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At the intersection of autism and psychosis

An investigation of causal pathways and shared risk factors

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A dissertation submitted to the University of Bristol in accordance with the requirements of the degree of Doctor of Philosophy in the Faculty of Health Sciences.

April 2022

Word Count: 37,529

Abstract

There is increasing evidence suggesting that autism and psychosis co-occur at higher rates than would be expected by chance. Little is known on the reasons underlying this, and several aetiological models have been proposed. In this thesis I assessed evidence on two aetiological models of the autism-psychosis co-occurrence, proposing that the two conditions are causally linked and/or share immunological pathways. I applied a combination of study designs, utilising phenotype and genotype data, to triangulate evidence and strengthen causal inference.

Towards assessing the autism-psychosis causal links, I investigated the associations between autism polygenic risk (PRS), autistic traits in childhood and psychotic experiences in adulthood using data from a population-based birth cohort (Chapter 3). I triangulated the study findings, by applying two-sample Mendelian randomization (MR) and multivariable MR to examine the causal effects of genetic liability to autism and autistic traits on psychotic experiences and schizophrenia (Chapter 4).

Towards investigating whether shared immunological pathways underly autism and psychosis, I firstly interrogated the causal role of immune response in autism. I utilised four distinct methodological approaches, including a nationwide cohort study, Linkage disequilibrium score regression, PRS and two-sample MR, to investigate the causal links between a parental inflammatory bowel disease and offspring autism (Chapter 5). I used information from this study to identify causal immunological markers for autism and assess their causal effects on schizophrenia, within a two-sample MR and genetic colocalisation framework (Chapter 6).

There was evidence to suggest that the autism-psychosis co-occurrence might be explained by causal links, driven by autism common variation, social communication difficulties and trauma in childhood. Causal immunological pathways were identified in both autism and schizophrenia, but they were unique for each condition. Overall the findings suggest that beyond underlying biological processes, phenotypic and environmental factors are central in the autism-psychosis co-occurrence.

Dedication and acknowledgements

I would like to express my heartfelt gratitude to my supervisors, Dr Dheeraj Rai, for his continuous support, encouragement (even in the darkest of times), and opportunities he gave me to learn and develop as a researcher; Dr Sarah Sullivan, Professor Stan Zammit and Dr Hannah Jones for their patience, time and valuable guidance throughout my PhD. I feel genuinely priviledged for the opportunity to work with this supervisory team.

I would also like to thank all my co-authors and collaborators for sharing their knowledge with me and their input. A special thank you goes to Professor Abigail Fraser, Dr Gemma Sharp, Dr Neil Davies, Dr Evie Stergiakouli, Dr Emma Anderson, Dr Alex Havdahl, Dr Jakob Grove, Dr Renee Gardner, Professor Golam Khandaker and Professor George Davey Smith. I am honoured that I have worked with them.

Work carried out in this thesis would not be possible without the support of my funder, the Wellcome Trust, as well as the participants, researchers, personel and funding bodies of the studies that their data have been used in this thesis, including the ALSPAC cohort, the UK Biobank, the PGC and iPSYCH autism and schizophrenia working groups, the 23andMe, Psychiatry Sweden, the MetaBrain Network, as well as inflammatory bowel disease and proteome genotyping studies.

I am grateful to all my colleagues, fellow PhD students and officemates (pre-pandemic!) for the stimulating discussions and support. A very -very- special thank you goes to my friends (in order of appearence) Jazz, Lucy, Amberly, Cat, Tom, James, Ilaria, Jamie, Josh, Roxanna, Jim, Amanda, Panagiota and Sean, for the discussions on epidemiology, the pints and the laughs. And a massive thank you belongs to Si for reminding me what really matters in life.

This thesis is dedicated to my mum, Litsa, my dad, Stelios, and my brother, George, for their endless support- I would have never been here without them.

Author’s declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

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List of Abbreviations

Abbreviation	Definition
ADHD	Attention Deficit Hyperactivity Disorder
ALSPAC	Avon Longitudinal Study of Parents and Children
AQ	Autism Spectrum Quotient
ASD	Autism Spectrum Disorder
CHR	Chromosome
BP	Base pair
CI	Confidence Interval
CNV	Copy Number Variation
CRP	C- Reactive Protein
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAF	Effect Allele Frequency
EMDR	Eye Movement Desensitization and Reprocessing
EPDS	Edinburgh Postnatal Depression Scale
EQ	Empathy Quotient
eQTL	expression Quantitative Trait Loci
GREML	Genome-based restricted maximum likelihood
GWAS	Genome Wide Association Study
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
ID	Intellectual Disabilities
IFN	Interferon
IL-	Interleukin
IRF	Interferon Regulatory Factor
IVW	Inverse Variance Weighted
KB	Kilobase
LD	Linkage Disequilibrium
LDSC	Linkage Disequilibrium Score Regression
MAR	Missing At Random
MCAR	Missing Completely At Random
MHC	Major Histocompatibility Complex
MHQ	Mental Health Questionnaire
MNAR	Missing Not At Random
MR	Mendelian randomization
MRI	Magnetic Resonance Imaging
mRNA	messenger ribonucleic acid
MVMR	Multivariable Mendelian randomization
NDE	Natural Direct Effect
NIE	Natural Indirect Effect
OR	Odds Ratio
PGC	Psychiatric Genomics Consortium
PLIKSi	Psychosis-Like Symptoms interview
pQTL	protein Quantitative Trait Loci

PRS	Polygenic Risk Score
PTV	Protein-truncating variants
SCDC	Social Communication Disorders Checklist
SD	Standard Deviation
SE	Standard Error
SNP	Single Nucleotide Polymorphism
SNV	Single Nucleotide Variant
SQ	Systemising Quotient
SSRI	Selective serotonin reuptake inhibitors
STRATOS	STRengthening Analytical Thinking for Observational Studies
TFH	T follicular helper
TGF	Transforming growth factor
TH	T-Helper
TREG	T- Regulatory
UC	Ulcerative Colitis
UKB	UK Biobank
WISC	Wechsler Intelligence Scale for Children

Publications

Work carried out in this thesis contributed to the following publications and preprints:

Dardani C, Schalbroeck R, Jones H, Strelchuk D, Hammerton G, Croft J, Madley-Dowd P, Sullivan S, Zammit S, Selten JP, Rai D. Childhood trauma as a mediator of the association between autistic traits and psychotic experiences: evidence from the ALSPAC birth cohort. PsyArXiv; 2021; doi: https://psyarxiv.com/ed8m5/ (Currently under review at *Schizophrenia Bulletin*)

CRediT author contribution statement:

Dardani C: Conceptualisation, Methodology, Software, Formal Analysis, Investigation, Writing-original draft, Visualisation; Schalbroeck R: Conceptualisation, Methodology, Writing-original draft; Jones H: Conceptualisation, Methodology, Software, Writing- review & editing, Supervision; Strelchuk D: Methodology, Writing- review & editing, Supervision; Hammerton G: Methodology, Software, Writing- review & editing; Croft J: Methodology, Writing- review & editing; Madley-Dowd P: Methodology, Writing- review and editing; Sullivan S: Conceptualisation, Methodology, Writing- review & editing, Supervision; Zammit S: Conceptualisation, Methodology, Writing- review & editing, Supervision; Selten JP: Conceptualisation, Methodology, Writing- review & editing, Supervision; Rai D: Conceptualisation, Methodology, Writing- review & editing, Supervision.

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Sadik A*, **Dardani C***, Pagoni P, Havdahl A, Stergiakouli E, Grove J, The iPSYCH Autism Spectrum Disorder Working Group, Khandaker GM, Sullivan SA, Zammit S, Jones HJ, Davey Smith G, Dalman C, Karlsson H, Gardner RM, Rai D. Parental inflammatory bowel disease and autism in the offspring: Triangulating the evidence using four complementary study designs. medRxiv; 2021; doi: https://www.medrxiv.org/content/10.1101/2021.06.09.21258393v1.full (Accepted: *Nature Medicine*)

CRediT author contribution statement:

Dardani C*: Conceptualisation, Methodology, Software, Formal Analysis, Investigation, Writing-original draft, Visualisation, Supervision; Sadik A*: Formal Analysis, Investigation, Writing-original draft; Pagoni P: Methodology, Writing- review & editing; Havdahl A: Methodology, Writing- review & editing; Stergiakouli E: Methodology, Writing- review & editing; Grove J: Methodology, Resources, Writing- review & editing; the iPSYCH Autism Spectrum Disorder Working Group: Resources; Khandaker GM: Methodology, Writing- review & editing; Sullivan SA: Methodology, Writing- review & editing; Zammit S: Methodology, Writing- review & editing; Jones HJ: Methodology, Software, Writing- review & editing; Davey Smith G: Methodology, Writing-review & editing; Dalman C: Methodology, Resources, Writing- review & editing; Karlsson H: Methodology, Writing- review & editing; Gardner RM: Methodology, Software, Formal Analysis, Investigation, Writing- original draft, Supervision; Rai D: Conceptualisation, Methodology, Writing-original draft, Supervision. *Joint first authors.

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Dardani C, Robinson JW, Zheng J, Sadik A, Pagoni P, Stergiakouli E, Gardner RM, Havdahl A, Grove J, The iPSYCH Autism Spectrum Disorder Working Group, Davey Smith G, Sullivan SA, Leppert B, Jones HJ, Zammit S, Khandaker GM, Rai D. Immunological pathways underlying autism: Findings from Mendelian randomization and genetic colocalisation analyses. medRxiv; 2022; doi: https://www.medrxiv.org/content/10.1101/2022.02.16.22271031v1 (Currently under review in *Biological Psychiatry*)

CRediT author contribution statement:

Dardani C: Conceptualisation, Methodology, Software, Formal Analysis, Investigation, Writing-original draft, Visualisation; Robinson J: Methodology, Software, Writing- review & editing, Supervision; Zheng J: Methodology, Writing- review & editing; Sadik A: Methodology, Writing-review & editing; Pagoni P: Methodology, Writing- review & editing; Stergiakouli E: Methodology, Writing- review & editing; Havdahl A: Methodology, Writing- review & editing; Grove J: Methodology, Resources, Writing- review & editing; The iPSYCH Autism Spectrum Disorder Working Group: Resources; Davey Smith G: Methodology, Writing- review & editing; Sullivan SA: Methodology, Writing- review & editing, Supervision; Leppert B: Conceptualisation, Methodology, Writing- review & editing; Jones HJ: Conceptualisation, Methodology, Writing- review & editing, Supervision; Zammit S: Methodology, Writing- review & editing, Supervision; Khandaker GM: Conceptualisation, Methodology, Writing- review & editing; Rai D: Conceptualisation, Methodology, Writing- review & editing; Supervision.

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Additional publications and preprints not included in the thesis:

Ly A, Leppert B, Rai D, Jones HJ, **Dardani C**, Stergiakouli E. Genetic liability to rheumatoid arthritis on autism and autistic traits: polygenic risk score and Mendelian randomization analyses. *Translational Psychiatry*, 12, 1–6 (2022); https://doi.org/10.1038/s41398-021-01772-2

Dardani C, Riglin L, Leppert B, Sanderson E, Rai D, Howe LD, Davey Smith G, Tilling K, Thapar A, Davies N, Anderson E, Stergiakouli E. Is genetic liability to ADHD and ASD causally linked to educational attainment? *International Journal of Epidemiology*, 50, 6, 2011-2023 (2021); https://doi.org/10.1093/ije/dyab107

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Disease. bioRxiv; 2020; doi: https://doi.org/10.1101/2020.04.15.043380 (Currently under review *Translational Psychiatry*)

Leppert B, Riglin L, Wooton RE, **Dardani C**, Thapar A, Staley JR, Tilling KM, Davey Smith G, Thapar A, Stergiakouli E. The effect of Attention Deficit/Hyperactivity Disorder on physical health outcomes: A two-sample Mendelian randomization study. *American Journal of Epidemiology*, 190, 1047-1055 (2020); https://doi.org/10.1093/aje/kwaa273

♦

"[Comorbidity] is simply a descriptor of an empirical statistical phenomenon that has no meaning in itself. It is of scientific and clinical interest only because it raises important questions about possible underlying mechanisms. But, for that reason, it constitutes the beginning, and not the end of a research endeavour."

Michael Rutter, Comorbidity: Concepts, claims and choices, 1997: 268.

Chapter 1

Introduction

Autism spectrum disorder (henceforth 'autism[1]') and psychosis spectrum conditions (henceforth 'psychosis'[2]), are typically chronic conditions that influence multiple areas of functioning and are associated with substantial difficulties for the individuals, their families and the societies worldwide. Although currently conceptualised as diagnostically distinct, their definitions have been historically intertwined (section 1.1), and there is increasing evidence suggesting that these conditions co-occur at higher rates than would be expected by chance, present phenotypic and genetic overlaps, and share environmental risk factors (section 1.2). Several aetiological models on the reasons underlying the autism-psychosis co-occurrence have been hypothesised, but research evidence so far has been sparse (section 1.3). A comprehensive approach utilising distinct study designs with different and unrelated sources of strengths and bias is necessary in order to further our current understanding on the reasons underlying the autism-psychosis co-occurrence and ultimately aid towards improving diagnostic and intervention strategies for the affected individuals (sections 2.1-2.3).

In this doctoral thesis, I applied a combination of study designs utilising phenotype and genotype data to assess evidence on two overarching aetiological models for the autism-psychosis co-occurrence: (i) causal pathways, (ii) shared risk factors.

♦

[1] Throughout the text the terms autism and autistic people/individuals are used, in line with recent evidence suggesting that these terms are preferred in the autistic community and are less stigmatising[366–368].

[2] The term is used in line with increasing evidence proposing a psychosis continuum, with schizophrenia lying at the severe end and psychotic experiences spanning to the general population [3,74]. A detailed discussion on the concept can be found in section 1.1.2.

1.1 The phenomenology and diagnostic concepts of autism and psychosis: History and current perspectives.

Autism and psychosis are defined by core features that are seemingly distinct. Autism is a neurodevelopmental condition currently characterised by two core features: i) difficulties in social communication and interaction, and ii) repetitive behaviours and restricted interests[1]. Social communication and interaction difficulties frequently encompass verbal as well as non-verbal aspects of communication and emotional reciprocity, whereas restricted interests and behaviours frequently include motor and verbal stereotyped or ritualised behaviour, fixated interests, resistance to change and hypo- or hyper- responsivity to sensory stimuli[1,2]. Core features of autism typically arise early in development and persist into adulthood, influencing multiple areas of functioning[2]. In contrast to autism, psychosis is predominantly defined by the presence of hallucinations and delusions, typically manifesting in late adolescence and early adulthood[1,3]. Hallucinations are perceptions in any sensory modality experienced by the individual, in the absence of external stimuli, whereas delusions are fixed beliefs that are firmly held by the individual regardless of the presence of conflicting evidence[1]. Despite apparent differences in the core features of autism and psychosis, diagnostic concepts relating to the two conditions have been historically intertwined.

1.1.1 History

The term '*autism*'[3] was introduced in 1911 by Eugen Bleuler to describe one of the core features of a newly defined nosological entity termed '*schizophrenia*'[4,5]. *Schizophrenia*, encompassed a group of conditions characterised by loosening of Associations (disorganised speech and thought), Ambivalence (inability to process information and act accordingly), Affective blunting (limited emotional expression) and *Autism* (withdrawal from reality and inappropriate affect)[4–6]. For almost over 30 years after its initial introduction, the term '*autism'* was used to describe adults and children presenting excessive fantasy, disconnect from reality and hallucinations[7]. The aetiology of *schizophrenia* and its feature, *autism*, were postulated to be attributed to altered brain function

[3] Terms italicized throughout the section (1.1.1) represent nosological entities that are no longer in use, or their content does not correspond to contemporary diagnostic concepts.

(influenced by observations on the links between syphilis and general paresis) as well as family dynamics and especially mother-child interactions (influenced by psychoanalytic theory)[6–8].

In 1943, Leo Kanner introduced '*autistic disturbances of affective contact*' or '*infantile autism'* to characterise a constellation of behavioural features he observed in 11 children: preference for isolation, limited emotional responsiveness and repetitive patterns of behaviours[5,7]. Despite this, the term *autism* was used interchangeably with the terms *childhood schizophrenia/psychosis* until the late 1960s, when there was a shift from case reports to epidemiological studies[3,7,9].

In the early 1970s, amassing evidence from cross-sectional and longitudinal investigations suggested that *schizophrenia* and *autism* were distinct with regards to their phenomenology and course. *Childhood schizophrenia* (as it was defined then) with an onset before the age of 3, appeared to be characterised by persistent difficulties in social interaction, language development and repetitive behaviours, while there was no evidence to suggest the presence of hallucinations or delusions[9,10]. These core difficulties seemed to be qualitatively different from features characterising other conditions e.g., specific language impairment, and their course across development appeared to be relatively stable[11,12]. On the contrary, *adolescent schizophrenia* with an onset after the age of 11, appeared to present several similarities to adult-onset *schizophrenia*, including hallucinations, delusions and a course characterised by remissions and relapses[9,10,12]. In light of this evidence, DSM-III (Diagnostic and Statistical Manual of Mental Disorders) introduced *autism* as a distinct from *schizophrenia* diagnostic entity. Specifically, *autism* as a criterion for the diagnosis of *schizophrenia* was removed, while *childhood schizophrenia* was no longer included in the diagnostic system (12,19). Instead, a new diagnostic category was introduced: *'Pervasive developmental disorders',* encompassing '*infantile autism'*, '*childhood onset pervasive developmental disorder*' and '*atypical pervasive developmental disorder'*[13].

After DSM-III, the diagnostic concepts of *autism* and *schizophrenia* evolved independently but almost in parallel. Increasing research evidence on the phenotypic manifestation and aetiology of the two diagnostic concepts, challenged their homogeneity and boundaries, leading to their current conceptualisation as spectra[3,14].

1.1.2 Current perspectives

1.1.2.1 From autism to the autism spectrum

Autism, as currently conceptualised, is among the most common neurodevelopmental conditions with an estimated worldwide prevalence of almost over 1.5% in developed countries[15,16]. The condition seems to be diagnosed more frequently in males than females (male to female ratio 4:1; please see [17,18] for evidence on the potential reasons underlying this)[16]. Autism is among the leading causes of disability in children under the age of 5 and is associated with a substantial burden for the individuals, their families and the societies[19]. Emerging evidence suggests that approximately 55% of autistic adults are diagnosed with at least one comorbid mental health condition[20], while a substantial proportion of autistic individuals present with a comorbid medical condition (e.g., epilepsy, 14.2%[21]). The increased prevalence of mental health and medical conditions in the autistic population has been associated with increased rates of polypharmacy (i.e., prescription of two or more medications), poor life outcomes and poor quality of life[22–25].

Autism is diagnosed on the basis of the presence of core social and non-social features (section 1.1). However, there is amassing evidence suggesting that the manifestation of these features is not homogeneous across autistic individuals and that they vary widely in terms of their quantity, quality and trajectories[1,14,26–28]. In addition to this, autistic individuals seem to present highly variable cognitive and verbal abilities. Specifically, it is estimated that 30-50% of autistic individuals have an intellectual disability (IQ≤70)[29–31], while approximately 20-30% are minimally verbal (absence or limited use of functional language)[32,33]

Evidence on the substantial heterogeneity in terms of behavioural, cognitive and verbal characteristics of autistic individuals, reflects the highly heterogeneous aetiology of the condition[34]. Autism is currently considered of multifactorial aetiology and there is no single unifying cause explaining the condition[34]. A recent meta-analysis of twin studies provided a heritability estimate of 64-91% suggesting a strong genetic component[35]. The latest autism genome-wide association study (GWAS) identified common genetic variants (i.e., genetic variants with a population frequency above 0.01) robustly associated with the condition spanning at five loci, and indicated that aggregates of multiple

common genetic variants (polygenic risk scores; PRS) explain variance in the phenotype in a dose-dependent way (although proportion of variance explained was small; mean variance across PRSs ≈2.5%)[36]. Rare genetic variation (e.g., copy number variants- CNVs, single nucleotide variants- SNVs, de novo protein truncating variants-PTVs) has been also found to be implicated[37]. According to emerging evidence, rare and common variation contribute to the autism phenotype in an additive way and through distinct mechanisms of action [38]. Finally, early life environmental factors have been found to be involved in the aetiology of autism, with a recent umbrella review of meta-analyses of observational studies, providing evidence for advanced maternal age, maternal hypertension and obesity, maternal SSRI use during pregnancy and pre-eclampsia[39], while there was some evidence to suggest a role of maternal infections during pregnancy[39].

The aetiological heterogeneity of autism has not only been identified across autistic individuals but also within individuals. Specifically, factor analytic studies of core autism features support a two-factor model, social communication and repetitive behaviours/restricted interests, while in samples of autistic twins the phenotypic and genetic correlations between the two domains have been found to be low or modest[40–42]. This suggests that there are distinct environmental and genetic contributions on the two core features of autism, and it has been proposed that it can have important implications in comorbidity research (this is additionally discussed later in this section)[43].

Evidence on the heterogeneity of the autism diagnostic category has been complemented by research focusing outside its boundaries, on sub-threshold features. A number of twin studies have indicated that twin pairs present high concordance for broader sub-threshold features of the condition[44], while evidence from family studies has suggested that parents and siblings of autistic individuals tend to also present sub-threshold features ('broad autism phenotype'- term used when measured in families [45]). In fact, there is evidence to suggest that the severity of the features in first degree relatives is positively correlated with the severity of the autistic individual's phenotypic expression[46–48]. Extensions of this stream of research to general population samples that are not necessarily genetically related (i.e., they are not parents/siblings of autistic individuals), has suggested that these

sub-threshold features ('autistic traits'- term used when measured in the general population) span to the general population, forming a continuum of severity on which autism lies at the extreme end[48–52].

Autistic traits are considered mild expressions of social and non-social features of the condition, such as: pragmatic language difficulties, difficulties in reciprocal social interaction, limited ability to identify and respond to others' mental states, rigid behaviour, circumscribed interests[53]. Several tools have been developed and used to aid measurement of social and non-social autistic traits, including the Social and Communication Checklist (SCDC[50]), the Children's Communication Checklist[54], the Autism Quotient (AQ[55]) and its extensions the Empathy Quotient (EQ) and the Systemising Quotient (SQ; systemising is the tendency to understand and analyse patterns and is considered to be a non-social autistic trait)[56].

Autistic traits have substantial aetiologic overlap with autism, as there is evidence suggesting that they present associations with autism-related environmental risk factors[57], while they have strong genetic correlations and polygenic associations with autism and autism-related comorbidities[43,58]. Furthermore, in line with research in samples of autistic individuals, they seem to be influenced by distinct genetic and environmental factors as suggested by twin and polygenic approaches in the general population[41,43,59].

Evidence on the heterogeneity autism, in terms of phenotypic presentation and aetiology across as well as within individuals, in combination with findings suggesting that autism lies at the extreme end of a continuum of severity spanning to the general population, led to the conceptualisation of the condition as a spectrum (Figure1.1)[52].

