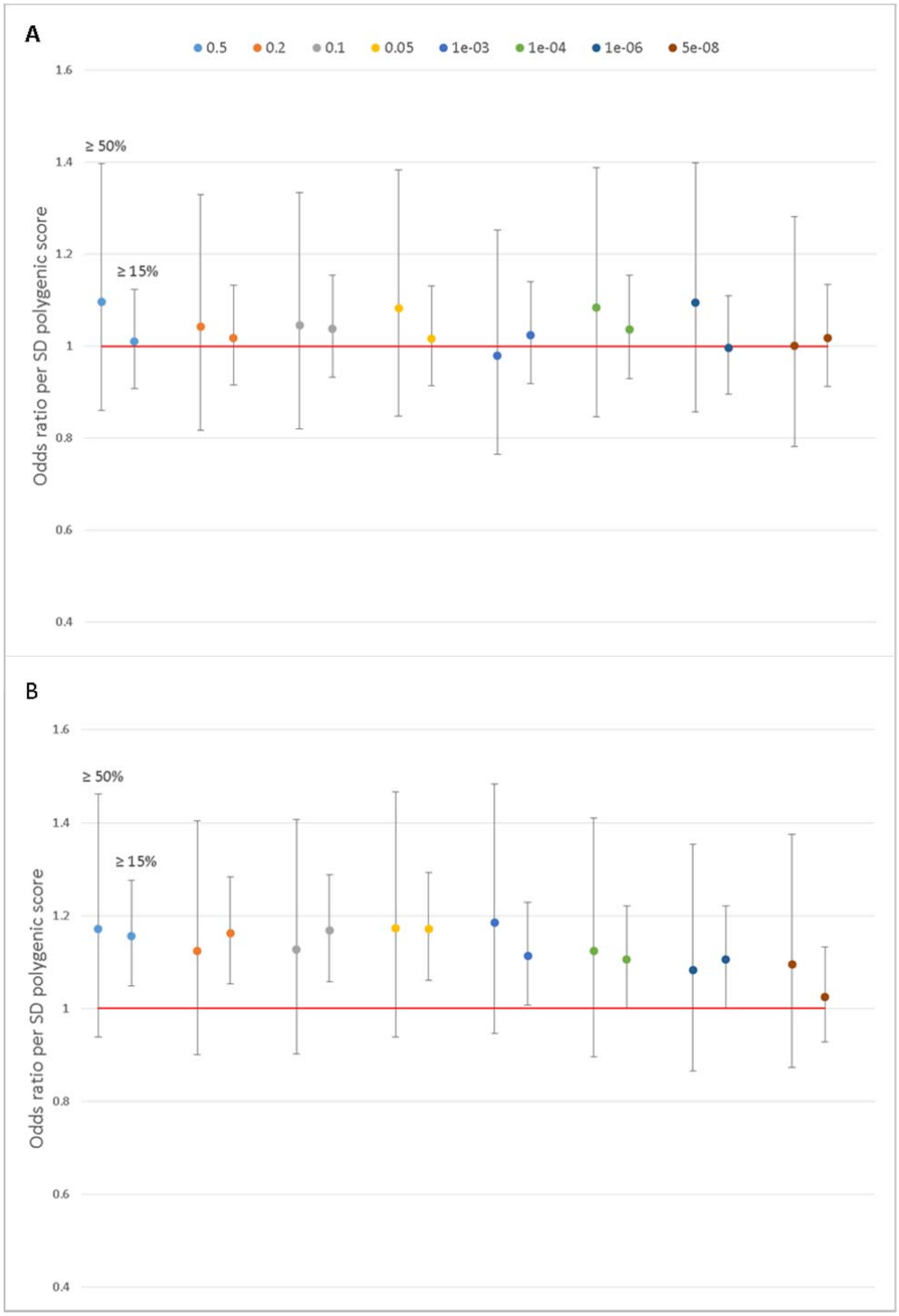
Psychotic experiences were assessed using PLIKSi at age 12 and 18 years with data from questionnaires (Ques) by A) sequentially adding in data from ages 16, 14, 13 and 11 years and B) adding in data from individuals who had completed at least 'n' questionnaires from any age. Odds ratio per standard deviation (SD) change in polygenic risk score are shown with upper and lower 95% confidence intervals. The range of p value thresholds used to create the polygenic risk scores are presented in the legend within the figure. Genome-wide significant polygenic risk score threshold (5×10^{-8}) was created from 111 genome wide significant schizophrenia SNPs as reported by PGC.[12]

eFigure 3. Associations Between Negative Symptoms (Varying Case Cutoff) and Polygenic Scores for Schizophrenia