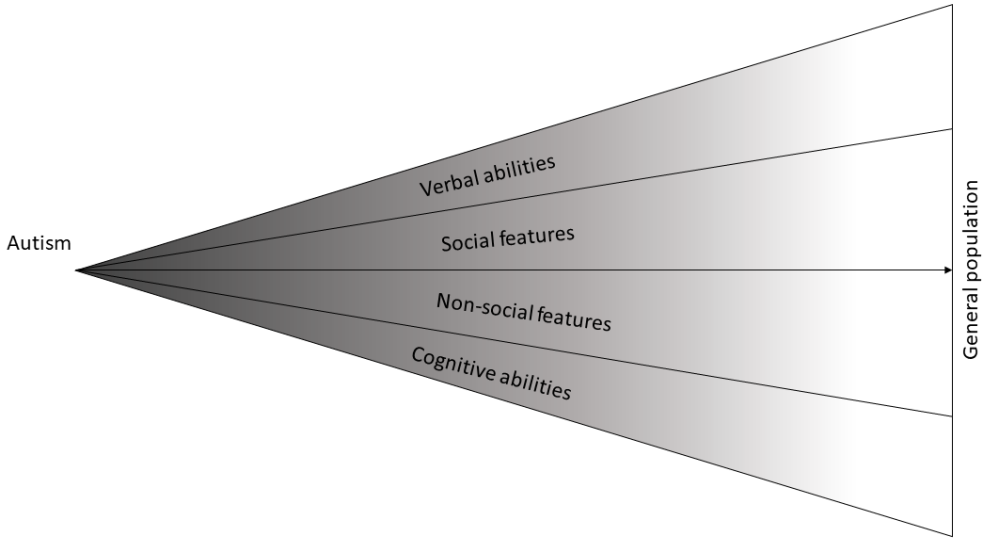

Figure 1.1 The autism spectrum as conceptualised by L. Wing who paralleled the heterogeneity and continuity of autism with a spectrum of coloured light[52].

Features of autism form a continuum of severity that spans to the general population, while they seem to be aetiologically independent[41,48,369]

1.1.2.2 From schizophrenia to the psychosis spectrum

Schizophrenia, as currently conceptualised in DSM-5, is a chronic condition with an estimated lifetime prevalence of approximately 0.87%[60]. The condition is diagnosed on the basis of the presence of psychotic symptoms such as hallucinations, delusions (positive symptoms), thought and speech disorganisation (disorganised symptoms) as well as anhedonia, social withdrawal, affective blunting (negative symptoms), and some cognitive features (e.g., working memory deficits)[61]. The condition is diagnosed slightly more often in males than females (male to female ratio 1.4:1), has a typical onset during late adolescence and early adulthood (approximately 20-25 years) and it is typically characterised by an episodic course which, however, is highly variable across individuals[61]. Schizophrenia is one of the leading causes of disability worldwide[60,62], and has been associated with lower life expectancy (≈20 years below general population) and poor quality of life[63,64].

Schizophrenia is of multifactorial aetiology and several genetic and environmental risk factors have been implicated. Evidence from twin studies suggests that it has a strong genetic component, with an estimated heritability of approximately 80%[65]. This has been further supported by available GWASs, with the latest one identifying 294 common genetic variants spanning at 270 loci, which explained approximately 2.6% of the variance (7.7% using PRSs including common variants with a p-value bellow 0.05)[66]. Rare variants have been also found to have a central role in schizophrenia, and there is evidence to suggest that that they have a substantial disruptive effect in genes associated with neurodevelopmental pathways and neurodevelopmental disorders[67–69]. Furthermore, several environmental risk factors have been implicated, with a recent umbrella review of meta-analyses of observational and Mendelian randomization (MR) studies providing evidence for history of birth complications, cannabis use and traumatic life events[70]. Other environmental risk factors for schizophrenia include urbanicity and migration[71], while there is amassing observational and MR evidence suggesting a causal role of atypical immune response[72,73].

Despite the current conceptualisation of schizophrenia as a discrete diagnostic entity, there is increasing evidence suggesting that the condition might actually lie at the extreme end of a continuum of psychosis severity[74]. Psychosis refers to a constellation of symptoms (section 1.1) that co-occur in the context of a number of conditions beyond schizophrenia (although they seem to have the highest frequency, severity and persistence in schizophrenia[75–77]). For example, it is estimated that 58% of individuals diagnosed with bipolar disorder and 39% of individuals with major depression have a lifetime history of psychotic symptoms[78,79], while they seem to manifest even in the context of medical conditions such as Parkinson's disease in which it is estimated that approximately 26% of diagnosed individuals have experienced psychotic symptoms[80].

In addition, sub-threshold positive psychotic experiences (hallucinations or delusions that occur outside the context of a psychiatric condition) seem to be frequent in the general population, having a median lifetime prevalence of 5.5%[81]. Psychotic experiences are estimated to have a relatively high prevalence in children and adolescents (median prevalence: 17% in children aged 9-12; 7.5% in adolescents aged 13-18 years[82]- although, it is important to note that there is a high variability in

prevalence estimates across studies due to different assessment methods e.g., self-reports, semi-structured questionnaires) and they are usually transient[83,84]. However, experiences that are accompanied by distress for the individual and are persistent have been found to be associated with transition to psychotic disorders[85].

Psychotic experiences present a substantial aetiologic overlap with schizophrenia. They seem to have a strong genetic component, with their heritability ranging between 15% to 59% (depending on type of experience) as estimated by twin studies[86]. The latest GWAS of psychotic experiences (any) in adulthood, despite identifying only two common genetic variants strongly associated with the phenotype, suggested genetic correlations with schizophrenia (r_G= 0.21; p= $7*10^{-05}$) [87]. Importantly, the study identified a high loading of CNVs previously implicated in schizophrenia, in individuals reporting psychotic experiences and particularly distressing psychotic experiences, consistent with existing observational evidence suggesting that psychotic experiences that are more distressing or more frequently recurring distress are more closely related to schizophrenia aetiology than psychotic experiences that are not distressing or frequent[87]. In addition, a recent GWAS of psychotic experiences and negative symptoms in adolescence did not find evidence of a genetic correlation with schizophrenia or other mental health conditions, indicating that adolescent psychotic experiences (and therefore potentially transient) do not index schizophrenia liability as strongly as adult psychotic experiences (and therefore potentially persistent experiences)[88]. However, it is worth noting that in this study persistence-transience of psychotic experiences was not directly tested, while additionally it is unknown the extent to which these findings were due to lack of power in the adolescent sample[88]. Psychotic experiences have been also found to be associated with known risk factors for schizophrenia, including birth complications, cannabis use, traumatic life events, inflammation and atypical immune response[89–94].

In summary, evidence suggesting that psychotic symptoms are not specific to schizophrenia, but frequently occur in the context of other conditions, in combination with evidence indicating that psychotic experiences are common in the general population and transient, but the degree of their

persistence and distress for the individual are defining factors for transition to psychotic disorders, led to the conceptualisation of the psychosis spectrum[3,74]. In this context, psychosis forms a continuum of severity distributed across the population, in which schizophrenia lies at its severe end, while psychotic experiences span to the general population (Figure 1.2).

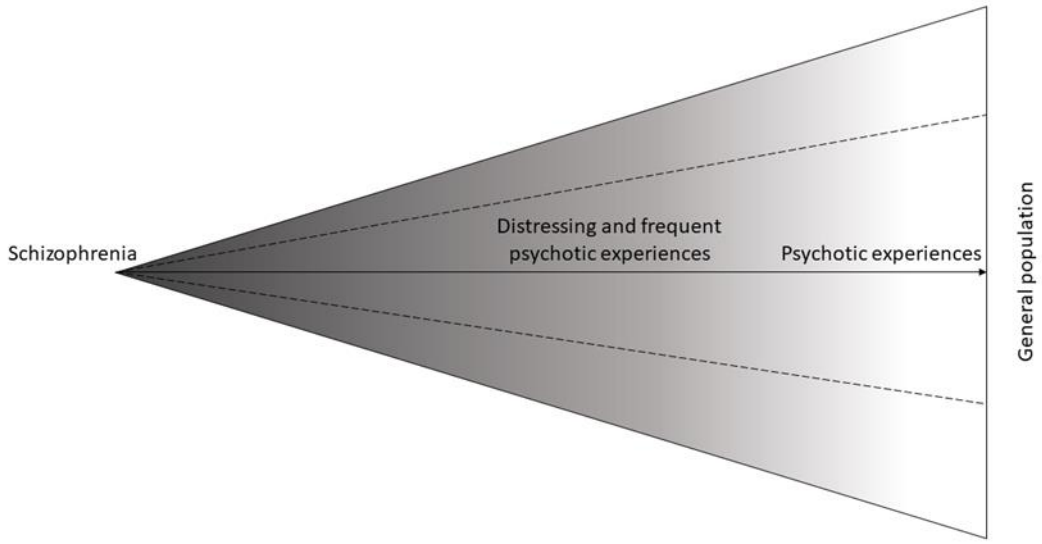

Figure 1.2 The psychosis spectrum in which schizophrenia lies at the severe end, and psychotic experiences span to the general population[3,74].

The spectrum includes several conditions beyond schizophrenia[3,74]. In addition there increasing research evidence suggesting that psychotic experiences comprise dimensions that show low to moderate correlations between them and potentially have distinct aetiological risk factors- denoted by the dotted lines in the figure[370,371]. It was beyond the aims of this thesis to investigate other conditions residing in the psychosis spectrum or utilise current understanding on the dimensions of psychotic experiences in the context of the studies conducted. However, details on how they might impact the findings of the present thesis and their potential utility for future research in the area of autism-psychosis comorbidity can be found in the Discussion section.

1.1.3 Section summary

Autism and psychosis, despite being historically intertwined, are currently conceptualised as two distinct spectra. The autism spectrum encompasses difficulties in aspects of social communication and interaction, as well as non-social features, including repetitive behaviours and sensory abnormalities, that arise early in childhood and persist to adulthood. Features of autism form a continuum of severity that spans to the general population, and they are increasingly recognised to be aetiologically independent. On the other hand, the psychosis spectrum is predominantly characterised by hallucinations and delusions that arise typically in adolescence and form a continuum of severity, on which schizophrenia lies at the severe end of the continuum, whereas transient, of no clinical significance, psychotic experiences span to the general population.

♦

1.2 At the intersection of autism and psychosis: A review of the evidence

Despite the diagnostic distinction and the apparent phenotypic differences between autism and psychosis, their relationship is being revisited in the light of evidence suggesting that they co-occur more frequently than expected by chance, have some phenotypic similarities, present genetic overlaps and share some environmental risk factors.

1.2.1 Co-occurrence along the autism-psychosis spectra

At the diagnostic level, the latest umbrella review of systematic reviews (Nstudies= 14) and meta-analyses (Nstudies= 12) of observational studies on the prevalence of psychiatric diagnoses in individuals with autism, suggested that the prevalence of psychosis (studies included had used definitions of DSM-5 diagnostic category 'schizophrenia spectrum and other psychotic disorders', or ICD-10 category 'Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders') ranged from 4% to 11.8% across meta-analyses (the range was much broader across systematic reviews)[95]. Psychosis prevalence estimates seem to fluctuate substantially across meta-analyses, and age appears to be a central factor for this. Specifically, Lai et al.[96] in a meta-analysis of studies using mixed age samples, reported a prevalence of 4% (95%CIs: 3-5; Nstudies=49). On the contrary, Lugo-Marin et al.[20] in a meta-analysis of studies in adult samples reported a prevalence estimate of 11.8% (95%CIs: 7.7-17.6; Nstudies=17), which seems to be in line with the latest published meta-analysis of studies in adult samples by Varcin et al.[97], reporting a prevalence estimate of 9.4% (95%CIs: 7.52, 11.72; Nstudies= 45). This discrepancy in prevalence estimates between studies of mixed age samples and studies restricted to adults, is potentially explained considering that the onset of psychotic disorders is typically in adulthood[61,97]. Overall, it seems that across studies, the estimated prevalence of psychosis in autistic individuals is higher than estimated in the general population (3% lifetime prevalence for all psychotic disorders and 0.87% for schizophrenia[60]).

Beyond their co-occurrence at the level of diagnosis, there is evidence suggesting that autism and psychosis tend to co-occur at a sub-threshold level as well. Specifically, a meta-analysis of cross-sectional, case-control and cohort studies investigating the prevalence of psychotic experiences in individuals with autism diagnoses and autistic traits, reported a prevalence estimate of 24% (95%CIs:

14-34; Nstudies= 9), a substantially higher prevalence than the general population (median lifetime prevalence: 5.5% and 17.7% in children/adolescents[81,82])[98]. However, the study presented several methodological limitations with the most important being the definition of psychotic experiences. Specifically, the authors included some studies that used very vague and broad terms to describe psychotic phenomena, leading, for example, to a pooled prevalence of delusions of 45% (95%CIs: 0-99), while a number of studies were from dually diagnosed clinical populations, i.e., populations with autism diagnosis and co-occurring mental health conditions including schizophrenia. At the same time, a meta-analysis of studies investigating the prevalence of autism diagnoses in individuals at clinical high-risk for psychosis/ at risk mental state (the term captures individuals that present prodromal symptoms of psychosis that are at risk but do not necessarily transition to psychosis[99]) reported a prevalence estimate of 11.6% (95%CIs: 2.1–44.2; Nstudies=4)[100]. However, this study was also hampered by methodological limitations with the most important being the small number of studies available. Specifically, two of the studies included in the analyses had overlapping samples which means that only three studies would be eligible for analyses (this has been discussed extensively in [101]). Finally, an increased prevalence of autistic traits in individuals with psychosis has been reported by a recent systematic review (1% to 52%; Nstudies=7)[102], although evidence from meta-analytic studies is necessary in order to reach more robust conclusions. Overall, there is some evidence to suggest that autism and psychosis frequently co-occur at a sub-threshold level, but at the moment it seems difficult to derive conclusions considering the limited number of studies available and the methodological limitations of the available meta-analytic studies so far[101].

1.2.2 Phenotypic overlap

Several parallels have been drawn between phenotypic features of autism and psychosis. It has been proposed that the DSM-5 criterion for autism 'deficits in social emotional reciprocity' can be comparable to the DSM-5 criterion for schizophrenia spectrum and other psychotic disorders 'diminished emotional expression'[1,103,104]. Similarly, it has been proposed that language delay in autism can be comparable to speech poverty in psychosis, and features of catatonia (mutism,

negativism, stereotypy, stupor) can occur in both conditions (it is actually a specifier in both diagnostic categories in DSM-5)[1,103–105].

On this basis, a number of studies aimed at assessing the potential phenotypic overlaps between autism and psychosis, in terms of behavioural features, cognition, brain structure and function. A meta-analysis of studies (Nstudies= 26) investigating the correlation between autistic and schizotypal traits in general population samples, found evidence of a moderate correlation between autistic traits and schizotypal traits (r= 0.48; 95%CIs:0.43-0.53) and particularly negative schizotypal traits (r=0.54; 95%CIs: 0.48-0.59)[106]. These estimates are comparable to estimates from a longitudinal general population study of 5,000 twins which found modest correlations between autistic traits and negative psychotic experiences (r= 0.47), and weak correlations with positive psychotic experiences (r= 0.14) at age 16[107]. Furthermore, similarities have been found in terms of social cognition between autistic individuals and individuals with psychosis. A meta-analysis of studies directly comparing performance in tasks assessing theory of mind (defined as the ability to attribute mental states to others[108]), and emotional processing between autistic individuals and individuals with psychosis (Nstudies= 33), identified comparable patterns of difficulties between the two groups[109]. In addition, evidence from neuroimaging investigations suggests that the two conditions share some features, with the largest to date structural and functional magnetic resonance imaging study (sMRI and fMRI respectively; Npsychosis=600; Nautism=1,000; Ncontrols= 1,700), identifying reductions in grey matter volume and density of the occipital gyrus and cerebellum as well as decreased connectivity within default mode and sensorimotor regions in both autism and psychosis[110]. It is important to note however, that several features unique to each condition were also identified[110].

1.2.3 Genetic overlap

There is increasing evidence suggesting that autism and psychosis might have shared genetic underpinnings. Specifically, family history of schizophrenia has been consistently found to be associated with offspring autism across a number of nationwide register-based studies (Denmark: N= 18,148; OR=4.8; 95%CIs, 2.4-9.5; Sweden: N= 475,965; OR= 2.9; 95%CIs: 2.5-34; Israel, N= 436,311, OR= 12.1; 95%CIs: 4.5-32.5)[111,112]. This has been further supported by recent evidence from

the Simons Simplex (SSC) collection and the Psychiatric Genomics Consortium (PGC) autism sample (N= 6,454 family trios and quads), suggesting that autistic probands seem to over-inherit schizophrenia risk alleles (as captured by PRS) from their parents compared to their unaffected siblings[38].

The central role of common genetic variation in both autism and psychosis has been further emphasised by increasing evidence suggesting that autism presents strong genetic correlations with schizophrenia (r_G= 0.21, p= $1*10^{-05}$; estimates based on Linkage disequilibrium-score regression analyses using summary-level data; LDSC), as well as psychotic experiences (r_G= 0.39; P = $2*10^{-04}$; estimates based on LDSC analyses using summary-level data)[66,87]. In addition, there is evidence suggesting polygenic associations between autism and psychosis. Common variant polygenic risk for autism has been found to be associated with psychotic experiences and particularly distressing psychotic experiences in the UKBiobank (Ncases= 2,146, Ncontrols= 122,066; OR= 1.10; 95%CIs: 1.05-1.15; p= $2*10^{-05}$)[87], while common variant polygenic risk for schizophrenia has been found to be associated with autism diagnosis in the iPSYCH sample (Ncases= 11,202, Ncontrols= 22,555)[36] as well as social communication and pragmatic language difficulties in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (N= 5,100–6,952)[113].

Beyond common genetic variation, autism and psychosis seem to present overlaps in terms of rare genetic variation. Specifically, autism and schizophrenia appear to present several overlapping CNVs (deletions or duplications of gene regions), with one of the most consistently replicated being the deletion at 22q11.2[114]. Individuals with 22q11.2 deletion (DiGeorge/velocardiofacial syndrome) present a range of congenital abnormalities and physical health conditions including heart defects, cleft palate, autoimmune conditions, gastrointestinal problems as well as autistic features, and are at increased risk of schizophrenia later in life[115,116]. Other overlapping CNVs between autism and schizophrenia involve 7q11.23, 15q11.2 and 16p11.2, which have been found to be implicated in synaptic function and immune response[117–119]. A number of these CNVs have been also found to be strongly associated with distressing psychotic experiences[87]. Several other types of rare variation (e.g.,

SNVs, PTVs) have been implicated in the aetiology of both autism and psychosis, while there is increasing research on potentially shared epigenetic alterations in both conditions[120–122].

1.2.4 Shared environmental risk factors

Beyond genetic overlaps, autism and psychosis seem to present some overlap in terms of environmental risk factors. Perinatal factors seem to be the most consistently identified risk factors for both autism and psychosis, and particularly obstetric complications including maternal hypertension, pre-eclampsia, hypoxia, placental complications and rhesus incompatibility[123]. In an umbrella review of 41 meta-analyses and MR studies investigating risk factors for psychosis, history of obstetric complications was robustly associated with psychosis (OR= 1.97; 95%CIs: 1.55-2.50), while in an umbrella review of 46 meta-analyses, factors related to obstetric complications such as maternal chronic hypertension (OR=1.48; 95%CIs: 1.29-1.70) and gestational hypertension (OR= 1.37; 95%CIs: 1.21-1.54) were found to be robustly associated with autism[39,70].

Furthermore, there is increasing interest in the potential role of inflammation and immune response in the aetiology of autism and psychosis. The latest meta-analysis of studies on prenatal and perinatal risk factors for psychosis (N=152), indicated a robust association between maternal infections during pregnancy and offspring psychosis (OR= 1.27; 95%CIs: 1.06-1.53)[124], while a meta-analysis of 15 cohort and case-control studies, found evidence of an association between maternal infections during pregnancy and offspring autism (OR= 1.13; 95%CIs: 1.03–1.23)[125]. In addition, there is some evidence from population-based cohorts suggesting associations between elevated levels of the inflammatory marker C-Reactive protein (CRP) in maternal serum during pregnancy and offspring schizophrenia later in life (N= 1,554; OR= 1.31; 95%CIs: 1.10-1.56)[126] as well as offspring autism (N= 1,354; OR=1.12, 95%CIs:1.02–1.24)[127]. Family history of autoimmune conditions, particularly type 1 diabetes and psoriasis, has been also found to be associated with increased risk of offspring psychosis as well as offspring autism[128,129], which provides an indication of some potentially shared underlying immunological pathways for both conditions. This seems to be at least partially supported by case-control studies suggesting that autistic individuals and individuals with psychosis present some similarities in terms of their immune profiles, e.g., elevated levels of serum Interleukin-6 (IL-

6)[130]. However, it is difficult to infer from these studies whether similarities in terms of immune profiles suggest shared causal immunological pathways, considering their small sample sizes and the possibility of reverse causation and selection bias. Further research in larger samples, systematically investigating immunological markers and pathways, and using methodological approaches minimising reverse causation and confounding bias, is necessary in order to elucidate whether and which immune pathways could be causally implicated in both autism and psychosis.

1.2.5 Section summary

Autism and psychosis seem to co-occur at elevated rates at a diagnostic as well as sub-threshold level. The two conditions seem to share some phenotypic features in terms of behaviour, cognition, brain structure and function. In addition, they seem to present a substantial genetic overlap and several shared common and rare variants have been identified. In terms of environmental risk factors, there is evidence suggesting that obstetric complications are risk factors for both autism and psychosis, while the potential role of shared immunological pathways in both conditions is still questionable.

♦

1.3 Aetiological models of the autism-psychosis co-occurrence

Little is currently known on the reasons underlying the autism-psychosis co-occurrence and several aetiological models have been proposed. These models can be categorised into four overarching themes, proposing that the two conditions: (i) co-occur due to chance or bias (chance model), (ii) are the same condition (multiformity model, stages model), (iii) form a condition with unique features (independence model, diametrical model), (iv) are distinct and they co-occur due to causal links and/or shared risk factors (causation model, associated liabilities model, multiple overlapping aetiologies model)[103,131,132].

In the context of the present thesis, I assessed evidence on the models hypothesising that the two conditions are distinct, and that their co-occurrence is explained due to causal pathways and/or shared risk factors (category iv). This decision was made considering that DSM-5 conceptualises autism and psychosis as distinct conditions, and that there are multiple potential clinical and research implications by investigating the causal links and shared risk factors of autism and psychosis. Specifically, there is increasing evidence suggesting that autistic individuals with psychosis are less likely to benefit from antipsychotic medication and they are more likely to receive higher doses of antipsychotic medication for prolonged periods of time[133,134]. Assessing evidence on the potential direct and indirect causal pathways between autism and psychosis may aid towards early and targeted intervention for the affected individuals. On the other hand, research into the potentially shared risk factors between the two conditions is a unique opportunity to elucidate common underlying aetiological processes and expand current understanding not only on their co-occurrence, but also on their aetiology[132].

1.3.1 Causal pathways

It has been proposed that autism and psychosis might be causally linked either via direct or indirect pathways. This implies that autism liability (as captured by traits or polygenic risk) might be a causal risk factor for psychosis (direct pathways), or factors related to autism liability might mediate the pathways to psychosis (indirect pathways)[103]. Assessing evidence on these potentially causal direct and indirect pathways has the potential to uncover early risk factors and lead to early and individualised interventions for the affected individuals.

The hypothesis of potentially causal links between autism and psychosis, seems to be supported by population-based cohort studies, in which since the temporal sequence of exposure and outcome is established, it is possible to assess evidence of causality[135]. Specifically, in a population-based cohort in Sweden, the Stockholm Youth Cohort, autism diagnosis before the age of 16, was found to be associated with psychosis later in life (N= 99,682; OR= 4.6; 95%CIs: 3.3-6.4)[136]. This evidence has been further supported by a population-based cohort in the UK, the ALSPAC cohort, in which associations were identified between autism diagnoses and psychotic experiences at age 12 (N= 5,359; OR= 2.81; 95%CIs: 1.07- 7.34)[137].

Beyond autism diagnosis, autistic traits in childhood seem to be associated with psychotic experiences in adolescence. Speech difficulties by age of 3 (maternal reports, N= 5,464) as well as persisting speech difficulties until the age of 7 (N= 5,453) were found to be associated with psychotic experiences at age 12 in the ALSPAC cohort (OR age 3= 1.58; 95%CIs= 1.19-1.20; OR age 7= 2.11; 95%CIs: 1.35-3.30) and more importantly, there was an association between the number of autistic traits in the domains of speech, social skills, repetitive behaviours until the age of 7 and psychotic experiences at age 12 (N= 5,468; OR= 1.66; 1.27-2.19)[138]. These findings were complemented by a more recent study in 5,359 participants of the ALSPAC cohort, in which social communication difficulties at age 8, coherence at age 9 and repetitive behaviours at age 6 were found to be associated with psychotic experiences by age 12 (OR= 1.11; 95%CIs: 1.03-1.19; OR= 1.16; 95%CIs: 1.08-1.24; OR= 1.11; 95%CIs: 1.04-1.19; social communication difficulties, coherence and repetitive behaviours respectively)[137]. In addition, in a population-based cohort study of 2,667 participants in Japan, there was evidence of an indirect pathway between autistic traits at age 10 and psychotic experiences at age 14, mediated by bullying victimisation at age 12[139].

Considering that psychotic experiences in childhood are typically transient and of no clinical significance (section 1.1.2), it is important to review evidence of associations between autistic traits and psychotic experiences after adolescence. There is currently only a limited number of studies utilising observational and polygenic approaches to assess the associations between autism liability and psychotic experiences until young adulthood. Specifically, in a sample of 9,282 twins from the

Child and Adolescent Twin Study in Sweden (CATSS) an association was identified between autistic traits in childhood and auditory hallucinations at age 18 (β= 0.09; 95%CIs: 0.05–0.13), which however attenuated substantially after adjusting for other neuropsychiatric conditions in childhood such as ADHD (β= −0.04; 95%CIs: −0.16–0.10)[140]. In addition, in a sample of 4,100 individuals from the ALSPAC cohort, autistic traits in childhood were found to be associated with psychotic experiences at age 18 (OR= 1.29; 95%CIs: 1.03-1.61), although the possibility of confounding bias in the identified associations was not explored[141]. Beyond approaches utilising phenotype data, there is also a small number of studies utilising genetic data and applying polygenic approaches. Specifically, autism PRS was found to be associated with psychotic experiences in adulthood in the UKBiobank (N= 124,212; OR= 1.10; 95%CIs: 1.05-1.15)[87], while in a sample of 2,096 participants of the IMAGEN study, there was evidence of an indirect pathway between autism PRS and psychotic experiences at age 18, mediated by peer problems between ages 14-18[142].

Overall, there is some evidence to suggest that the associations between autism liability and psychotic experiences extend beyond adolescence, however there are substantial limitations in the available studies so far, hampering attempts to understand the complex relationship between autism and psychosis. Firstly, in the case of observational studies, it is currently unknown whether the identified associations suggest causal relationships, or they are due to confounding. A particularly important confounder in the associations between autistic traits and psychotic experiences in adulthood could be genetic liability to schizophrenia. Schizophrenia presents strong genetic correlations with both autism (r_G= 0.24; p= 7*10^{-09}) and psychotic experiences (r_G= 0.21; p= 7*$^{-05}$) and therefore, could potentially distort their identified associations[87]. Secondly, in the case of polygenic approaches (for example approaches using autism PRS as the exposure), inferring causality can be challenged due to the influence of pleiotropy[143]. Pleiotropy is the phenomenon in which common genetic variants influence multiple traits via independent pathways[144] and therefore in a causal scenario, there is the risk that common genetic variants associated with the exposure, actually bypass it and drive associations through other genetically correlated traits[143,145]. PRS approaches cannot disentangle and account for the influence of pleiotropy which in the case of autism-psychosis associations can be particularly

relevant- for example, there is increasing evidence suggesting that autism and schizophrenia present strong genetic correlations and causal links with IQ[66,87,146,147](further details on this can be found in Chapter 2). Third, with regards to indirect pathways linking autism and psychosis, little is known on the potentially mediating role of one of the most consistently identified risk factors for psychosis, trauma in childhood[70,91].

There are two final considerations with regards to research on the potentially causal links between autism and psychosis and they are related to current conceptualisations of the two conditions. Firstly, studies investigating the associations between autism liability and psychotic experiences in adulthood have conceptualised autism liability as a unity and not as a constellation of aetiologically distinct social and non-social features (section 1.1.2). Incorporating this conceptualisation of autism in study designs is necessary in order to identify potentially unique links between specific autism features and psychosis later in life. Secondly, one of the ultimate aims of research into the associations between autism liability and psychotic experiences is to reflect on potentially subsequent risk of psychotic disorders. However, psychotic experiences are not necessarily associated with transition to psychotic disorders (section 1.1.2) and therefore any identified links between autism liability and psychotic experiences, do not necessarily reflect psychotic disorder risk. On this basis, it is important to assess the potential causal links of autism liability along the psychosis continuum, from psychotic experiences to schizophrenia.

1.3.2 Shared risk factors

It has been hypothesised that immunological processes might constitute a shared pathway to autism and psychosis[130]. According to this hypothesis, the phenotypic features that autism and psychosis share, could be a result of shared underlying causal immunological mechanisms[130]. In the case of psychosis, there is increasing understanding on the role of immune response in the aetiology of the condition and a number of causal immunological markers have been identified through a combination of observational, polygenic and MR approaches[73]. In comparison, little is currently known on the causal role of immune response in autism. On this basis, deriving conclusions on whether shared immunological processes underly autism and psychosis could be considered premature.

In the field of psychosis research, mounting evidence on the associations between maternal infections during pregnancy and offspring psychosis[124], along with evidence suggesting increased prevalence of autoimmune conditions in individuals with psychosis (approximately 45% based on a Danish registry-based study)[128] oriented investigations towards understanding the potential role of immune response in the aetiology of the condition. Longitudinal evidence from general population cohorts suggested associations between atopic conditions in childhood (until age 10) and psychotic experiences at age 13 (asthma: N= 49,23; OR= 1.33; 95%CIs: 1.04-1.69; eczema: N= 4,923; OR= 1.37; 95%CIs: 1.08-1.74)[93], as well as associations between early childhood infection and psychotic experiences at age 13[92,148]. On this basis, several immunological markers and their causal role in psychosis were investigated, with IL-6 being one of the most consistently identified and replicated. In two meta-analyses of cross-sectional studies, cases at clinical high risk of psychosis (N= 16) as well as cases with a schizophrenia diagnosis (N= 58) were found to have substantially higher concentrations of circulating blood IL-6 compared to controls[149,150]. This evidence has been complemented by longitudinal population-based studies, identifying associations between higher levels of serum IL-6 at age 9 and psychotic experiences at age 18 (N= 2,522; OR=1.81; 95%CIs: 1.01-3.28) as well as psychotic disorder at age 24 (N= 2,224; OR= 1.56; 95%CIs: 1.09–2.21)[94,151]. Finally, MR approaches have provided support for a causal role of IL-6 in psychosis, by suggesting a causal effect of genetically proxied levels of IL-6 on risk of schizophrenia (OR= 1.24; 95%CIs: 1.05–1.47) and by providing robust evidence that the identified causal links are unlikely to be influenced by reverse causation[152].

In comparison, hypotheses implicating immune response in the aetiology of autism have been based predominantly on observational evidence suggesting associations between maternal infections during pregnancy as well as parental autoimmune conditions and offspring autism[153,154]. In a recent meta-analysis of 11 cohort and case-control studies, there was evidence of an association between family history of autoimmune conditions and offspring autism, particularly hypothyroidism (OR= 1.64; 95%CIs: 1.07–2.50), psoriasis (OR= 1.59; 95%CIs: 1.28–1.97), type 1 diabetes (OR= 1.49; 95%CIs: 1.23–1.81), rheumatoid arthritis (OR= 1.51; 95% CIs: 1.19–1.91)[129]. In addition, three recent meta-

analyses of case-control studies (N= 25, N= 38, N= 61) provided evidence of atypical concentrations for over 10 pro- and anti-inflammatory cytokines in autistic individuals, including IL-6[155–157]. However, it is difficult to infer a causal role of immunological markers and pathways relying only on observational evidence. Causal inference based on observational approaches can be hampered by residual confounding (poorly measured or unmeasured confounders), reverse causation (particularly cross-sectional and case-control investigations), bias resulting from misclassification of the exposure or the outcome, missing data (particularly cohort studies), and recall and selection bias[158].

Towards assessing the potentially causal role of immune response in autism, a comprehensive approach would be required allowing the triangulation of observational and polygenic approaches[158] as well as the identification of potentially causal immunological markers. On this basis, investigating the associations between parental autoimmune conditions and autism can provide a unique opportunity to identify causal immunological pathways. Autoimmune conditions are characterised by immune response to autoantigens[159]. Available data on parental autoimmune condition diagnoses in nationwide registers allow the application of observational approaches, while available GWAS studies of autoimmune conditions allow the application of polygenic and MR approaches.

Once causal relationships between parental autoimmune conditions and offspring autism are established, it will be possible to utilise current understanding on the immunological markers implicated across different autoimmune conditions[160], and therefore, orient investigations towards potentially causal immunological markers for autism. Importantly, the increasing availability of GWASs on a broad range of immunological proteins[161–165] in combination with the availability of large GWAS data on autism[36] and schizophrenia[66] allow the assessment of potentially shared causal immunological pathways for both conditions in large samples (Nautism= 46,350; Nschizophrenia= 306,011), using causal inference approaches aimed at minimising residual confounding and reverse causation bias and able to detect the influence of pleiotropy, such as MR[166,167].

1.3.3 Section summary

Although several aetiological models have been proposed to explain the autism-psychosis co-occurrence, understanding whether the co-occurrence is explained by causal links and/or shared

immunological pathways can have important clinical and research implications. Hypotheses on the potential causal links between autism and psychosis have been based predominantly on observational evidence investigating associations between autistic traits in childhood and psychotic experiences in adolescence. Little is known on whether these associations persist to adulthood. The small number of available observational studies so far, have not assessed the potential influence of confounding factors and particularly genetic liability to schizophrenia, while studies utilising polygenic approaches cannot detect and account for the potential influence of pleiotropy. Furthermore, it is unknown whether the associations between autism, autistic traits, and psychotic experiences, extend to other conditions of the psychosis spectrum and particularly schizophrenia. In the case of shared risk factors, it has been hypothesised that immunological processes might constitute a shared pathway to autism and psychosis. However, the potential causal influence of immunological processes in autism has not been clarified yet and further research allowing triangulation of evidence from observational and polygenic approaches is necessary. In addition, there is a limited number of studies systematically assessing the causal influence of immunological pathways on both autism and psychosis and they have been hampered by small samples and potential confounding and reverse causation bias.

♦

1.4 Thesis aims

The present thesis aimed at assessing evidence on two distinct aetiological models for the autism-psychosis co-occurrence: causal pathways and shared risk factors. I used genetic and phenotypic data and applied a combination of study designs to triangulate evidence and strengthen causal inference (Chapter 2).

Aim 1: To assess the direct and indirect causal links between autism and psychosis.

1. Using genetic and phenotypic data from a population-based cohort, I aimed to assess evidence on the hypothesis that autism liability (as captured by PRS and autistic traits in childhood) would be associated with psychotic experiences in adulthood (Chapter 3).

2. Using publicly available GWAS summary data and applying two-sample MR, I assessed evidence on the hypothesis that genetic liability to autism and autistic traits would have causal effects on psychotic experiences and schizophrenia (Chapter 4).

Aim 2: To determine whether shared immunological pathways underly autism and psychosis.

3. I aimed to interrogate the potentially causal role of immune response in autism, by utilizing four distinct methodological approaches, including a nationwide cohort study, LD score regression, PRS analysis and two-sample MR, to assess evidence on the hypothesis that parental inflammatory bowel disease (IBD) would be causally linked to offspring autism (Chapter 5).

4. Using publicly available GWAS summary data and applying two-sample MR and genetic colocalisation analyses, I aimed at assessing evidence on the hypothesis that immunological markers causally implicated in autism, would be also causal for schizophrenia (Chapter 6).

Table 1.1 provides a summary of the thesis aims and research questions.

Table 1.1 Summary of thesis aims and research questions.

Aim	Research Question	Chapter
To assess the direct and indirect causal links between autism and psychosis.	Is autism liability (PRS/traits) associated with psychotic experiences in adulthood?	3
	Does genetic liability to autism and social/non-social autistic traits have causal effects on psychotic experiences and schizophrenia?	4
To determine whether shared immunological pathways underly autism and psychosis.	Is immune response causally implicated in autism?	5
	Are immunological markers causally implicated in autism, also causal for schizophrenia?	6

Chapter 2

Methodological approaches

In the present thesis, I aimed to assess evidence on the hypotheses that autism and psychosis co-occur due to: (i) direct and indirect causal links, (ii) and/or shared causal immunological pathways underlying the two conditions. I applied a combination of epidemiological study designs, utilising phenotypic and genetic data, in order to address limitations of previous studies in the field, gain insights into distinct aspects of the exposure-outcome relationships, and strengthen causal inference.

Understanding whether a relationship between an exposure and an outcome is causal, is a central concept in epidemiology (aetiological epidemiology)[158]. Evidence of causality is essential in order to introduce and/or improve prevention and intervention strategies. However, in practise, discerning causation from correlation and association can be difficult. Correlations and associations between traits do not necessarily suggest a causal relationship, but instead they might be a result of chance, different sources of bias and confounding[168,169]. For example, observed associations between autism and psychosis might be because of some phenotypic similarities between the two conditions leading to misdiagnosis of psychosis in autistic individuals (misclassification bias), and not because there is a causal relationship between the two conditions. It is worth mentioning though, that even in cases that associations are not causal, understanding the reasons underlying them can have an important impact towards informing public health policies. In the case of the above example, understanding that the associations between autism and psychosis are not causal, but instead a result of misclassification bias, could help towards improving diagnostic practices in autistic individuals[104].

Across available observational approaches intending to assess causal relationships between an exposure and an outcome (Figure 2.1), no single approach can provide definitive evidence of causality, since each one of them can be limited by various biases[170]. Instead, the application of more than two approaches with complementary strengths and different and unrelated (orthogonal) sources of bias, in the context of the same underlying research question (triangulation), can improve causal inference[158,170]. Converging evidence across approaches can increase confidence in the causal nature

of the exposure-outcome relationship, whereas conflicting evidence can reveal information about the potential sources of bias influencing the exposure-outcome relationship, and orient future research[158]. In the following section I will briefly describe approaches used for causal inference in the context of observational and genetic epidemiology, focusing on approaches that are relevant to the research presented in this thesis.

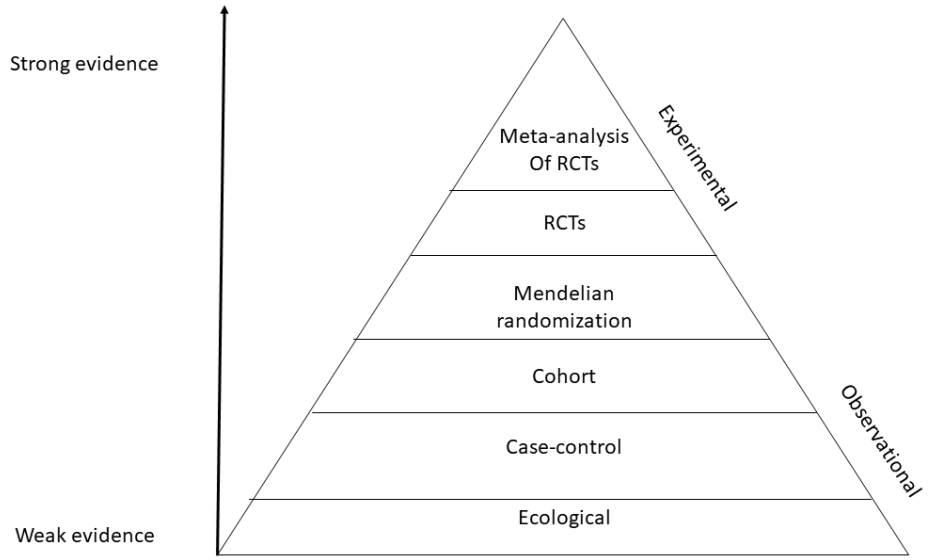

Figure 2.1 Hierarchy of evidence quality across experimental and observational approaches.

Figure adapted from Davies et al., 2018[143]. As suggested by the original authors, despite this hierarchy, triangulation across approaches is necessary for causal inference.

2.1 Observational epidemiology

As illustrated in Figure 2.1, among observational study designs, cohort studies are the most powerful to identify causal relationships between an exposure and an outcome. In cohort studies participants are selected based on the presence of the exposure (exposed vs unexposed), regardless of the presence or absence of the outcome, and they are followed up over time to assess whether the outcome of interest will occur in the exposed versus the unexposed participants[171]. Cohort studies present a number of advantages in relation to other observational study designs. Specifically, they minimise the possibility of reverse causation since there is an established temporal relationship between the exposure and the outcome and, they are particularly useful for the investigation of rare exposures, considering that participants can be selected based on the presence of the exposure[171]. However, cohort studies can be limited by measured or unmeasured confounding, exposure or outcome misclassification as well as participant loss to follow up[135,158,171].

Confounding can arise by factors that are related to both exposure and outcome and it drive association estimates either towards or away from the null. Multivariable regression analyses allow to account for the possible influence of confounding factors that would influence the exposure-outcome associations[158,170]. However, they cannot account for the potential influence of residual confounding (unmeasured or poorly measured confounders). Residual confounding is difficult to be dealt with in the context of traditional observational studies. For this reason, triangulation of evidence across different approaches is necessary[158]. Approaches such as instrumental variables analyses can aid towards minimising the possibility of residual confounding. Specifically, instrumental variables analyses allow the assessment of the causal effects of an exposure on an outcome by using instruments (genetic or non-genetic variables) to proxy for the exposure of interest[158,172]. The instruments must have a robust association with the exposure, they must act on the outcome entirely via the exposure, and they must be unrelated to any of the confounders of the exposure-outcome associations (minimising this way residual confounding)[158]. An example of non-genetic instrumental variables can be schooling laws and reforms to assess the effects of education on health outcomes[173,174], while in the context of this example, a genetic instrumental variable would be

common genetic variants robustly associated with educational attainment[175]- Mendelian randomization (MR)[145,176] and further details on the approach can be found in section 2.2.3.

Misclassification of the exposure or the outcome and is an additional source of bias. It can be non-differential, i.e., exposure and outcome have been measured with error, and differential, i.e., measurement error in the exposure is related to the outcome and vice versa. Exposure or outcome misclassification can bias the association estimates either away or towards the null[177,178]. For this reason, triangulation of evidence across different samples and through approaches that enable the refinement of the exposure or the outcome is necessary[158]. For example, a possible way (although not the only one) to refine the exposure would be the use of PRS and MR approaches. PRS and MR approaches, utilise common genetic variants to estimate the underlying genetic liability to an exposure of interest regardless of whether the exposure has been phenotypically expressed or not. Details on PRS and MR approaches, their differences and limitations can be found in sections 2.2.2 and 2.2.3.

Missing data due to participant loss to follow-up can substantially impact the estimated associations between exposure and outcome. A common way to deal with missing data is conducting analyses only using complete cases, but this can result in loss of power, precision and in some cases spurious associations[179]. Bias in complete case analyses is dependent on the underlying reasons of missingness[180]. These reasons include: (i) data are missing completely at random (MCAR), which implies that a random sample of data is missing and participants with complete data do not systematically differ from participants with missing data; (ii) data are missing at random (MAR), which implies that the probability of a participant having missing data is dependent on observed values and not on missing values; (iii) data are missing not at random (MNAR), which implies that the probability of a participant having missing data is dependent on missing values, even after taking into consideration the observed data[180,181]. In the case of MCAR and MAR, complete case analyses can potentially lead to unbiased association estimates[182]. However, distinguishing between MAR and MNAR is not possible using observed data and therefore the risk of bias in a complete case analysis cannot be excluded. However, statistical approaches such as multiple imputation can aid towards minimising the risk of bias and increase the power of the analyses[179,180].

Multiple imputation is a widely used approach to handle missing data. In multiple imputation, missing values are imputed from the predictive distribution of the missing data, based on the distribution of the observed data and multiple datasets are created in order to allow for the uncertainty of the missing data[180]. During this stage, if there is information on variables that could predict missing values (auxiliary variables) can be entered in the multiple imputation models to make this way the MAR assumption more plausible. Across each imputed dataset, regression models are fitted, their association estimates are averaged across all imputed datasets, and standard errors are combined using Rubin's rules[183], to account for the variability across the datasets[180].

In addition to the assessment of the associations between an exposure and an outcome, it is possible to investigate the underlying mechanisms of association. Mediation analyses can provide evidence on the extent to which the identified association between an exposure and an outcome is due to an intermediate variable (mediator) that is on the causal pathway between the exposure and outcome. Counterfactual mediation (or causal mediation) allows to decompose the total effect of the exposure on the outcome that acts: (i) through the mediator (natural indirect effect), and (ii) through mechanisms that bypass the mediator (natural direct effect)[184]. However, it is important to note that the approach relies on strong assumptions: (i) no unmeasured confounding between exposure-outcome, (ii) no unmeasured confounding between mediator-outcome, (iii) no unmeasured confounding between exposure-mediator, (iv) no mediator-outcome confounders that are influenced by the exposure[185]. If these assumptions hold, counterfactual approaches to mediation estimate the average change in the outcome in the exposed and unexposed groups, under different conditions, i.e., if the value of the exposure and mediator are fixed or change[170,184]. In contrast to traditional mediation approaches, counterfactual mediation approaches allow the inclusion of binary mediators and outcomes, and interaction between exposure and mediator[184,186].