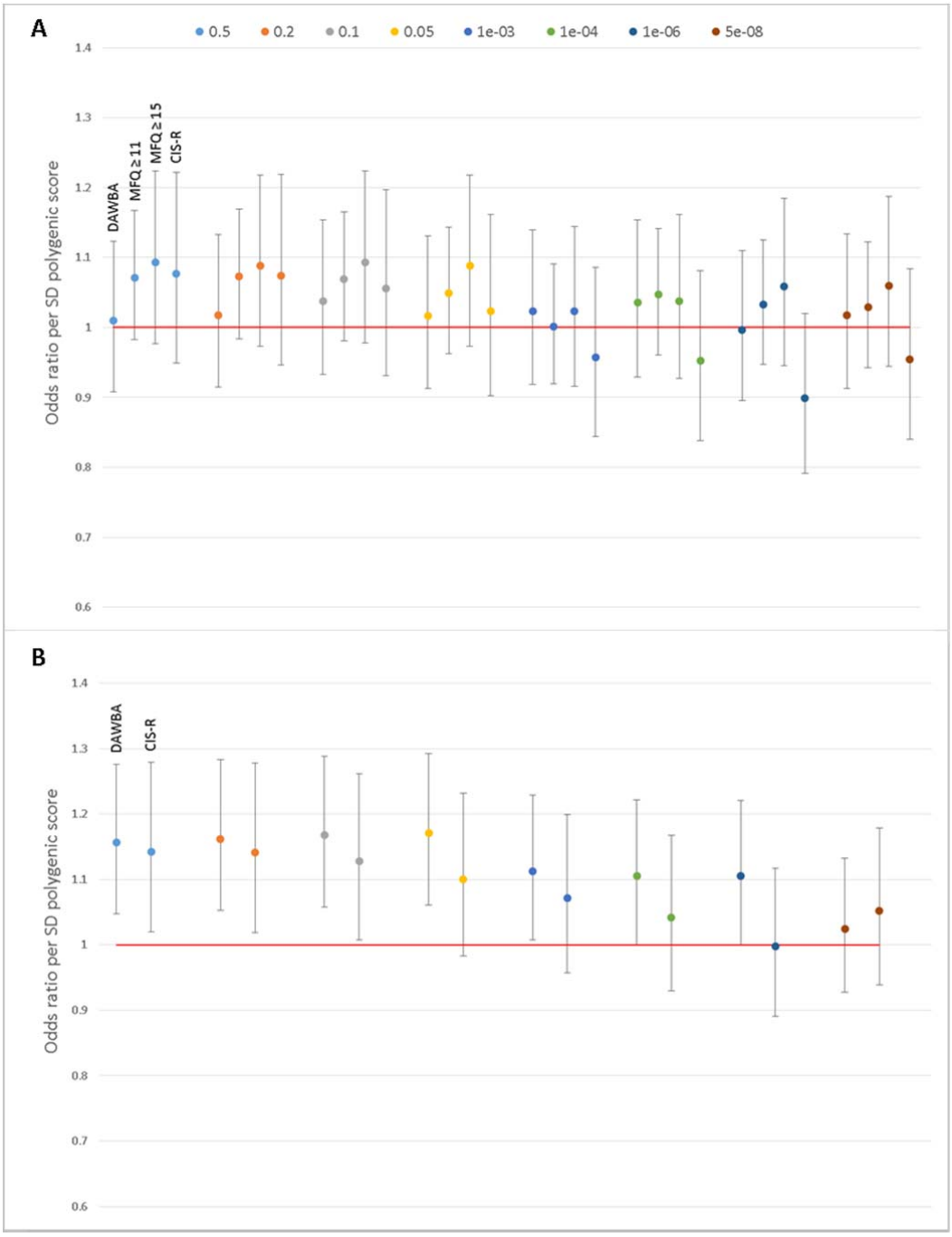
Associations are presented between negative symptoms (varying case cut-off) and polygenic scores for schizophrenia generated using a *p* value threshold of A) 0.05 and B) 1 x 10^{-4}. The number of negative symptom cases was determined using negative symptom score cut-offs (*n*) where individuals with a score equal to or above *n* were classed as cases and those with scores less than *n* were classed as controls. Odds ratio per standard deviation (SD) change in polygenic risk score are shown with upper and lower 95% confidence intervals. Grey bars: % number of negative symptom cases generated per cut-off.

eFigure 4. Comparisons Between DAWBA Diagnosis Cutoffs in Relation to the Association of Depressive and Anxiety Disorder to Polygenic Scores for Schizophrenia



Comparisons are presented between DAWBA diagnosis based on ≥50% probability and ≥15% probability of disorder in relation to the association of A) depressive disorder and B) anxiety disorder to polygenic scores for schizophrenia. Odds ratio per standard deviation (SD) change in polygenic risk score are shown with upper and lower 95% confidence intervals. The range of p value thresholds used to create the polygenic risk scores are presented in the legend within the figure. Genome-wide significant polygenic risk score threshold (5e-08) was created from 111 genome wide significant schizophrenia SNPs as reported by PGC.[12]

eFigure 5. Comparisons Between DAWBA, MFQ, and CIS-R Diagnosis in Relation to the Association of Depressive and Anxiety Disorder to Polygenic Scores for Schizophrenia



Comparisons are presented between DAWBA (≥15% probability of disorder), MFQ (using ≥11 and ≥15 score cut-off; where available) and CIS-R diagnosis in relation to the association of A) depressive disorder and B) anxiety disorder to polygenic scores for schizophrenia. Odds ratio per standard deviation (SD) change in polygenic risk score are shown with upper and lower 95% confidence intervals. The range of p value thresholds used to create the polygenic risk scores are presented in the legend within the figure. Genome-wide significant polygenic risk score threshold (5e-08) was created from 111 genome wide significant schizophrenia SNPs as reported by PGC.[12]