2.2 Genetic epidemiology

Genetic epidemiology is focused on the study of the genetic determinants of physical and mental health conditions in the population and enables the use of genetic data in an epidemiological

framework to assess correlations, associations and causal relationships between traits, overcoming some of the limitations of observational approaches[187].

One of the most powerful tools in genetic epidemiology are GWAS. GWASs test for associations between genetic variants and phenotypes in a population, in a hypothesis-free manner. Typically, GWASs focus on single nucleotide polymorphisms (SNPs), which refer to a variation in a single base pair of the DNA and are common in the population (frequency >1%). Associations with the phenotypes of interest are assessed using linear (continuous phenotype) or logistic (binary phenotype) regression models and reported in blocks of SNPs (loci), i.e., SNPs that are co-inherited and correlated referred to as being in high linkage disequilibrium (LD)[188]. Loci that pass a p-value threshold $\leq 5*10^{-08}$ are typically considered to be associated with the phenotype of interest at genome-wide significance.

It is increasingly being recognised that for complex traits such as autism, schizophrenia and IQ, the genome-wide significant loci are of small effect size, explain only a small proportion of the genetic and phenotypic variance, and they span across the genome[189]. In fact, complex traits seem to be influenced by a large number of variants bellow the genome-wide threshold and of small effect size- these traits are referred to as polygenic[190]. In polygenic traits, liability to the trait is conceptualised to be normally distributed to the population and individuals are expected to express the phenotype after a threshold of genetic and environmental risk as well as chance, has been exceeded. Individuals close but below the threshold are expected to present some sub-phenotypic features[191–193] (the liability-threshold model of inheritance is visualised in Figure 2.2).

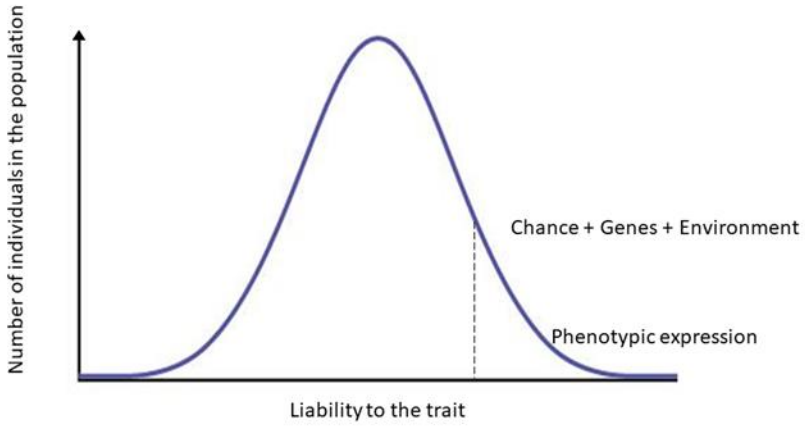

Figure 2.2 The liability-threshold model of inheritance.

Liability to a trait is normally distributed in the population and the phenotype will be expressed after a threshold of environmental and genetic factors as well as chance, has been exceeded[191–193]. Figure adapted from Howe et al., 2018[372]

2.2.1 Linkage Disequilibrium Score Regression (LDSC)

LDSC[194] enables the assessment of SNP heritability for a single trait as well as the estimation of the genetic correlation between multiple traits by utilising full GWAS summary data. In the context of the research presented in this thesis, LDSC was used to estimate genetic correlation. The importance of estimating genetic correlations between two traits, relies on the fact that it can explain whether phenotypic correlations between two traits are influenced by genetic overlap or they are solely due to environmental factors- evidence of a substantial genetic correlation between traits suggests that their phenotypic correlations are at least partially explained by shared underlying genetics[195].

The method harnesses the LD patterns in the genome to estimate a score for each SNP (LD score). This score is based on the principles of polygenicity and reflects whether a SNP is in a high LD region and therefore tagging larger proportions of the genome and potentially more causal variants for the trait of interest (higher LD score), than SNPs that are in low LD regions (low LD score)[196]. SNP association statistics with each trait of interest are multiplied (Z score trait A * Z score trait B) and

their product is regressed on their LD score, with the regression slope indicating the genetic correlation of the traits[194,196].

A major advantage of the approach is that it does not require individual level genotype data, in contrast to other available approaches (e.g., genetic restricted maximum likelihood analysis; GREML). However, it is important to note that the method gives an estimation of the genetic correlation between two traits but does not indicate causal relationships- two traits might present strong genetic correlations due to pleiotropy and not necessarily causality.

2.2.2 Polygenic risk scores (PRS)

PRS approaches enable the estimation of an individual's underlying genetic liability to a complex trait. PRS require individual level genotype data, and are calculated as the sum of the individual's risk alleles, weighted by the effect sizes of each variant identified in the GWAS of the trait[197]. PRS can be calculated for a subset of variants based on a p-value specified threshold, e.g., $5*10^{-08}$. Considering that variance in most polygenic traits is unlikely to be explained by genome-wide significant variants, PRS using subsets of variants meeting more relaxed association thresholds e.g., $p \leq 0.05$ might capture more variance in the phenotype- which is the case for polygenic traits. Ideally, PRS estimated across different p-value thresholds, should be tested for association with the corresponding phenotype in the available sample (referring to the target sample) so that the PRS that captures the most variance in the phenotype can be used for subsequent analysis. However, this is not always possible and depends on the available phenotypic data in the sample.

In the context of the research presented in this thesis, PRS were used to estimate associations with outcomes of interest, e.g., psychotic experiences. The advantage of this approach relies on the fact that PRS capture genetic liability to the exposure, regardless of whether the exposure has been phenotypically expressed. Therefore they are particularly important for the triangulation of evidence from traditional observational approaches, since they allow the refinement of the exposure used in the context of the observational study (i.e., they can potentially overcome misclassification bias of an observational study)[158]. However, as mentioned above, making sure that the PRS capture adequate variance in the phenotype can be challenging. In addition, evidence of association does not

necessarily mean causation and identified associations can be potentially influenced by pleiotropy, especially in scores that have been estimated at lower p-value thresholds, i.e., using variants that are not robustly with the trait of interest and their effects on the trait might be via other pathways (Figure 2.3).

It is worth noting here, that pleiotropy is not always problematic for causal inference. An example of this (adapted by Davies et al. 2019[175] and Dardani et al., 2021[147]) can be based on emerging evidence suggesting causal effects of genetic liability to higher educational attainment and IQ on autism. Educational attainment and IQ present strong genetic correlations and therefore, common genetic variants influencing educational attainment are expected to also influence IQ (pleiotropic variants). If common genetic variants influencing IQ have causal effects on autism, via their effects on educational attainment, then the identified links between genetic liability to higher IQ and autism could be causal (vertical pleiotropy). However, if common genetic variants influencing IQ have effects on autism entirely via educational attainment, i.e., bypassing IQ, then this could lead to spurious conclusions with regards to the associations between IQ and autism (horizontal pleiotropy). Figure 2.3 visualises these two scenarios. Although PRS approaches do not allow the detection and assessment of pleiotropy, MR approaches do, and therefore triangulation of evidence from PRS approaches with MR is necessary for causal inference.

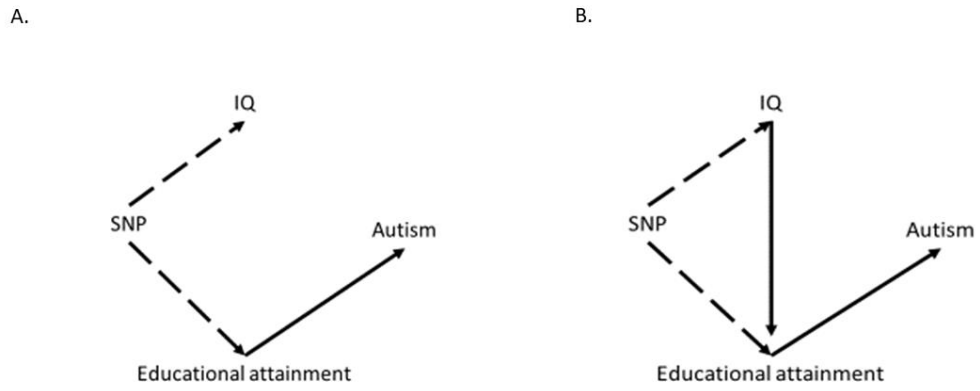

Figure 2.3 Illustration of horizontal (A) and vertical pleiotropy (B).

If common genetic variants associated with an exposure have effects on the outcome entirely via other pathways, i.e., bypassing the exposure, this phenomenon is referred to as horizontal pleiotropy and it can lead to spurious associations (A). On the contrary, in the case of vertical pleiotropy (B) the identified associations can be causal. Figure adapted from Dardani et al., 2021[147].

2.2.3 Mendelian randomization (MR)

MR is a causal inference approach that can overcome limitations of observational and PRS approaches. MR is based on the principles of instrumental variables analyses, utilising germline genetic variants as instruments for exposures to assess their causal effects on outcomes of interest[166,167]. Since genetic variants are randomly assorted at meiosis and fixed at conception, the method is effective in minimising confounding and reverse causation bias that hamper observational studies[166,176]. In contrast to PRS approaches that estimate associations, under certain assumptions that the instruments should satisfy, MR can generate unbiased causal effect estimates. Specifically, the instruments: (i) must be robustly associated with the exposure, (ii) they must not be associated with any confounders of the exposure-outcome associations, (iii) they should have effects on the outcome entirely through the exposure (i.e., no horizontal pleiotropy)[198]- the assumptions are visualised in Figure 2.4.

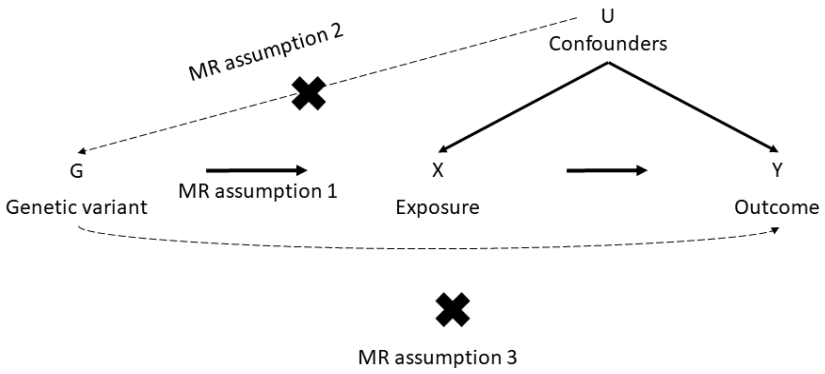

Figure 2.4 Directed acyclic graph (DAG) visualising the three MR assumptions.

Specifically, the method can yield unbiased causal effect estimates under assumptions that the instruments should satisfy: they must be robustly associated with the exposure (MR assumption 1), they must not be associated with any measured or unmeasured confounders of the exposure-outcome associations (MR assumption 2), they should operate on the outcome entirely through the exposure (i.e. no horizontal pleiotropy). Figure adapted from Dardani et al., 2022[211].

MR can be performed in a one-sample and a two-sample setting. In the one-sample setting, the causal effect of the genetic instruments on the outcome is estimated using individual level data, where the exposure and outcome are measured within a single dataset, whereas in the two-sample setting instrument-exposure and instrument-outcome effect sizes and standard errors are extracted from separate GWASs conducted in independent samples, that are representative of the same underlying population[199]. Two-sample MR can increase the statistical power and precision of the causal estimates because it does not require measured exposure, outcome, and genotyped data on all participants within a single sample and therefore, causal estimates can be calculated using multiple large-scale GWASs. Across all analyses presented in the thesis, a two-sample framework was used.

In the context of univariable two-sample MR, when exposures are instrumented by a single genetic variant (usually when proteomic and transcriptomic exposures are used), causal effect estimates are generated using the Wald ratio, which is the ratio of the SNP-outcome/SNP-exposure coefficients[200]. In cases of multiple instruments (typically when complex trait GWAS are used), the causal effect

estimates are generated using the inverse variance weighted (IVW) approach, which is a generalized weighted linear regression of the SNP-outcome coefficients on the SNP-exposure coefficients, with an intercept term constrained to zero[201]. The method assumes that all SNPs included in the analyses are valid instruments and that horizontal pleiotropy is absent or balanced.

The validity of the instruments and the MR assumptions can be assessed using a series of sensitivity analyses when there are multiple instruments for the exposure. The strength of the instruments can be assessed using the F-statistic which is a function of the proportion of variance in the phenotype explained by the genetic instruments[202]. Evidence on the potential influence of pleiotropy in the causal effect estimates can be assessed using: the MR Egger regression, the weighted median and the weighted mode methods.

MR Egger regression is a generalized weighted linear regression of the SNP-outcome coefficients on the SNP-exposure coefficients, having an unconstrained intercept term. The method provides a causal effect estimate accounting for potential pleiotropy[201]. The weighted median method generates a causal effect estimate assuming that at least 50% of the weights in the analyses stem from valid instruments[203]. The weighted mode provides a causal effect estimate assuming that the most common weighted effect estimates stem from valid instruments[204].

In addition to sensitivity analyses testing for the influence of pleiotropy, an extension of MR, multivariable MR (MVMR), enables the inclusion of multiple exposures within the models and allows the estimation of their direct effects on the outcome, independent of other genetically correlated exposures[205]. This can be particularly relevant in the case of autism, considering its genetic correlations and causal links with IQ[36,146,147]. For example, in a scenario of vertical pleiotropy in which genetic liability to autism has causal effects on schizophrenia via its effects on IQ (Figure 2.5), univariable MR would provide a total causal effect estimate of genetic liability to autism on schizophrenia, whereas MVMR would allow to distinguish the effects of genetic liability to autism, from the ones of IQ, on schizophrenia. In another possible scenario, IQ might be a confounder of the genetic liability to autism-schizophrenia causal pathways i.e., having effects on both autism and

schizophrenia (Figure 2.5). MVMR would be again a powerful approach to assess the direct, independent of IQ, causal effects of genetic liability to autism on schizophrenia.

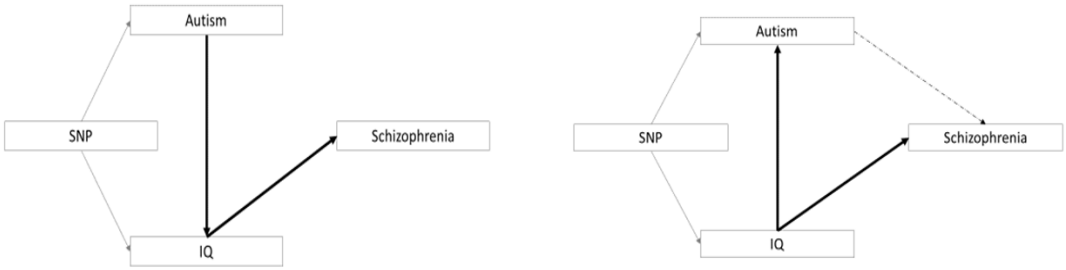

Figure 2.5 Possible causal pathways linking genetic liability to autism, IQ and schizophrenia.

In both scenarios, univariable MR would provide a total causal effect estimate of genetic liability to autism on schizophrenia, whereas MVMR would allow to estimate the direct, independent of IQ effects of genetic liability to autism on schizophrenia.

2.2.4 Genetic colocalisation

Genetic colocalisation approaches are typically applied as complementary approaches to GWAS to elucidate whether identified variants within loci are causal and functional for the trait[206]. The method assesses whether two independent association signals within the same locus that have been generated by two separate GWAS are consistent with a shared causal variant[207]. The approach can be particularly informative towards understanding biological pathways underlying complex traits. For example, a recent study comparing association signals generated from a GWAS of IBD and a GWAS capturing messenger RNA (mRNA) levels (expression Quantitative Loci- eQTL study) in immune cell populations ($CD4^+$, $CD8^+$, $CD19^+$, $CD14^+$, $CD15^+$), found evidence that IBD-associated variants colocalise with variants capturing mRNA expression (eQTLs) in $CD4^+$ T cells, suggesting a potentially causal role of $CD4^+$ T cells and their functions in the aetiology of IBD[208,209].

In the context of the research presented in this thesis, colocalisation was used as a complementary approach to MR. Specifically, in cases that an exposure is instrumented by a single variant, sensitivity analyses to test the evidence of causal effects provided by the Wald ratio cannot be conducted. In these cases, colocalisation approaches can complement MR approaches by elucidating a distinct aspect of the identified causal relationship between an exposure and an outcome[210]. Evidence of MR causal effects and colocalisation, can strengthen causal inference. Specifically, colocalisation allows the assessment of the hypothesis that any identified causal effects are driven by the same causal variant influencing both exposure and outcome, instead of distinct causal variants that are in LD with each other[211,207]. In practice, the approach is harnessing SNP coverage within the same specified locus for two traits of interest and tests whether the association signals for each trait at the specified locus are suggestive of a shared causal variant and therefore a potentially common underlying biological mechanism[211,207]. Colocalisation analyses in the context of the present thesis were relevant for the investigation of shared causal immunological pathways underlying autism and schizophrenia. Figure 2.6 provides a visual summary of genetic colocalisation.

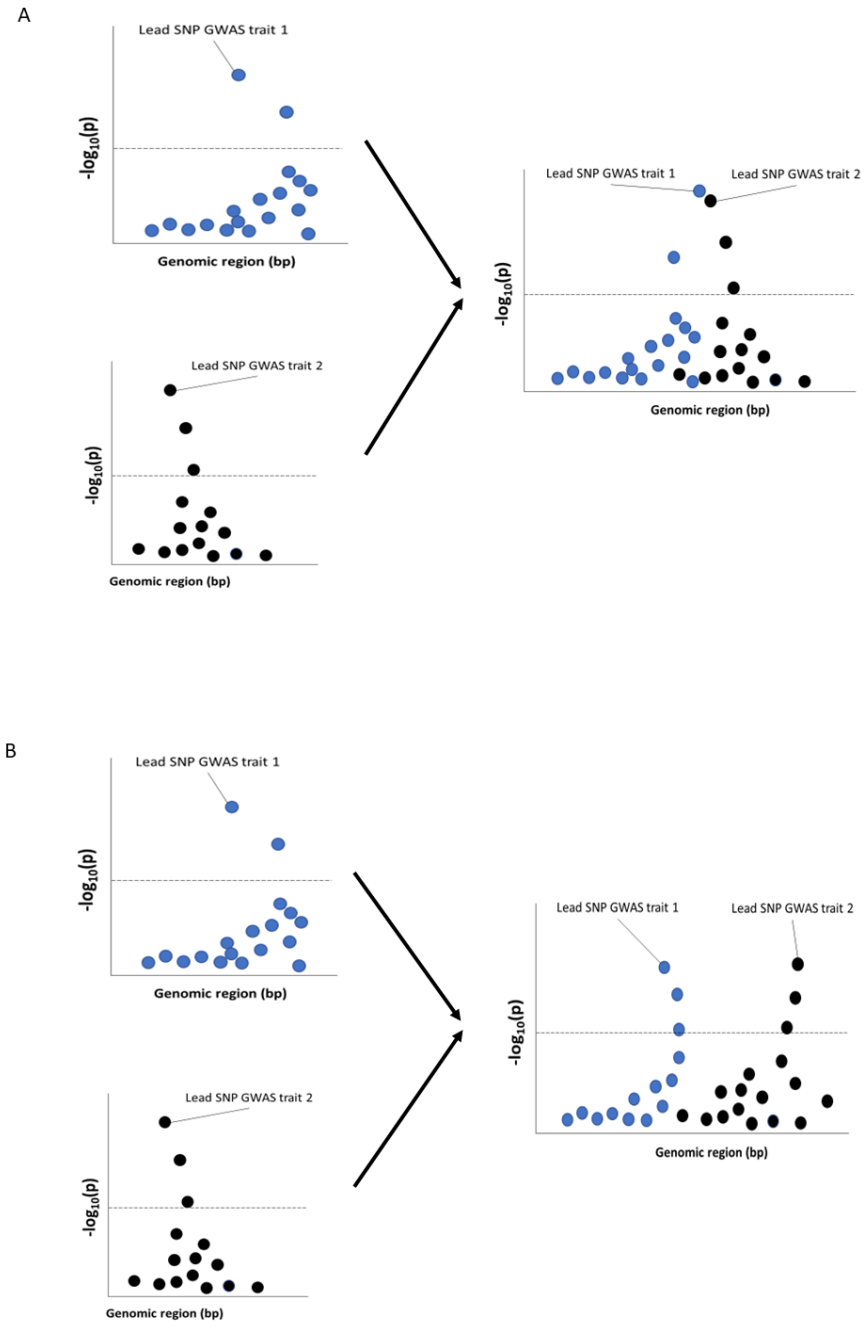

Figure 2.6 Visual summary of genetic colocalisation.

The method assesses whether two independent association signals within the same locus that have been generated by two separate GWAS are consistent with a shared causal variant[207]. In case A, the two association signals seem to colocalise in the specified region, whereas in case B they do not. Locus plots are used only for the illustrative purposes of the example, and genetic colocalisation is utilising rigorous statistical testing of the probability that the two independent signals colocalise (further details can be found in Chapter 6). Figure adapted from Cano-Gamez et al[208].

2.3 Section summary

Understanding whether a relationship between an exposure and an outcome is causal can be particularly challenging. A methodological approach in isolation cannot provide definitive evidence of causality, due to potential bias. Instead, a combination of approaches with complementary strengths and different and unrelated (orthogonal) sources of bias, applied in the context of the same research question, can strengthen causal inference. For this reason, in the present thesis a combination of distinct approaches utilising phenotypic and genetic data were utilised. Table 2.1 provides a summary of the thesis aims, research questions, methodological approaches and data sources utilised in the present thesis.

Table 2.1 Summary of thesis aims, research questions, methodological approaches and data sources.

Aim	Research Question	Chapter	Methodological approach	Data sources
To assess the direct and indirect causal links between autism and psychosis.	Is autism liability (PRS/traits) associated with psychotic experiences in adulthood?	3	**Polygenic risk score analysis** and **multivariable regression** to investigate the associations between autism polygenic risk and psychotic experiences in adulthood.	Genotype and phenotype from the ALSPAC birth cohort.
			Multivariable regression analysis to investigate the associations between social/non-social autistic traits and psychotic experiences in adulthood.	
			Multivariable regression analysis to assess the potential confounding influence of schizophrenia polygenic risk in any of the identified associations.	
			Counterfactual mediation analysis to assess the potential mediating role of trauma in childhood in any of the identified associations.	
	Does genetic liability to autism and social/non-social autistic traits have causal effects on psychotic experiences and schizophrenia?	4	**Two-sample MR** to estimate the total causal effects of genetic liability to autism and social/non-social autistic traits on psychotic experiences as well as schizophrenia.	GWAS summary-level data.
			Multivariable two-sample MR to estimate the direct, independent of the potential pleiotropic influence of IQ, causal effects of genetic liability to autism and social/non-social autistic traits on psychotic experiences as well as schizophrenia.	
To determine whether shared immunological pathways underly autism and psychosis.	Is immune response causally implicated in autism?	5	**Multivariable regression analysis** to investigate the associations between parental diagnoses of inflammatory bowel disease and offspring autism.	Phenotype data from nationwide health registers in Sweden.
			LD score regression analysis to assess the genetic correlation between inflammatory bowel disease and autism.	GWAS summary-level data.
			Polygenic risk score analysis and **multivariable regression** to investigate the associations between maternal polygenic risk for inflammatory bowel disease and offspring autism.	Genotype and phenotype data from the ALSPAC birth cohort.

Table 2.1**.** Continued from above.

Aim	Research Question	Chapter	Methodological approach	Data sources
To determine whether shared immunological pathways underly autism and psychosis.	Is immune response causally implicated in autism?	5	**Two-sample MR** to assess the causal effects of genetic liability to inflammatory bowel disease on autism.	GWAS summary-level data
	Are immunological markers causally implicated in autism, also causal for schizophrenia?	6	**Two-sample MR** analyses to assess the causal effects of genetically proxied immunological markers on autism and schizophrenia.	GWAS summary-level data
			Genetic colocalisation analyses to assess whether any identified causal effects are consistent with a shared causal variant influencing levels of immunological markers as well as autism and/or schizophrenia.	GWAS summary-level data

♦

Part I: Causal Pathways

Chapter 3

The associations between autism polygenic risk, autistic traits in childhood and psychotic experiences in adulthood

Content from this chapter is included in the following preprint:

Dardani C, Schalbroeck R, Jones H, Strelchuk D, Hammerton G, Croft J, Madley-Dowd P, Sullivan S, Zammit S, Selten JP, Rai D. Childhood trauma as a mediator of the association between autistic traits and psychotic experiences: evidence from the ALSPAC birth cohort. PsyArXiv; 2021; doi: https://psyarxiv.com/ed8m5/ (Currently under consideration at *Schizophrenia Bulletin*)

♦

3.1 Introduction

In Chapter 1 I discussed that current understanding on the potentially causal links between autism and psychosis has been largely based on longitudinal studies focusing on the associations between autistic traits in childhood and psychotic experiences in early adolescence. For example, two studies in the ALSPAC birth cohort, found that autistic traits until age 9, were associated with psychotic experiences by age 12[137,138]. In addition, there is some evidence suggesting that these associations might be mediated by adverse childhood experiences. Specifically, the only available study in the field applying a formal mediation approach (i.e., not adjusting for the mediator), found evidence of a mediating role of bullying victimisation at age 12 in the associations between autistic traits and psychotic experiences at age 14[139]. However, psychotic experiences in early adolescence are typically transient and of no clinical significance[83,84]- instead, experiences that are accompanied by distress for the individual and are persistent have been found to be associated with transition to psychotic disorders[85].

There is currently a limited number of studies utilising polygenic and observational approaches to investigate the links between autism liability (polygenic risk and traits) and psychotic experiences in adulthood. Specifically, autism polygenic risk has been found to be associated with psychotic experiences in adulthood in UK Biobank[87], while in the population-based IMAGEN cohort, the associations between autism polygenic risk and psychotic experiences at age 18 appeared to be mediated by difficulties in social functioning and peer problems[142]. With regards to observational

studies, there was evidence in the CATSS study of an association between autistic traits in childhood and auditory hallucinations at age 18, which however attenuated substantially after adjusting for other neuropsychiatric conditions in childhood such as ADHD[140]. In the ALSPAC cohort, there was evidence consistent with between autistic traits in childhood and psychotic experiences in adulthood, although the possibility of confounding bias in the identified associations was not explored[141].

Overall, there is some evidence to suggest associations between autism liability and psychotic experiences in adulthood, although several aspects of their relationship have been un-/under-explored. Firstly, it is necessary to further interrogate the associations between autism polygenic risk and psychotic experiences in other available cohorts- particularly considering that different cohorts might present different confounder structure and selection bias (e.g., UK Biobank "healthy volunteer" bias[212,213]). Secondly, little is currently known on whether the identified associations between autistic traits and psychotic experiences are a result of confounding and particularly genetic confounding by schizophrenia polygenic risk, considering that autism and psychotic experiences present strong genetic correlations with schizophrenia[36,87]. Thirdly, the potential mediating role of childhood trauma, one of the most consistently reported environmental risk factors for psychotic experiences and psychotic disorder[91,214], remains unclear. This can be particularly important considering evidence suggesting that childhood maltreatment and/or bullying victimization is more common in autistic individuals, individuals with higher polygenic risk for autism and childhood autistic traits[215–218].

Using data from a UK population-based cohort, the ALSPAC birth cohort, I investigated:

(i) whether common variant autism polygenic risk (captured by PRS), and childhood autistic traits assessed between ages 3-9, are associated with psychotic experiences measured at ages 18 and/or 24;

(ii) the possible confounding influence of schizophrenia common variant polygenic risk (captured by PRS);

(iii) the extent to which any identified associations were mediated by trauma experienced between ages 5-11.

3.2 Methods

3.2.1 Cohort Description

I used data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based cohort study of children born to 14,541 pregnant mothers residing in the former county of Avon, United Kingdom, with an expected delivery date between 1 April 1991 and 31 December 1992. Of these pregnancies, there were 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, eligible samples who did not join the study initially were contacted, and additional participants were recruited. This resulted in a total of 15,454 pregnancies and 15,589 foetuses, of which 14,901 were alive at 1 year of age. Depending on the analysis conducted, I restricted the sample to participants with complete genotype data, autistic traits, traumatic experiences, psychotic experiences and confounders.

Further information on the ALSPAC cohort is available on the ALSPAC website (http://www.bristol.ac.uk/alspac) and elsewhere[26,27]. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/). Some data were collected using REDCap[28,29]. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

3.2.2 Genetic Data

A total of 9,912 ALSPAC children were genotyped on the Illumina HumanHap550-quad chip genotyping platforms by 23andme subcontracting the Wellcome Trust Sanger Institute, Cambridge, UK and the Laboratory Corporation of America, Burlington, NC, US. After standard quality control (details on quality control in the ALSPAC cohort can be found elsewhere[219]) and excluding participants who had withdrawn consent, genetic data were available for 7,977 children of European ancestry. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004).

3.2.3 Phenotypic Data

3.2.3.1 Autistic traits

I used a measure of broad autistic traits, estimated in ALSPAC as the mean score of seven factors identified in a previous factor analysis of 93 available measures related to autism[220]. This factor was found to strongly predict cases of autism ascertained through clinical records in ALSPAC, independent of the factor analysis[220]. Additionally, I used four other measures of autistic traits, which were also independent predictors of an autism diagnosis in the ALSPAC cohort[220]. These included social communication difficulties assessed with the Social Communication Disorder Checklist (SCDC) at age 7 years[50], difficulties in pragmatic language use assessed with the coherence subscale of the Children's Communication Checklist at age 9 years[221], sociability assessed with a subscale of the Emotionality, Activity and Sociability Temperament Scale at age 3 years[222], and repetitive behaviour assessed with measures obtained from the Development and Well-Being Assessment at age 5 years[223]. Participants who had scores within the approximately highest 10% of the measure distribution were classified as being 'case positive' for the autistic trait[224].

3.2.3.2 Psychotic experiences

Psychotic experiences were assessed at ages 18 and 24 using the semi-structured Psychosis-Like Symptoms interview (PLIKSi), administered by trained psychologists, and scored according to criteria predefined by the World Health Organization[225]. The PLIKSi consists of 12 core questions covering hallucinations, delusions, and thought interference. Participants were asked about experiences that had occurred since age 12 years and until the ages 18 and/or 24. Psychotic experiences were considered present if one or more of the experiences was rated by the interviewer as suspected or definitely present, and if this was not attributable to falling asleep or waking up, fever, or substance use. I additionally examined psychotic experiences that had been distressing and/or frequent, since these experiences are more clinically relevant and predictive of psychotic disorder[84]. In sensitivity analyses I excluded reports of tactile hallucinations, since these experiences might be difficult to distinguish from the heightened tactile perception often seen in autism[226].

3.2.3.3 Childhood trauma

The measures of childhood trauma and their associations with psychotic experiences have been described in detail elsewhere[91]. In brief, I used a measure of childhood trauma between ages 5 and 11 based on responses to 57 questions from questionnaires and interviews about domestic violence (presence of regular acts of physical violence taking place in the home), physical abuse (physical harm to the participant from caregivers or other adults), emotional abuse (emotional cruelty to the participant from caregivers or other adults), emotional neglect (caregivers not taking an interest in the participant's life), sexual abuse (adults or older children forcing the participant into sexual activity, including attempts to do so), and bullying victimization (regular name-calling, blackmail, or assault by peers). Measures assessed contemporaneously by the participant and their caregivers between participant ages 5 to 11, were supplemented with data from a participant-completed questionnaire at age 22, as all data on sexual abuse, and most data on physical and emotional abuse prior to age 11, were based on parental report. Each type of trauma was coded as present or not, and a single trauma variable was created representing exposure to any type of trauma[91].

3.2.4 Analyses

3.2.4.1 Analysis plan

I firstly investigated the associations between autism polygenic risk and psychotic experiences at the age 18 and/or 24 assessments (section 3.2.4.2). Then, I moved on to assess the relationship between autistic traits and psychotic experiences (section 3.2.4.3). Mediation analyses were performed in cases that there was evidence of associations between the exposure(s) of interest and the outcome (section 3.2.4.4).

3.2.4.2 Investigating the associations between autism polygenic risk and psychotic experiences

Polygenic risk score calculation

PRS for autism were calculated using PLINK version 1.9, applying the method described by the Psychiatric Genomics Consortium (PGC)[227]. Using the latest genome-wide association study (GWAS) summary data for autism[36] as the discovery sample, I extracted SNPs, corresponding alleles, effect sizes and p-values. SNPs with mismatching alleles between the discovery and the ALSPAC

genotyped sample were removed. I additionally removed the Major Histocompatibility Complex (MHC) region (25 Mb – 34 Mb), except for one SNP representing the strongest signal within the region. This approach was followed in the original method outlined by the PGC, due to the complex LD structure of the MHC region[227]. Using ALSPAC data as reference panel, SNPs were clumped with an r^2 of 0.25 and a physical distance threshold of 500 kB. I calculated PRS for each participant across 13 p-value thresholds ($5*10^{-08}$ to 0.5), standardized by subtracting the mean and dividing by the standard deviation.

Statistical analyses

I performed logistic regressions using STATA/MP 15 to examine associations between each autism PRS threshold and psychotic experiences outcomes. Analyses were adjusted for child's sex and the first 10 principal components of the ALSPAC genotype data to avoid population stratification bias.

3.2.4.3 Investigating the associations between autistic traits and psychotic experiences

Potential Confounders

In analyses investigating the associations between autistic traits and psychotic experiences, confounders were considered on the basis of existing evidence suggesting associations with autistic traits, traumatic events (for subsequent mediation analyses), and psychotic experiences[217,228,229]. These included child sex (male/female), maternal parity (≤ 1 child versus ≥ 2 children), major financial problems in the family when the child was 8 months old (yes/no), maternal highest educational attainment (32 weeks gestation), maternal age (at delivery), maternal Crown-Crisp anxiety scores[230] (18 weeks gestation), maternal depression measured with the Edinburgh Postnatal Depression Scale[231] (EPDS; 18 weeks gestation scores ≥ 13), and child IQ scores at age 8 assessed with the Wechsler Intelligence Scale for Children third edition[232] (WISC-III).

In children with available genotype data, I calculated schizophrenia PRS using the schizophrenia GWAS summary data[227] (available at the time of analyses) as the discovery sample[227], following the process described in the PRS analyses section above. I used scores corresponding to a 0.05 p-value threshold, as this threshold has been found to optimally capture schizophrenia liability across different

samples[227] and assessed their potential confounding role in the associations between autistic traits and psychotic experiences.

Statistical analyses

Statistical analyses were conducted in STATA/MP version 15. I compared individuals with and without autistic traits on confounder data, traumatic experiences, and psychotic experiences using Pearson χ^2-test, independent-samples *t*-tests, and logistic regression analyses.

Using logistic regression, I estimated odds ratios (ORs) and 95% confidence intervals (95% CIs) for the associations between autistic traits in childhood and psychotic experiences in young adulthood. I performed crude models and confounder-adjusted analyses, including a separate analysis adjusting for schizophrenia PRS in the sample with available genotype data.

Missing data

I performed multiple imputation by chained equations[233], using the STATA *ice* command. Confounder and outcome data were imputed for the sample with complete data on each autistic trait exposure. I created 100 imputed datasets using information from variables included in the analyses as well as auxiliary variables associated with the variables of interest and attrition, to make the missing-at-random assumption plausible[180]. Based on established guidelines on auxiliary variables selection[179], I entered in the models exposure, outcome, confounders and auxiliary variables. The decision was based not only on their potential associations with exposure, outcome, mediator, confounders, but also on their completeness. Specifically, based on the recently published framework for the treatment of missing data, developed in the context of the STRATOS initiative (STRengthening Analytical Thinking for Observational Studies), it is recommended to include a small number of auxiliary variables that are strong predictors of missing values and they show the lowest possible missingness[179]. On this basis the following auxiliary variables were included in the models: (i) maternal marital status: assessed via questionnaire during 8 weeks of gestation. The measure was available in 13,545 mothers (13% missingness); (ii) home ownership status: assessed via questionnaire during 8 weeks of gestation. The measure was available in 13,487 mothers (14%

missingness); (iii) Crowding index: assessed via questionnaire during 8 weeks of gestation and defined as the proportion of people per room. The measure was available in 13,247 mothers (15% missingness).

I used linear regression models for imputation of normally distributed variables, logistic regression models for binary variables, and the inbuilt *match* command for predictive mean matching to impute non-normal continuously distributed variables.

3.2.4.4 Investigating the potential mediating role of trauma in childhood

As outlined in the analysis plan, section 3.2.4.1, mediation analyses were performed in cases that there was evidence of associations between the exposure(s) of interest and the outcome. Mediation analyses were performed using the g-formula package in STATA[186]. I used the parametric g-formula using Monte Carlo simulations to estimate the natural direct effect (NDE) of the exposure(s) of interest on psychotic experiences, and the natural indirect effect (NIE) that was mediated via traumatic experiences between ages 5 to 11. I performed unadjusted as well as adjusted models for confounders. As described in the confounders section above, confounders were selected on the basis of existing evidence suggesting associations with autistic traits, traumatic events, and psychotic experiences[217,228,229]. Mediation analyses were additionally performed adjusting for schizophrenia polygenic risk. Corresponding 95% CIs were estimated using the standard errors from 1000 non-parametric bootstrap resamples. The proportion mediated (PM) was calculated as[234]: $[(OR_{NDE}*(OR_{NIE}-1)) / (OR_{NDE}*OR_{NIE}-1)]*100$.

For imputation of missing data, I used the inbuilt g-formula imputation commands[186], allowing simultaneous imputation of missing data and mediation analyses, entering in the models the same auxiliary variables I used for the primary analyses.

3.3 Results

A summary of the available sample sizes for each analysis conducted can be found in Figure 3.1.

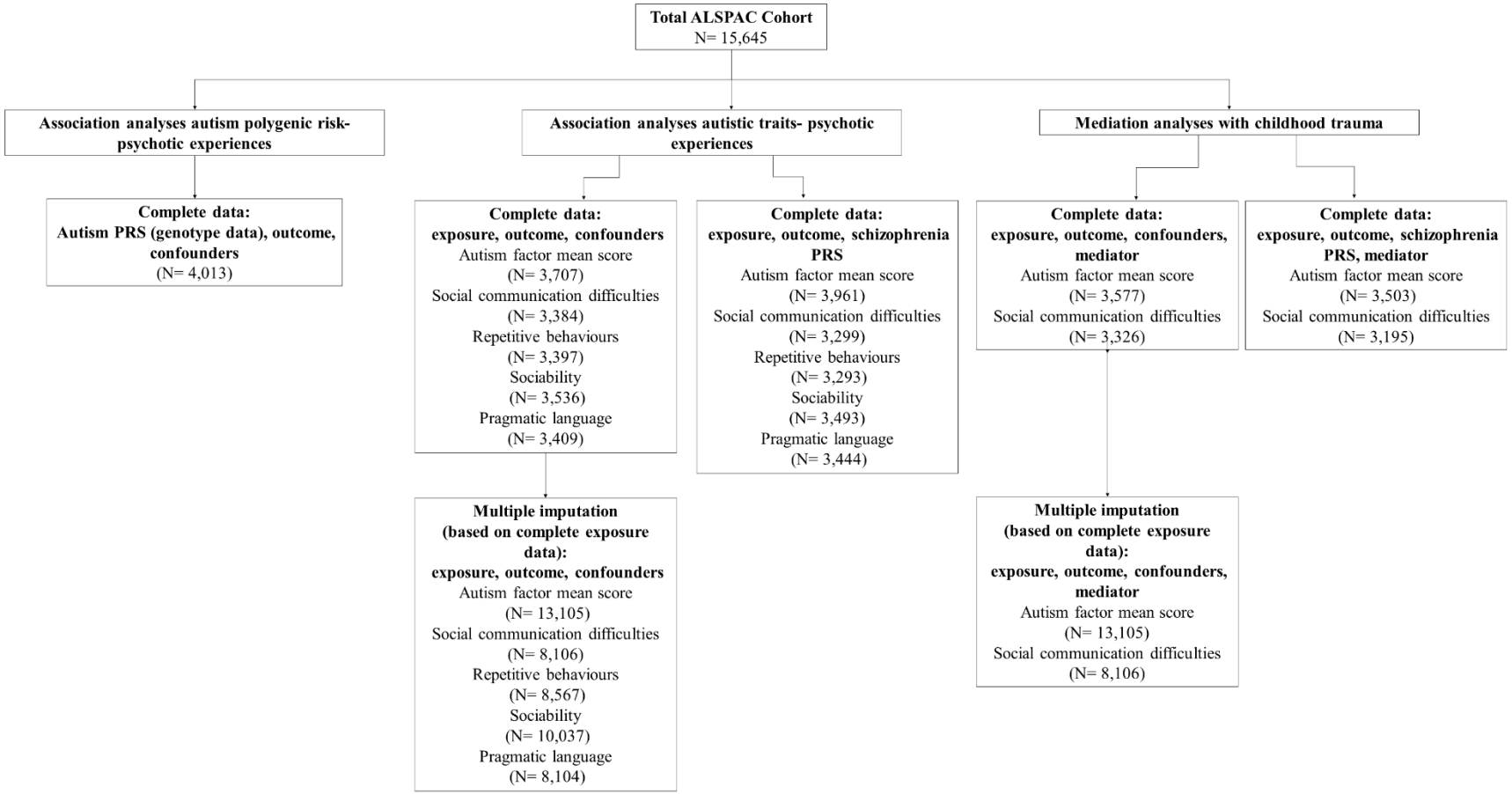

Figure 3.1 Available sample size for each analysis conducted in the context of the present study.

PRS: polygenic risk score

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3.3.1 Associations between autism polygenic risk and psychotic experiences

In total 4,013 children had available genotype and psychotic experiences data (Figure 3.1). Of these children, 44% were male, 13% reported psychotic experiences and 6% reported distressing or frequent psychotic experiences at the age 18 and/or 24 assessments.

There was no evidence to suggest associations between participant PRS for autism across all p-value thresholds, and any psychotic experiences measure (Figure 3.2 and Appendix Tables A1-A4).

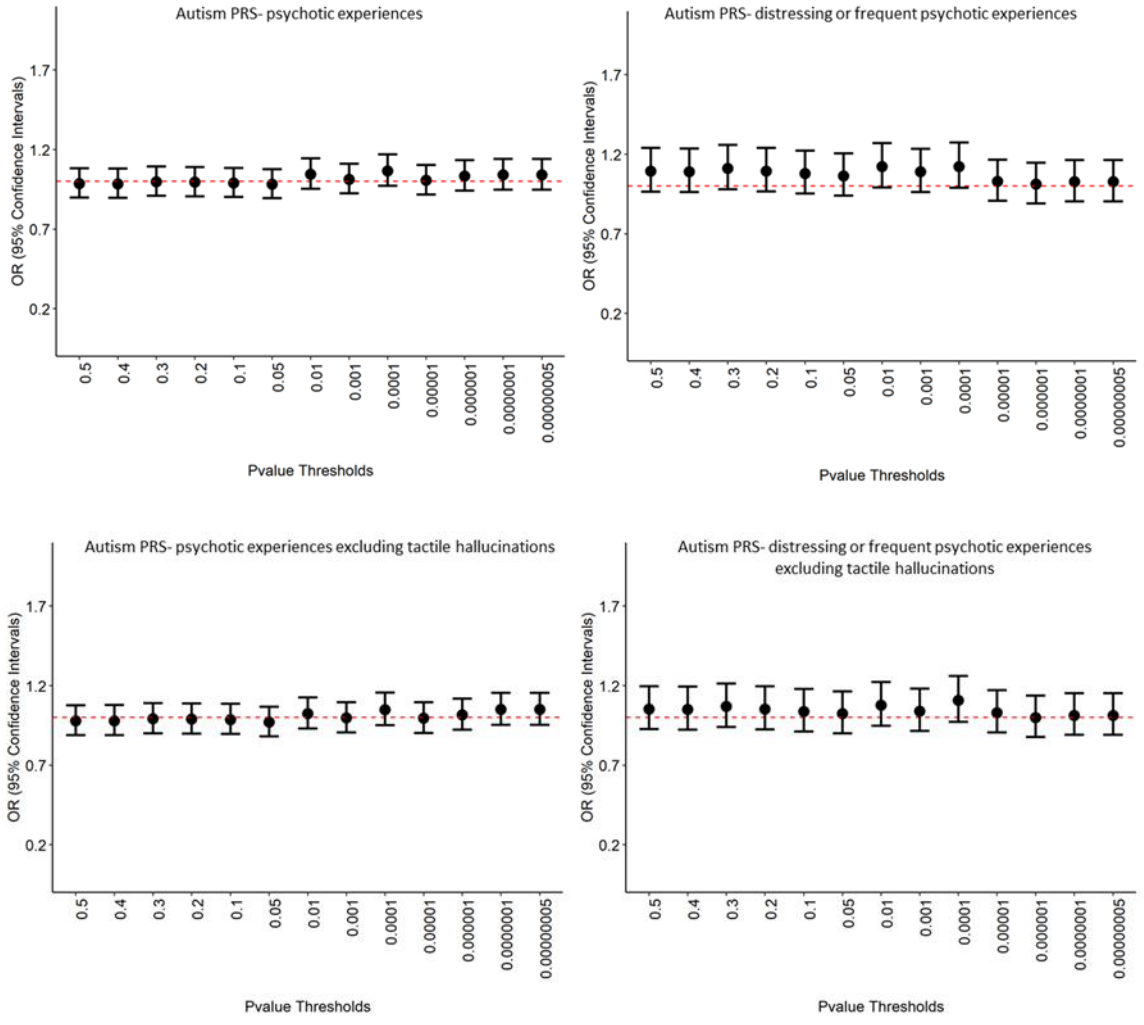

Figure 3.2 Associations between autism PRS across 13 p-value thresholds and psychotic experiences assessed at age 18 and/or 24.

PRS: polygenic risk score; OR: Odds ratio.

3.3.2 Associations between autistic traits and psychotic experiences in adulthood

The maximum available sample size before imputation was 3,707 for the analyses examining the associations between autistic traits and psychotic experiences (Figure 3.1). Children scoring highest on all the autistic traits were more likely to be male, present lower total IQ scores (Table 3.1) and experience trauma between ages 5–11 (only exception sociability; Appendix Table A5).

Participants with complete data on exposure, outcome confounders, were more likely to be female, have a higher socioeconomic background, and present higher total IQ scores, while they were less likely to have experienced trauma in childhood and psychotic experiences later in life, compared to those with incomplete data (details can be found in Appendix Tables A6-A7). After imputing data, the maximum sample size for the analyses was 13,105 individuals.

In complete case analyses (shown in Table 3.2), there was evidence of associations between autism factor mean score and psychotic experiences (OR_{CRUDE} = 1.13, 95%CIs: 1.02–1.26, P= 0.03) as well as distressing and/or frequent psychotic experiences (OR_{CRUDE} = 1.20, 95%CIs: 1.04–1.38, P= 0.01). The associations remained of comparable magnitude after adjusting for confounders ($OR_{ADJUSTED}$ = 1.09, 95%CIs: 0.97–1.23, P = 0.15; $OR_{ADJUSTED}$ = 1.19, 95%CIs: 1.01–1.39, P= 0.03), and for schizophrenia polygenic risk (Appendix Table A8). Sensitivity analyses restricted to psychotic experiences without tactile hallucinations yielded comparable estimates (Table 3.2). Additionally, there was evidence of associations between social communication difficulties and psychotic experiences (OR_{CRUDE} = 1.43, 95%CIs: 1.01–2.03, P= 0.04) as well as distressing and/or frequent psychotic experiences (OR_{CRUDE} = 1.60, 95%CIs: 1.02–2.52, P= 0.04). Effect estimates were of comparable magnitude when adjusting for confounders ($OR_{ADJUSTED}$ = 1.34, 95%CIs: 0.94–1.91, P= 0.11; $OR_{ADJUSTED}$ = 1.54, 95%CIs: 0.97–2.45, P= 0.07), schizophrenia polygenic risk (Appendix Table A8), and restricted to psychotic experiences without tactile hallucinations (Table 3.2).

The imputed data analysis (Appendix Table A9) supported the identified associations, as estimates were of comparable magnitude to the primary analyses, and with greater precision. There was no evidence to suggest an association between the variables of repetitive behaviour, pragmatic language, and sociability with any psychotic experiences measure (Table 3.2).

Table 3.1 Characteristics of individuals with and without autistic traits[1].

	Autism factor mean score[2] (n = 5,800)			**Social communication difficulties (n = 5,106)**			**Repetitive behaviours (n = 5,127)**			**Pragmatic language (n = 5,086)**			**Sociability (n = 5,434)**		
Variable	Yes	No	P[3]	Yes	No	P[3]	Yes	No	P[3]	Yes	No	P[3]	Yes	No	P[3]
Total n (%)	457 (7.9)	5,343 (92.1)	N/A	461 (9)	4,645 (91)	N/A	313 (6.1)	4,814 (93.9)	N/A	450 (8.9)	4,636 (91.2)	N/A	600 (11)	4,834 (89)	N/A
Male sex, n (%)	330 (72.2)	2,571 (48.1)	<0.001	298 (64.4)	2,257 (48.6)	<0.001	194 (62)	2,377 (49.4)	<0.001	284 (63.1)	2,250 (48.5)	<0.001	354 (59)	2,379 (49.2)	<0.001
Parity (<=1 child), n (%)	354 (77.5)	4,449 (83.3)	0.002	367 (79.6)	3,888 (83.7)	0.02	259 (82.8)	4,011 (83.3)	0.79	369 (82)	3,873 (83.5)	0.40	491 (81.8)	4,024 (83.2)	0.39
Maternal educational attainment (university degree), n (%)	70 (15.3)	904 (16.9)	0.38	71 (15.4)	841 (18.1)	0.15	59 (18.9)	836 (17.4)	0.50	75 (16.7)	825 (17.8)	0.55	91 (15.2)	834 (17.3)	0.20
Mother's age at delivery, mean (SD)	29.2 (4.6)	29.4 (4.4)	0.51	29.2 (4.6)	29.5 (4.4)	0.11	29.4 (4.5)	29.5 (4.4)	0.60	29.5 (4.3)	29.5 (4.4)	0.91	29.2 (4.3)	29.4 (4.4)	0.33
Maternal depression during pregnancy (EPDS >= 12), n (%)	99 (21.7)	716 (13.4)	<0.001	102 (22.1)	590 (12.7)	<0.001	60 (19.2)	628 (13.1)	0.002	90 (20)	604 (13.3)	<0.001	88 (14.7)	649 (13.4)	0.40
Total IQ score (WISC-III), mean (SD)	93.6 (18.1)	105.8 (15.9)	<0.001	99.6 (19.1)	106.2 (15.9)	<0.001	101.8 (18.4)	105.7 (16.2)	<0.001	96.1 (17.9)	106.5 (15.8)	<0.001	103.4 (15.9)	105.2 (16.5)	0.01
Maternal anxiety during pregnancy, mean (SD)	5.4 (3.6)	4.5 (3.3)	<0.001	5.4 (3.6)	4.48 (3.3)	<0.001	5.7 (3.4)	4.5 (3.3)	<0.001	5.2 (3.6)	4.5 (3.3)	<0.001	4.6 (3.4)	4.6 (3.3)	0.92
Major financial problems (present), n (%)	81 (17.7)	705 (13.2)	0.01	91 (19.7)	575 (12.4)	<0.001	48 (15.3)	614 (12.8)	0.19	63 (14)	591 (12.8)	0.45	79 (13.2)	642 (13.3)	0.94

SD, standard deviation; EPDS, Edinburgh Postnatal Depression Scale; IQ, Intelligence Quotient; WISC-III, Wechsler Intelligence Scale for Children third edition.

[1] Characteristics are shown for observations with complete data on exposure and confounders.

[2] Dichotomised (worst 10th percentile) for the purposes of the sample descriptive statistics.

[3] The p-values for n (%) and mean (SD) are based on Pearson $\chi 2$ test and independent-samples t-test, respectively.

Table 3.2 Associations between autistic traits and psychotic experiences[1,2].

		Including tactile hallucinations								Excluding tactile hallucinations							
		Psychotic experiences				Psychotic experiences, distressing and/or frequent				Psychotic experiences				Psychotic experiences, distressing and/or frequent			
		Unadjusted		Adjusted[3]		Unadjusted		Adjusted[3]		Unadjusted		Adjusted[3]		Unadjusted		Adjusted[3]	
Exposure	**n**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**
Autism factor mean score	3,707	1.13 (1.02–1.26)	0.03	1.09 (0.97–1.23)	0.15	1.20 (1.04–1.38)	0.01	1.19 (1.01–1.39)	0.03	1.15 (1.03–1.28)	0.01	1.09 (0.96–1.23)	0.17	1.18 (1.02–1.36)	0.03	1.14 (0.97–1.35)	0.11
Social communication difficulties	3,384	1.43 (1.01–2.03)	0.04	1.34 (0.94–1.91)	0.11	1.60 (1.02–2.52)	0.04	1.54 (0.97–2.45)	0.07	1.49 (1.04–2.12)	0.03	1.36 (0.95–1.96)	0.10	1.69 (1.07–2.67)	0.02	1.61 (1.01–2.56)	0.05
Repetitive behaviour	3,397	0.98 (0.63–1.54)	0.94	0.94 (0.60–1.48)	0.78	1.17 (0.65–2.09)	0.61	1.14 (0.64–2.06)	0.66	0.98 (0.61–1.56)	0.74	0.92 (0.58–1.48)	0.74	1.13 (0.62–2.06)	0.70	1.09 (0.59–2.01)	0.78
Sociability	3,536	1.28 (0.94–1.73)	0.12	1.27 (0.94–1.73)	0.12	1.31 (0.87–1.98)	0.20	1.33 (0.88–2.02)	0.18	1.25 (0.92–1.72)	0.16	1.25 (0.91–1.71)	0.18	1.20 (0.78–1.86)	0.40	1.22 (0.79–1.88)	0.38
Pragmatic language	3,409	1.08 (0.75–1.55)	0.68	1.00 (0.69–1.45)	0.99	1.45 (0.92–2.28)	0.11	1.37 (0.85–2.18)	0.19	1.15 (0.80–1.66)	0.45	1.04 (0.71–1.52)	0.82	1.54 (0.98–2.42)	0.06	1.43 (0.89–2.29)	0.14

OR, odds ratio; CIs, confidence intervals.

[1] Estimates based on observations with complete data on exposure, outcome, and confounders.

[2]Psychotic experiences assessed at ages 18 and/or 24.

[3] Adjusted for child sex (male/female), parity (≤ 1 child versus ≥ 2 children), major financial problems in the family when the child was 8 months old (yes/no), maternal highest educational attainment, maternal age (at delivery), maternal Crown-Crisp anxiety scores (18 weeks gestation), maternal depression measured with the Edinburgh Postnatal Depression Scale (EPDS; 18 weeks gestation scores ≥ 13), and child IQ scores at age 8 assessed with the Wechsler Intelligence Scale for Children third edition (WISC-III).

3.3.3 The mediating role of childhood trauma

Considering that there was evidence of associations between autism factor mean score and psychotic experiences, as well as social communication difficulties and psychotic experiences, mediation an analyses were conducted for these two exposures. Figure 3.3 illustrates these analyses.

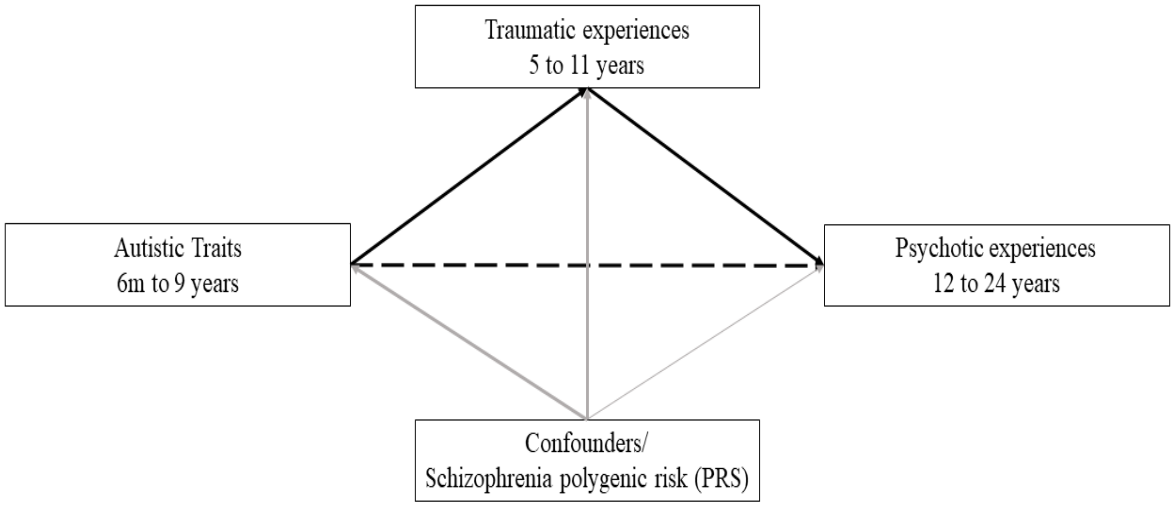

Figure 3.3 Schematic depiction of the mediation analyses.

Solid black lines represent the potential indirect effects between exposure (autistic traits) and outcome (psychotic experiences), while dashed black lines represent the potential direct effects. Grey lines represent potential confounding. Although there seems to be an overlap between exposure and mediators, the rationale of the analyses was based on the neurodevelopmental origins of autistic traits, i.e,. that they are present since birth, regardless of assessment age. This is supported by previous studies in the ALSPAC cohort, suggesting associations between autism polygenic risk and the autistic measures used in the present analyses. Details can be found at: Rai et al., 2018; Pourcain et al., 2017.

The results of the mediation analyses are shown in Table 3.3. Autism factor mean score, social communication difficulties, and psychotic experiences were associated with traumatic experiences at ages 5 to 11 (Appendix Table A5).

There was evidence to suggest that the associations between autism factor mean score and psychotic experiences were mediated by childhood traumatic experiences in crude and adjusted for confounder models (NIE OR_{CRUDE} = 1.06, 95%CIs: 1.03–1.08, P < 0.001, PM = 45%; NIE $OR_{ADJUSTED}$ = 1.04, 95%CIs: 1.02–1.06, P< 0.001, PM = 41%). Analyses with psychotic experiences that were distressing and/or frequent yielded comparable natural indirect effect estimates (NIE OR_{CRUDE} = 1.07, 95%CIs: 1.04–1.1, P < 0.001, PM = 35%; NIE $OR_{ADJUSTED}$ = 1.05, 95%CI 1.02–1.07, P< 0.001, PM = 28%).

Additionally, there was evidence consistent with a mediating effect of childhood traumatic experiences in the associations between social communication difficulties and psychotic experiences in crude and adjusted models (NIE OR_{CRUDE} = 1.15, 95%CIs: 1.08–1.22, P< 0.001, PM = 41%; NIE $OR_{ADJUSTED}$ = 1.11, 95%CIs: 1.05–1.18, P< 0.001, PM = 38%). Comparable natural indirect effect estimates were identified in analyses assessing psychotic experiences that were distressing and/or frequent (NIE OR_{CRUDE} = 1.18, 95%CIs: 1.09–1.27, P< 0.001, PM = 40%; NIE $OR_{ADJUSTED}$ = 1.15, 95%CIs: 1.06–1.23, P< 0.001, PM = 36%).

Findings of the mediation analyses were comparable when I assessed associations with psychotic experiences excluding tactile hallucinations (Appendix Table A10), adjusted for schizophrenia PRS (Appendix Table A11) and imputed missing data (Appendix Table A12).

Table 3.3 Results of the mediation analyses with childhood trauma for the associations between autism mean factor score, social communication difficulties and psychotic experiences.

	Unadjusted		Adjusted[2]	
Estimate[1]	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**
Exposure: Autism mean factor score; Outcome: psychotic experiences measured at ages 18 and/or 24 (n = 3,577)				
Natural direct effect	1.08 (0.97–1.21)	0.18	1.06 (0.94–1.20)	0.36
Natural indirect effect	1.06 (1.03–1.08)	<0.001	1.04 (1.02–1.06)	<0.001
Total effect	1.14 (1.02–1.28)	0.02	1.10 (0.97–1.25)	0.14
Proportion mediated	45%		41%	
Exposure: Autism mean factor score; Outcome: psychotic experiences measured at ages 18 and/or 24, distressing/frequent (n = 3,577)				
Natural direct effect	1.15 (0.98–1.35)	0.10	1.15 (0.96–1.37)	0.12
Natural indirect effect	1.07 (1.04–1.10)	<0.001	1.05 (1.02–1.07)	<0.001
Total effect	1.23 (1.04–1.44)	0.01	1.20 (1.01–1.44)	0.04
Proportion mediated	35%		28%	
Exposure: Social communication difficulties; Outcome: psychotic experiences measured at ages 18 and/or 24 (n = 3,326)				
Natural direct effect	1.27 (0.90–1.80)	0.17	1.22 (0.86–1.73)	0.26
Natural indirect effect	1.15 (1.08–1.22)	<0.001	1.11 (1.05–1.18)	<0.001
Total effect	1.46 (1.03–2.06)	0.03	1.36 (0.96–1.92)	0.08
Proportion mediated	41%		38%	
Exposure: Social communication difficulties; Outcome: psychotic experiences measured at ages 18 and/or 24, distressing/frequent (n = 3,326)				
Natural direct effect	1.38 (0.87–2.18)	0.17	1.37 (0.87–2.15)	0.18
Natural indirect effect	1.18 (1.09–1.27)	<0.001	1.15 (1.06–1.23)	<0.001
Total effect	1.62 (1.03–2.55)	0.04	1.57 (1.00–2.45)	0.05
Proportion mediated	40%		36%	

OR, odds ratio; CI, confidence interval.

[1] Estimates based on observations with complete data on exposure, mediator, outcome, and confounders.

[2] Adjusted for the following confounders: child sex, parity, major financial problems, maternal highest educational attainment, maternal anxiety, maternal depression, and child IQ.

3.4 Discussion

3.4.1 Summary of findings

Using population-based birth cohort data, I examined the association between autism polygenic risk, autistic traits in childhood, and psychotic experiences in adulthood. In addition, I assessed the potential confounding role of schizophrenia polygenic risk, and the potential mediating role of childhood trauma. I found that broad autistic traits, as captured by autism factor mean score, and social communication difficulties were associated with psychotic experiences up to age 24. These associations were found to be substantially mediated by trauma in early childhood, and not confounded by schizophrenia polygenic risk. There was no evidence to suggest associations between autism polygenic risk as well as measures of repetitive behaviour, pragmatic language, or sociability and psychotic experiences outcomes.

3.4.2 Comparison to previous evidence

The present study extends previous evidence suggesting associations between autistic traits in childhood and psychotic experiences at age 12[137,138], as well as evidence suggesting associations with psychotic experiences at age 18[140,141]. Specifically, present findings suggest that the associations between autistic traits and psychotic experiences in adulthood are unlikely to be due to either genetic or environmental confounding factors- although importantly, in the case of genetic confounding current PRS approaches capture only a small proportion of genetic variation[235], and in the case of environmental confounding the possibility of unmeasured confounding cannot be excluded. The present findings additionally, emphasise that social communication difficulties in particular, might be important risk factors for later life psychotic outcomes. This is in line with evidence suggesting that difficulties in social functioning are potentially predictive of conversion to psychosis in samples of adolescents and young adults at clinical high risk[236]. In addition, recent evidence from the population-based IMAGEN study, suggested that difficulties in social functioning are mediating the pathways between autism polygenic risk and psychotic experiences at age 18[142], further emphasising the importance of social communication difficulties in psychotic outcomes.

Furthermore, there was evidence suggesting that a substantial proportion of the identified associations was mediated by experiences of interpersonal trauma in childhood. The experience of trauma in childhood is a well-established risk factor for psychotic disorder[91,214,237]. The present findings indicate that trauma may be an important pathway between autistic features and later onset of psychotic experiences, and more work is necessary to examine how (the consequences of) trauma can best be prevented, identified, and intervened in autistic individuals. For instance, there is early work showing that eye movement desensitization and reprocessing (EMDR), a NICE-recommended psychological therapy for post-traumatic stress disorder[238], can be safely and effectively used among individuals with a psychotic disorder[239], and its efficacy for autistic individuals with psychotic symptoms could be assessed. Additionally, elucidating the mechanisms through which traumatic experiences lead to psychosis such as locus of control, and negative schemas, building on work in non-autistic populations, can be an important avenue for future research[237,240].

In contrast to previous studies, in the present study there was no evidence to suggest that autism polygenic risk is associated with psychotic experiences in adulthood. It is important to note that the magnitude and direction of the association estimates of the present study particularly with regards to distressing and/or frequent psychotic experiences, are comparable to the ones in a previous study in UK Biobank and differences in the precision of the association estimates are likely to reflect differences in sample size (e.g., for PRS corresponding to a p threshold 0.05, OR in UK Biobank was 1.10 with 95%CIs: 1.05-1.15, Nsample>120,000[87], whereas in the present study for the same threshold the OR was 1.06 with 95%CIs: 0.94- 1.21, Nsample= 4,013). On this basis, potential associations between autism polygenic risk and psychotic experiences in adulthood cannot be excluded and further research is necessary. A potentially valuable approach to elucidate the links between autism common variant genetic liability to autism and psychotic experiences could be the application of two-sample Mendelian randomization (MR), a method that by using two independent GWAS datasets for the exposure and the outcome respectively, can improve statistical power and precision, as in contrast to PRS approaches, it does not require exposure, outcome and genotype data available in a single sample[199].

3.4.3 Strengths & limitations

Strengths of the present study include its longitudinal design and long-term follow-up as well as the integration of genomic and observational data from in a general population-based cohort.

The study also has several limitations. First, as in most current studies utilising PRS approaches, the variance explained by the autism and schizophrenia PRS is relatively small and therefore the possibility of polygenic associations and genetic confounding cannot be ruled out. In addition, only common variation was assessed, although there is increasing evidence the rare variation such as CNVs might contribute to the autism psychosis co-occurence[87]. Second, the complete-records analysis might have been influenced by selection bias due to attrition. However, analyses using imputed data yielded results comparable to the complete-records association estimates, suggesting that the findings are unlikely to be biased by attrition. Third, a substantial number of models were run in the context of the present study. Although this could increase the likelihood of false-positives, the vast majority of the tests conducted were not independent but interrogated an aspect of the autistic traits-psychotic experiences relationship, with the consistency of the association estimates across analyses increasing confidence that the findings are robust. With regards to the mediation analyses, there was a partial overlap in time between the measurement of autistic traits and exposure to trauma. Although this exposure-mediator overlap might have inflated the estimates, the previously-reported association between social communication difficulties with autism PRS indicates their developmental origins[217,241]. Finally, although in the context of the present study I adjusted for several confounders that could influence the autistic traits-psychotic experiences associations, the possibility of residual confounding (as in every observational analysis), cannot be excluded.

3.5 Conclusions and chapter summary

In summary, using genotype and phenotype data from a population-based birth cohort, the present study provides evidence to suggest that broad autistic traits and especially social communication difficulties in childhood, are associated with psychotic experiences in adulthood. A substantial proportion of these associations were found to be mediated by experience of trauma in childhood. On

the contrary, autism polygenic risk did not appear to be associated with psychotic experiences. The present findings emphasise that phenotypic expression of social communication difficulties and environmental factors such as trauma, might be risk factors for psychotic experiences in adulthood. However, the relatively smaller sample size available for PRS analyses challenges deriving conclusions on the potential contribution of common variant genetic liability to autism on psychotic experiences, while the possibility of residual confounding challenges conclusions on whether the identified associations between autistic traits and psychotic experiences are causal. Triangulation of the present study findings using approaches improving statistical power and robust to residual confounding is necessary in order to elucidate the links between autism and psychosis.

♦

Chapter 4

Causal effects of common variant genetic liability to autism and autistic traits on psychotic experiences and schizophrenia

The following Chapter is utilising 23andMe data, under data access agreement and permission from 23andMe.

♦

4.1 Introduction

In Chapter 3, I found no evidence to suggest associations between autism polygenic risk and psychotic experiences in adulthood, while there was evidence to suggest associations between autistic traits, particularly social communication difficulties, and psychotic experiences in adulthood. I discussed that triangulating evidence can aid conclusions on the potential causal pathways linking autism and psychotic experiences, particularly using approaches that can improve statistical power and precision and are robust to residual confounding. In the present Chapter, I will describe a study utilising two-sample Mendelian randomization (MR) to triangulate the above findings by investigating the causal effects of common variant genetic liability to autism and autistic traits on psychotic experiences, in a sample of 6,123 cases with psychotic experiences and 121,843 controls from the UK Biobank[87].

However, psychotic experiences are only a part of the psychosis spectrum[3,74]. Little is known on the causal links of autism and autistic traits with other conditions of the psychosis spectrum, and particularly its extreme end, schizophrenia. Specifically, conducting adequately powered studies to investigate the associations between autism polygenic risk as well as diagnoses, and schizophrenia later in life can be challenging considering that schizophrenia is a rare outcome (lifetime prevalence of schizophrenia= 0.87%[60,81]). Furthermore, evidence suggesting strong genetic correlations between autism, autistic traits and schizophrenia[36,43], does not necessarily suggest causal relationships[168]. To complicate matters, there is increasing evidence indicating associations between schizophrenia polygenic risk and autism features[113,242]. On this basis, the application of two-sample MR approaches can potentially offer valuable insights into the causal links between genetic liability to autism, autistic

traits and schizophrenia. Specifically, the method allows the assessment of causal effects bidirectionally (genetic liability to autism/autistic traits → schizophrenia; genetic liability to schizophrenia → autism/autistic traits), minimises limitations of observational studies and particularly residual confounding, and maximises power considering (in contrast to PRS and one-sample MR approaches), it does not require exposure, outcome and genotype data available within a single sample.

Overall, two-sample MR can be a powerful approach to assess the causal effects of genetic liability to autism and autistic traits at the two extremes of the psychosis spectrum (psychotic experiences and schizophrenia). In addition, a recent extension of the approach, multivariable MR (MVMR), allows the estimation of direct causal effects, independently of other genetically correlated traits that might confound or mediate the causal pathway (MVMR is applicable in both scenarios[205,243]). This can be particularly important in the context of the present study, considering that IQ presents strong genetic correlations and causal links with autism[36,147], autistic traits[43] and schizophrenia[66,146]. For example, IQ could potentially confound the causal pathways between genetic liability to autism and schizophrenia, considering recent evidence suggesting that it has a positive causal effect on autism[147] and a negative on schizophrenia[146].

Using GWAS summary data on autism, autistic traits, psychotic experiences and schizophrenia, I applied two-sample MR and MVMR to investigate the total and independent of IQ causal effects of:

(i) common variant genetic liability to autism on schizophrenia and psychotic experiences,

(ii) common variant genetic liability to social and non-social autistic traits on schizophrenia and psychotic experiences,

(iii) common variant genetic liability to schizophrenia on autism as well as social and non-social autistic traits.

4.2 Methods

4.2.1 Two-sample Mendelian randomization

An overview of the method and its assumptions can be found in Chapter 2. In brief, MR is a causal inference approach based on the principles of instrumental variables analysis[145,176]. Using common genetic variants as instruments for an exposure of interest, allows the assessment of their causal effects on outcomes[145,167]. Importantly, the method can provide unbiased causal effect estimates under strict assumptions that the instruments should satisfy: (i) they must be robustly associated with the exposure, (ii) they must not be associated with any confounders of the exposure-outcome associations, (iii) they should operate on the outcome entirely through the exposure (i.e., no horizontal pleiotropy)[198]. In the context of the present study I applied two-sample MR in which the effects of the genetic instruments on the exposure and on the outcome are extracted from separate GWASs that have been conducted in independent samples from the same underlying population[199].

4.2.2 Genetic instrument definition

I used GWAS summary data for autism[36], schizophrenia[66], and psychotic experiences[87]. In the case of social autistic traits I used available GWAS summary data on social communication difficulties (phenotype identical to the one used in analyses of Chapter 3, i.e., phenotype assessed with the Social and Communication Disorders Checklist-SCDC- in the ALSPAC cohort)[43] and self-reported empathy (phenotype indexing social autistic traits)[244], whereas in the case of non-social autistic traits I used GWAS summary data on self-reported systemising[43] (phenotype indexing non-social autistic traits and was selected because no other non-social autistic traits GWAS was available at the time of the analyses). Information on the phenotype definition, sample sizes, participants and ancestry can be found in Table 4.1. Further information can be found in the original publications.

In order to retain as many instruments as possible in the analyses, I implemented an approach comparable to proxy lookup[245]. Specifically, instruments were selected from the overlapping set of single nucleotide polymorphisms (SNPs) between each exposure and each outcome GWAS. After restricting to a common set of SNPs across the GWASs, the identified variants were clumped in PLINK 1.9 using the 1000Genomes European ancestry reference panel, and an r^2= 0.01, within a

10,000 kb window. Among the independent variants, instruments were defined using a genome-wide significance threshold of $p <= 5*10^{-08}$. In the case of autism, social communication difficulties, empathy, and systemising GWASs, this threshold yielded <= 2 instruments. To increase the power of these analyses and allow the implementation of sensitivity analyses, I relaxed the p-value threshold to $5*10^{-07}$ (leading to the inclusion of more instruments). A similar approach for genetic instrument definition has been used in previous studies[246,247]. Finally, following the approach described above I extracted instruments for psychotic experiences. However, I did not perform any analyses with psychotic experiences as the exposure, due to the small number of genetic instruments (n<= 2, even after applying the relaxed p-value threshold $5*10^{-07}$). Figures B1-B10 in the Appendix, depict the process of instrument definition for each analysis. Details on the effect sizes, standard errors and p-values of the instruments can be found in the Appendix Tables B9-B23.

Table 4.1 Details of the genome-wide association studies (GWASs) used in the present study.

Phenotype	Phenotype Definition	Ncases	Ncontrols	Ntotal	Sample	Ancestry
Autism	Autism diagnosis	18,381	27,969	46,350	PGC+iPSYCH	European
Social communication difficulties	Mother reposted Social and Communication Disorders Checklist (SCDC) scores- higher scores indicating more difficulties.	NA	NA	5,421	ALSPAC	European
Empathy	Self-reported Empathy Quotient (EQ) scores- higher scores indicating more empathising abilities, i.e. the ability to recognize other peoples' intentions and feelings.	NA	NA	46,861	23andMe	European
Systemising	Self-reported Systemising Quotient-Revised (SQ-R) scores- higher scores indicating higher systemising tendency, i.e. higher tendency towards searching and recognising patterns and identifying input-operation-output relationships.	NA	NA	51,564	23andMe	European
Schizophrenia	Schizophrenia/schizoaffective disorder diagnosis	69,369	236,642	306,011	91 cohorts	Predominantly European (80%)
Psychotic experiences	Self-reported any psychotic experiences in Mental Health Questionnaire (MHQ)	6,123	121,843	127,966	UK Biobank	European

4.2.3 Harmonisation

In order for the causal effect estimates of both exposure and outcome to be expressed per increasing allele, the alleles of the outcome variants were harmonised on the exposure. In cases of palindromic SNPs, I used effect allele frequency to infer the strand and harmonise accordingly. The only exception was the social communication difficulties GWAS, in which effect allele frequency was not provided, and therefore all palindromic SNPs were excluded from the analyses.

4.2.4 Inverse Variance Weighted MR

The Inverse Variance Weighted (IVW) method was used, which is a weighted generalised linear regression of the SNP-outcome coefficients on the SNP-exposure coefficients, with the intercept term constrained to zero, giving an overall causal effect estimate of the exposure on the outcome[201].

4.2.5 Instrument Strength

To assess the possibility of weak instrument bias influencing the IVW, I estimated the mean F statistic of the instruments included in the analysis. As a rule of thumb, the IVW is unlikely to suffer from weak instrument bias if mean $F>10$[248].

4.2.6 Sensitivity Analyses

I assessed the consistency of the IVW causal effect estimates using a series of sensitivity analyses, including: MR Egger regression[201,249], Weighted Median[250], Weighted Mode[204]. Detailed information on each sensitivity analysis conducted in the present study can be found in Table 4.2.

As around 20% of participants in the latest schizophrenia GWAS used for the primary analyses were of East Asian ancestry[66], I assessed the possibility of bias by population structure influencing the causal effect estimates[143] by repeating analyses using the Ripke et al., 2014 schizophrenia GWAS summary data[227] on participants of European ancestry only. Details on the genetic instruments for these analyses can be found in Appendix Tables B11, B14, B17, B20, B23.

Table 4.2 Sensitivity analyses to test the robustness of the Mendelian randomization (MR) causal effect estimates.

METHOD	DESCRIPTION
MR Egger Regression	Generates a causal effect estimate by performing a generalised linear regression of the SNP-outcome coefficients on the SNP-exposure coefficients with an unconstrained intercept term. This way, the intercept parameter indicates the pleiotropic effect* of the SNPs on the outcome, while the slope offers a causal effect estimate accounting for any pleiotropic effects. The method assumes that there is no measurement error in the instruments (NOME assumption)[201].
I2GX	Adaptation of the I2 statistic within the two-sample MR context. Assesses the degree of regression dilution in the MR-Egger causal estimate, due to uncertainty in the SNP-exposure estimates[249].
SIMEX corrected MR Egger	MR Egger causal effect estimate adjusted for regression dilution[249].
Weighted Median	Generates a causal effect estimate based on the ratios of the SNP-outcome effects to the SNP-exposure effects assuming that at least 50% of weights in the analyses stem from valid instruments[250].
Weighted Mode	Finds the most common effect estimate of the instruments and assumes that it stems from valid instruments. Generates a causal effect estimate using the mode of a smoothed empirical density function of the individual instruments, weighted by each instrument's relative precision[204].

*Pleiotropic effects: The SNP has direct effects on the outcome through pathways other than the exposure. The presence of pleiotropic effects invalidate**s** one of the main MR assumptions.

4.2.7 Assessing the possible influence of IQ in the identified effects

I assessed the possible influence of IQ in the estimated causal effects, by following two approaches:

(i) Univariable two-sample MR using GWAS summary data on autism excluding intellectual disability cases.

The IQ range of participants in the latest autism GWAS, used in the present analyses, was broad and a small proportion of participants presented intellectual disabilities (IQ<70)[36]. Considering this, I used autism GWAS summary data from a sub-sample of the iPSYCH excluding all intellectual disability cases (Ncases= 11,203; Ncontrols= 22,555) and investigated causal links with schizophrenia and psychotic experiences by performing univariable two-sample MR. Instrument definition, harmonisation, primary and sensitivity analyses were conducted based on the principles described in the methods above. Appendix Figures B5 & B10 visualise the process of instrument definition, and Appendix Tables B21-B23 contain detailed information on the instruments used.

(ii) Multivariable two-sample MR

I used the latest (by the time of the analyses) GWAS for IQ[146] and extracted 212 genome-wide significant ($p=<5*10^{-08}$) and independent instruments ($r^2=0.01$; 10,000kb window). These instruments were entered in the models of each analysis, in order to estimate the direct effects of genetic liability to autism and autistic traits on risk of schizophrenia and psychotic experiences, independent of IQ. The full list of instruments for each analysis was clumped ($r^2=0.01$; 10,000kb window), harmonised, and entered in an IVW regression model. The same process was followed for the analyses investigating the direct, independent of IQ, effects of genetic liability to schizophrenia on autism and autistic traits. Details on the MVMR method and analytic process have been described elsewhere[251]. The instruments for IQ used in the analyses can be found in Appendix Table B24.

Finally, in the presence of evidence suggesting bidirectional causal links between common variant genetic liability to schizophrenia and IQ[66,146], I acknowledged the possibility that IQ might be a collider in the causal pathway linking autism, autistic traits and schizophrenia. Specifically, if common variant genetic liability to autism and autistic traits has causal effects on IQ, then this would

suggest that IQ might be a collider and entering it in the models would amplify bias in the causal effect estimates[252]. An illustration of this possibility can be found in Figure 4.1. I assessed this possibility by conducting MR analyses on the causal effects of genetic liability to autism, social communication difficulties, empathy, systemising on IQ.

All univariable two-sample MR analyses were performed using the TwoSampleMR R package[253]. All multivariable Mendelian randomization analyses were performed in R version 3.5.1.

A summary of the study aims, and analyses is provided in Table 4.3 (please note that sensitivity analyses are not included in this table).

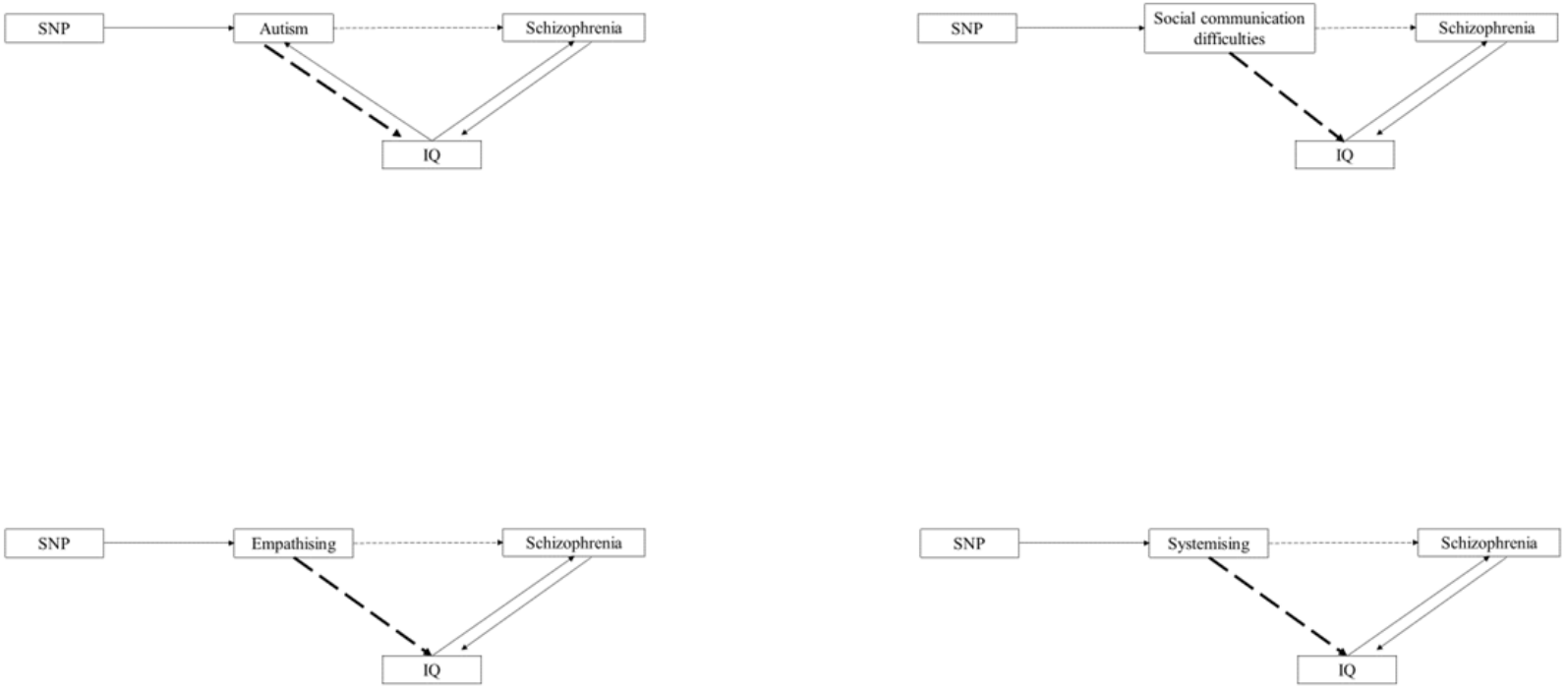

Figure 4.1 The possibility of collider bias in the present multivariable MR analyses.

Based on previous MR evidence, common variant genetic liability to schizophrenia presents a bidirectional causal relationship with IQ. If common variant genetic liability to autism and autistic traits has causal effects on IQ, then this might suggest that IQ is a collider. Please note that the figure is not a directed acyclic graph (DAG). Solid arrows have been oriented based on previous evidence by Savage et al., 2018; Dardani et al., 2021, Ripke et al., 2020. Dashed arrows indicate the causal links that were investigated in the present study to assess the possibility of collider bias.

Table 4.3 Summary of aims, exposures, outcomes and methods of the present study. G denotes genetic instrument.

Study Aim	Exposures	Outcome	Method
Causal effects of genetic liability to autism on the two extremes of the psychosis spectrum.	G→ Autism	Psychotic experiences	Univariable two-sample MR
		Schizophrenia	
The influence of IQ on the causal effects.	G→ Autism excluding ID	Psychotic experiences	Univariable two-sample MR
		Schizophrenia	
	G→ Autism ↘ IQ	Psychotic experiences	Multivariable MR
		Schizophrenia	
Causal effects of genetic liability to social and non-social autistic traits on the two extremes of the psychosis spectrum.	G→ Autistic traits	Psychotic experiences	Univariable two-sample MR
		Schizophrenia	
The influence of IQ on the causal effects.	G→ Autism ↘ IQ	Psychotic experiences	Multivariable MR
		Schizophrenia	
Causal effects of genetic liability to schizophrenia on autism.	G→ Schizophrenia	Autism	Univariable two-sample MR
The influence of IQ on the causal effects.	G→ Schizophrenia	Autism excluding ID	Univariable two-sample MR
	G→ Schizophrenia ↘ IQ	Autism	Multivariable MR
Causal effects of genetic liability to schizophrenia on social and non-social autistic traits	G→ Schizophrenia	Autistic traits	Univariable two-sample MR
The influence of IQ on the causal effects.	G→ Schizophrenia ↘ IQ	Autistic traits	Multivariable MR

4.3 Results

4.3.1 Causal effects of genetic liability to autism on risk of schizophrenia and psychotic experiences

Causal effects on risk of schizophrenia

The mean F statistic of the autism instruments was 28 (F range: 26- 36) suggesting good instrument strength. Univariable MR analyses provided no evidence of a causal effect of genetic liability to autism on risk of schizophrenia ($_{IVW}$OR= 1.01; 95%CIs: 0.85 to 1.19; p= 0.91; Table 4.4). The direction of causal effect estimates was largely consistent across sensitivity analyses and the confidence intervals were overlapping (Appendix Table B25). Analyses with the European ancestry only schizophrenia GWAS yielded comparable effect estimates and overlapping confidence intervals to the primary analyses (Appendix Table B26).

The influence of IQ on the causal effects

The mean F statistic of the instruments extracted from the autism GWAS which excluded ID cases, was 29 (F range: 26- 37), indicating adequate instrument strength. In line with the primary analyses, there was no evidence to suggest a causal effect on risk of schizophrenia ($_{IVW}$OR= 1.06; 95%CIs: 0.96 to 1.17; p= 0.27; Table 4.4; Appendix Tables B27-B28).

MVMR analyses, using instruments for both autism and IQ in the IVW regression models, provided evidence of a direct, independent of IQ, effect of genetic liability to autism on risk of schizophrenia ($_{IVW}$OR= 1.24; 95%CIs: 1.11 to 1.38; p= 0.0002; Table 4.4; Appendix Tables B29-B30). There was no evidence to suggest that IQ was a collider on the causal pathway, i.e., there was no evidence to suggest a causal effect of genetic liability to autism on IQ (Appendix Table B31 and Figure 4.2).

Causal effects on psychotic experiences

The mean F statistic of the autism instruments was 28 (F range: 26-36). There was no evidence to suggest a causal effect of genetic liability to autism on psychotic experiences ($_{IVW}$OR= 1.1; 95%CIs: 0.93 to 1.3; p= 0.26; Table 4.4). Causal effect estimates were largely consistent across analyses and the confidence intervals were overlapping (Appendix Table B32).

The influence of IQ on the causal effects

The mean F statistic of the instruments extracted from the autism GWAS which excluded ID cases was 29 (F range: 26- 37). There was no evidence to suggest a causal effect of genetic liability to autism on psychotic experiences ($_{IVW}$OR= 0.98; 95%CIs: 0.86 to 1.11; p= 0.74; Table 4.4; Appendix Table B33). This was further supported by MVMR analyses, providing no evidence of any direct, independent of IQ, effect of genetic liability to autism on psychotic experiences ($_{IVW}$OR= 1.06; 95%CIs: 0.96 to 1.18; p= 0.26; Table 4.4; Appendix Table B34).

4.3.2 Causal effects of common variant genetic liability to autistic traits on risk of schizophrenia and psychotic experiences

Causal effects on risk of schizophrenia

The mean F statistic of the social communication, empathy and systemising instruments was 27 (F range: 26-28), 27 (F range: 26- 30), and 28 (F range: 26- 31) respectively. There was no evidence to suggest a causal effect of common variant genetic liability to any of the autistic traits on risk of schizophrenia (SCDC: $_{IVW}$OR= 1.2; 95%CIs: 0.82 to 1.75; p= 0.34; EQ: $_{IVW}$OR= 0.99; 95%CIs: 0.96 to 1.02; p= 0.44; SQ: $_{IVW}$OR= 1; 95%CIs: 0.99 to 1.02; p= 0.83; Table 4.4). This was further supported by sensitivity analyses (Appendix Tables B35-B40).

The influence of IQ on the causal effects

MVMR analyses did not provide evidence of direct, independent of IQ, effects of common variant genetic liability to any of the autistic traits on risk of schizophrenia (SCDC: $_{IVW}$OR= 1.44; 95%CIs: 0.83 to 2.48; p= 0.19; EQ: $_{IVW}$OR= 1.01; 95%CIs: 0.98 to 1.03; p= 0.52; SQ: $_{IVW}$OR= 1; 95%CIs: 0.99 to 1.02; p= 0.83; Table 4.4; Appendix Tables B41-B46). IQ was unlikely to be a collider in the causal pathways with the only exception being social communication difficulties as there was evidence to suggest a potential causal effect of genetic liability to social communication difficulties on IQ (Appendix Tables B47-B52 and Figure 4.2).

Causal effects on psychotic experiences

The mean F statistic of the social communication, empathy and systemising instruments was 27 (F range: 26-28), 27 (F range: 26- 30), and 28 (F range: 26- 31) respectively. There was no evidence to suggest a causal effect of common variant genetic liability to (higher) empathy and systemising on psychotic experiences (EQ: $_{IVW}$OR= 1.02; 95%CIs: 0.96 to 1.08; p= 0.59; SQ: $_{IVW}$OR= 1.01; 95%CIs: 0.98 to 1.03; p= 0.73; Table 4.4; Appendix Tables B53, B54). There was stronger evidence (albeit still weak) of a causal effect of common variant genetic liability to social communication difficulties on psychotic experiences (SCDC: $_{IVW}$OR= 2.2; 95%CIs: 0.96 to 5.02; p= 0.06; Table 4.4). Although the causal effect estimates were consistent across sensitivity analyses, the confidence intervals were wide indicating the limited power of this analysis (Appendix Table B55).

The influence of IQ in the causal effects

After entering IQ in the models, there was no evidence to suggest a direct causal effect of common variant genetic liability to social communication difficulties and (higher) empathy on psychotic experiences (SCDC: $_{IVW}$OR= 1.14; 95%CIs: 0.67 to 1.93; p= 0.63; EQ: $_{IVW}$OR= 0.99; 95%CIs: 0.97 to 1.02; p= 0.63), and some weak evidence of a direct causal effect of systemising (SQ: $_{IVW}$OR= 1.02; 95%CIs: 1 to 1.03; p= 0.02; Table 4.4; Appendix Tables B56-B58).

Table 4.4 Causal effect estimates, corresponding 95% confidence intervals and p-values of the analyses investigating causal effects of common variant genetic liability to autism and autistic traits on risk of schizophrenia and psychotic experiences.

Exposure (common variant genetic liability)	Outcome	Method	Estimated Effect	OR	95% CIs	P
Autism	Schizophrenia	Two-sample MR	Total	1.01	0.85 to 1.19	0.91
Autism excluding ID cases	Schizophrenia	Two-sample MR	Total	1.06	0.96 to 1.17	0.27
Autism	Schizophrenia	MVMR	Direct, independent of IQ	1.24	1.11 to 1.38	0.0002
Autism	Psychotic Experiences	Two-sample MR	Total	1.1	0.93 to 1.3	0.26
Autism excluding ID cases	Psychotic Experiences	Two-sample MR	Total	0.98	0.86 to 1.11	0.74
Autism	Psychotic Experiences	MVMR	Direct, independent of IQ	1.06	0.96 to 1.18	0.26
Social Communication Difficulties	Schizophrenia	Two-sample MR	Total	1.2	0.82 to 1.75	0.34
Social Communication Difficulties	Schizophrenia	MVMR	Direct, independent of IQ	1.44	0.83 to 2.48	0.19
Social Communication Difficulties	Psychotic Experiences	Two-sample MR	Total	2.2	0.96 to 5.02	0.06
Social Communication Difficulties	Psychotic Experiences	MVMR	Direct, independent of IQ	1.14	0.67 to 1.93	0.63
Empathy	Schizophrenia	Two-sample MR	Total	0.99	0.96 to 1.02	0.44
Empathy	Schizophrenia	MVMR	Direct, independent of IQ	1.01	0.98 to 1.03	0.52
Empathy	Psychotic Experiences	Two-sample MR	Total	1.02	0.96 to 1.08	0.59
Empathy	Psychotic Experiences	MVMR	Direct, independent of IQ	0.99	0.97 to 1.02	0.63
Systemising	Schizophrenia	Two-sample MR	Total	1	0.99 to 1.02	0.83
Systemising	Schizophrenia	MVMR	Direct, independent of IQ	1	0.99 to 1.02	0.97
Systemising	Psychotic Experiences	Two-sample MR	Total	1.01	0.98 to 1.03	0.73
Systemising	Psychotic Experiences	Two-sample MR	Direct, independent of IQ	1.02	1 to 1.03	0.02

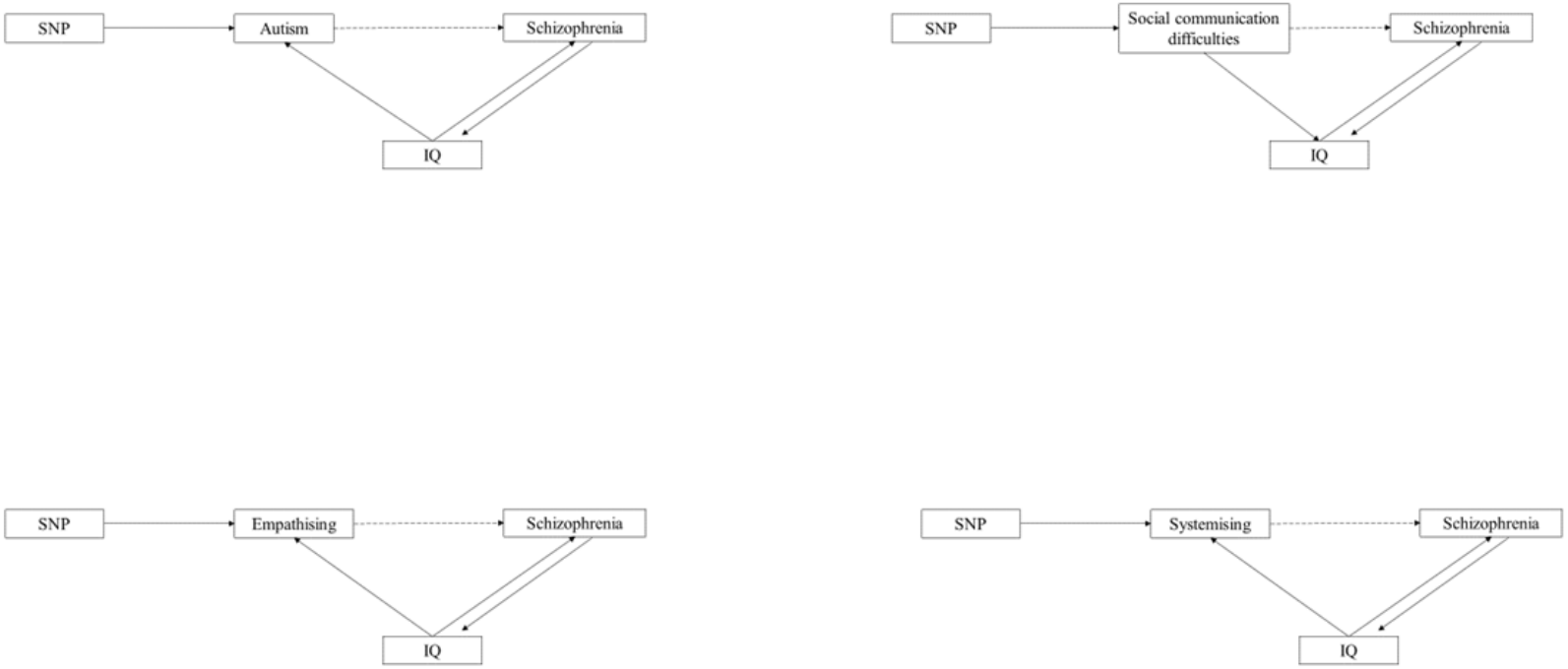

Figure 4.2 Causal relationships between common variant genetic liability to autism, autistic traits and IQ identified in the present study

4.3.3. Causal effects of common variant genetic liability to schizophrenia on autism and autistic traits

Following the above section on whether the genetic liability to autism influences the risk of schizophrenia, I then proceeded to look at the reverse direction. This section shows the results of analyses I conducted to investigate the effects of genetic liability to schizophrenia on the risk of autism and autistic traits

Causal effects on autism

The mean F statistic of the schizophrenia instruments was 44 (F range: 30- 175). There was evidence to suggest a causal effect of common variant genetic liability to schizophrenia on autism ($_{IVW}$OR= 1.15; 95%CIs: 1.1 to 1.19; p= 1e-10; Table 4.5; Appendix Table B59). Effect estimates were consistent across sensitivity analyses as well as after using instruments extracted from the European ancestry only schizophrenia GWAS (Appendix Table B60).

The influence of IQ in the causal effects

Analyses using the autism GWAS excluding ID cases as the outcome, yielded comparable effect estimates to the primary analyses ($_{IVW}$OR= 1.15; 95%CIs: 1.09 to 1.2; p= 2e-08; Table 4.5; Appendix Tables B61-B62). This was further supported by MVMR analyses, investigating the direct, independent of IQ, causal effects of common variant genetic liability to schizophrenia on autism ($_{IVW}$OR= 1.19; 95%CIs: 1.13 to 1.24; p= 1e-12; Table 4.5; Appendix Tables B63-B64).

Causal effects on autistic traits

There was evidence to suggest a causal effect of common variant genetic liability to schizophrenia on social communication difficulties ($_{IVW}$ β= 0.02; 95%CIs: 0.007 to 0.03; p= 0.002; Table 4.5). Causal effect estimates across sensitivity analyses were consistent and confidence intervals were overlapping (Appendix Tables B65-B66). There was some evidence of a causal effect on empathy ($_{IVW}$ β= 0.31; 95%CIs: 0.07 to 0.55; p= 0.01; Table 4.5; Appendix Tables B67-B68) and there was weak evidence to suggest an effect on systemising ($_{IVW}$ β= 0.34; 95%CIs: -0.06 to 0.74; p= 0.09; Table 4.5; Appendix Tables B69-B70).

The influence of IQ in the causal effects

After entering IQ in the IVW models, there was evidence of a direct, independent of IQ, effect of genetic liability to schizophrenia on social communication difficulties ($_{IVW}$ β= 0.02; 95%CIs: 0.005 to 0.03; p= 0.006; Table 4.5; Appendix Tables B71-B72), but not empathy ($_{IVW}$ β= 0.17; 95%CIs: -0.08 to 0.41; p= 0.18; Table 4.5; Appendix Tables B73-B74) or systemising ($_{IVW}$ β= 0.38; 95%CIs: -0.02 to 0.77; p= 0.06; Table 4.5; Appendix Tables B75-B76).

Table 4.5 Causal effect estimates, corresponding 95% confidence intervals and p-values of the analyses investigating causal effects of genetic liability to schizophrenia on autism and autistic traits.

Exposure (common variant genetic liability)	Outcome	Method	Estimated Effect	OR	95% CIs	P
Schizophrenia	Autism	Two-sample MR	Total	1.15	1.1 to 1.19	1.31E-10
Schizophrenia	Autism excluding ID cases	Two-sample MR	Total	1.15	1.09 to 1.2	2.30E-08
Schizophrenia	Autism	MVMR	Direct, independent of IQ	1.19	1.13 to 1.24	1.35E-12
Exposure (common variant genetic liability)	**Outcome**	**Method**	**Estimated Effect**	**β**	**95% CIs**	**P**
Schizophrenia	Social Communication Difficulties	Two-sample MR	Total	0.02	0.01 to 0.04	0.002
Schizophrenia	Social Communication Difficulties	MVMR	Direct, independent of IQ	0.02	0.005 to 0.03	0.006
Schizophrenia	Empathy	Two-sample MR	Total	0.31	0.07 to 0.55	0.01
Schizophrenia	Empathy	MVMR	Direct, independent of IQ	0.17	-0.08 to 0.41	0.18
Schizophrenia	Systemising	Two-sample MR	Total	0.34	-0.06 to 0.74	0.09
Schizophrenia	Systemising	MVMR	Direct, independent of IQ	0.38	-0.02 to 0.77	0.06

4.4 Discussion

4.4.1 Summary of findings

Within an MR and MVMR framework, I investigated the causal links between common variant genetic liability to autism, autistic traits, schizophrenia and psychotic experiences. In summary, there was no evidence of a total causal effect of genetic liability to autism and autistic traits on schizophrenia, although MVMR analyses indicated a direct, independent of IQ, effect of genetic liability to autism on schizophrenia. Furthermore, there was no evidence of a total or direct causal effect of genetic liability to autism, empathy, and systemising on psychotic experiences, but there was some evidence to suggest a causal effect of genetic liability to social communication difficulties on psychotic experiences. Finally, there was evidence of total and direct, independent of IQ, effects of common variant genetic liability to schizophrenia on autism as well as social communication difficulties.

4.4.2 Comparison to previous evidence

The finding of a direct, but not a total, effect of common variant genetic liability to autism on risk of schizophrenia, can be explained in the context of evidence on the potential role of IQ in autism and schizophrenia. Specifically, parental common variant genetic liability to higher IQ has been found to be causally related to autism[146,254], and there is evidence suggesting that probands with autism tend to over-inherit IQ increasing genetic variants compared to their unaffected siblings[38]. This is further supported by recent MR evidence indicating causal effects of common variant genetic liability to higher IQ on autism[147]. In contrast, genetic liability to higher IQ appears to be linked to lower risk for schizophrenia[146], and more importantly, high IQ has been found to attenuate the risk even in individuals with high polygenic loading for schizophrenia[255]. Therefore, IQ appears to be a confounder of the genetic liability to autism-schizophrenia causal pathway (which is also evident in Figure 4.2) that, at least partly, masks the causal effects.

Based on the above, in the present study there was evidence suggesting that common variant genetic liability to autism causally influences risk for schizophrenia over and above the risk-decreasing effect of common variant genetic liability to higher IQ on schizophrenia. Schizophrenia risk in people

carrying increased common variant genetic liability to autism, could be influenced through phenotypic or sub-phenotypic features of autism, which are independent of IQ. Such phenotypic and sub-phenotypic features could be anxiety[256,257], structural and functional brain alterations as well as neurocognitive features[258]. This could be particularly important especially considering current challenges and limited availability of mental health intervention approaches for people with autism and intellectual disabilities[259,260].

In the case of psychotic experiences, there was no evidence to suggest a causal effect of common variant genetic liability to autism. This finding seems to support findings from Chapter 3, in which there was no evidence of associations between autism polygenic risk and psychotic experiences in adulthood. Furthermore, there was some weak evidence to support a potentially causal role of common variant genetic liability to social communication difficulties on psychotic experiences. Despite the limited power of this analysis, the result is in line with the findings of the study in Chapter 2, in which there was evidence of associations between social communication difficulties in childhood and psychotic experiences in adulthood. Observational evidence in Chapter 2, in combination with present MR evidence are consistent with a potentially causal role of genetic liability and phenotypic expression of social communication difficulties in psychotic experiences later in life.

Finally, there was evidence of a total and direct, independent of IQ, causal effect of genetic liability to schizophrenia on autism and social communication difficulties in childhood. These findings are in support of accumulating evidence suggesting associations between family history of schizophrenia and offspring autism[112] as well as associations between polygenic risk for schizophrenia and social communication difficulties in childhood as measured by the Social and Communication Disorders Checklist[113]. The pathways via which genetic liability to schizophrenia might causally influence autism are largely unknown, although there is recent evidence suggesting that autistic individuals tend to over-inherit schizophrenia polygenic risk from their parents (compared to their non-autistic siblings)[38]. In the context of the present study, it was beyond my aims to investigate whether the identified effects are parental in origin but future studies utilising novel extensions of MR such as within-families MR are expected to offer valuable insights[261].

4.4.3 Strengths and limitations

This study benefitted from using latest and largest GWAS summary data for each phenotype of interest. I performed several sensitivity analyses to test the robustness of the findings and investigated the possible role of IQ in the identified causal effects by using two distinct approaches- univariable two-sample MR using GWAS summary data on autism excluding intellectual disability cases, and MVMR. Finally, I tested the possibility of collider bias influencing the findings by investigating the bidirectional causal links of common variant genetic liability to autism and autistic traits with IQ.

However, there are limitations that should be considered. Firstly, I conducted multiple tests due to the number of exposures under study. This could have led to a number of false positives[262]. For this reason, I based the interpretation of the findings on the magnitude of the effects, the consistency of the effect estimates across sensitivity analyses as well as existing evidence in the literature. Secondly, the analyses did not all have the same power and therefore are not directly comparable (e.g., common genetic liability to autism on schizophrenia vs common genetic liability to autism on risk of psychotic experiences). This limitation can be overcome by application of these methods to data from future, larger GWAS. Finally, the results using GWAS summary data on self-reported phenotypes (empathy, systemising, psychotic experiences) should be interpreted with caution, as there is evidence suggesting that case definition based on self-reports can yield genetic associations of very low specificity to the phenotype of interest and therefore bias study findings[263].

4.5 Conclusions and chapter summary

The present study highlights that over and above IQ, phenotypic and sub-phenotypic manifestations of common variant genetic liability to autism could causally influence schizophrenia risk. In addition, it triangulates the findings of Chapter 2, by identifying a potentially causal effect of common variant genetic liability to social communication difficulties on risk of psychotic experiences in adulthood. Future research into the potential synergy of autism common genetic variation, autism phenotypic expressions, cognitive, and social factors, is necessary in order to improve current understanding on the causal mechanisms underlying the autism-psychosis co-occurrence and inform interventions for autistic individuals with psychotic disorders.

Part II: Shared Immunological Pathways

Chapter 5

Uncovering the causal role of immune response in autism to orient investigations on shared causal immunological markers with schizophrenia.

This chapter closely resembles sections from the following preprint:

Sadik A, Dardani C*, Pagoni P, Havdahl A, Stergiakouli E, Grove J, The iPSYCH Autism Spectrum Disorder Working Group, Khandaker GM, Sullivan SA, Zammit S, Jones HJ, Davey Smith G, Dalman C, Karlsson H, Gardner RM, Rai D. Parental inflammatory bowel disease and autism in the offspring: Triangulating the evidence using four complementary study designs. medRxiv; 2021; doi: https://www.medrxiv.org/content/10.1101/2021.06.09.21258393v1.full (Accepted/in press *Nature Medicine*)

*Joint first author

♦

5.1 Introduction

Beyond the causal pathways linking autism to psychosis, another potential explanation for their co-occurrence, could be shared risk factors. In Chapter 1, I reviewed evidence on the hypothesis that immunological processes might constitute a shared pathway to autism and psychosis[130]. According to this hypothesis, the phenotypic features that autism and psychosis share, could be a result of shared underlying immune mechanisms acting in utero, whereas their distinct features could be a result of genetic, epigenetic and immunomodulatory mechanisms (referring to mechanisms that respond to inflammation) specific to each condition[130,264].

Accumulating evidence from observational and polygenic approaches have led to an increasing understanding on the potential causal role of immunological pathways (especially the IL6/IL6R pathway) in psychosis[265,266]. For example, elevated levels of maternal C-Reactive Protein (CRP-acute phase protein that is produced after activation of the IL6/IL6R pathway[267]) in pregnancy, have been found to be associated with offspring schizophrenia later in life[126]. However, in the case of autism, the potentially causal role of immune response is still unclear. Although there is observational evidence suggesting associations between atypical levels of acute phase proteins in maternal blood serum, maternal infections during pregnancy as well as parental autoimmune conditions and offspring autism[153,268,269], it is unknown whether these observational associations are causal or instead a result of

confounding. Identifying whether immune response is causally implicated in autism is an important first step towards identifying causal immunological pathways that might be shared with psychosis.

In the following study I used a comprehensive approach to: (i) triangulate observational evidence relating to associations between maternal immune response and offspring autism, and (ii) identify specific potentially causal immunological pathways in autism. Specifically, I assessed the associations between parental inflammatory bowel disease (IBD) and offspring autism. IBD is a chronic autoimmune condition associated with immune system dysregulation and intestinal microbiome alterations[270]. It has two major subtypes, Crohn's disease and ulcerative colitis (UC). There is increasing understanding on the immunological pathways implicated in IBD, with studies suggesting that T-cell subsets and their product cytokines have a central role in the onset, and course of the condition[271–274]. Therefore, evidence on a potentially causal link between parental IBD and offspring autism, can orient investigations on specific cytokines that might have causal effects on autism.

I conducted four complementary studies (see Figure 5.1 for a summary) to investigate: (1) associations between parental diagnoses of IBD and offspring autism in a nationwide cohort in Sweden; (2) genetic correlation between IBD and autism using genome-wide association study (GWAS) summary statistics; (3) polygenic associations between maternal common variant genetic liability to IBD and offspring autistic traits in a large UK birth cohort; and (4) potential causal effects of common variant genetic liability to IBD on autism and the possibility of reverse causation using bidirectional two-sample Mendelian randomization (MR). Each approach applied in the context of the present study has distinct strengths and sources of bias, thus providing complementary evidence on distinct aspects of the parental IBD-offspring autism associations (see Table 5.1 for a summary).

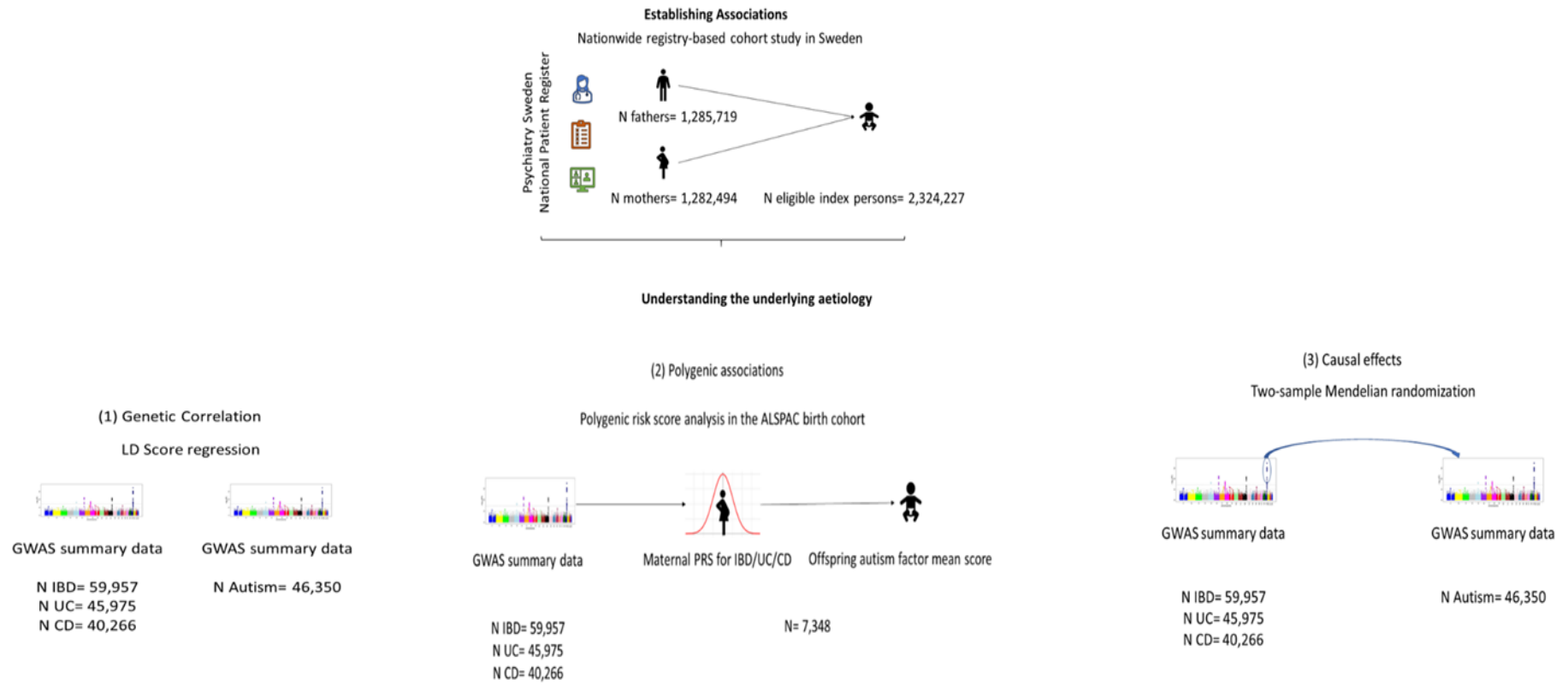

Figure 5.1 Summary of studies conducted in the present study, aiming at investigating the links between parental diagnoses of IBD and offspring autism and elucidating their underlying aetiology.

GWAS: Genome-wide association study; IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease.

Table 5.1 Summary of the research questions, data sources, key strengths and limitations of each methodological approach applied in the context of the present study.

Method	Research question	Data sources	Key strengths	Key limitations
Nationwide registry-based cohort study in Sweden	Are parental diagnoses of IBD associated with autism in the offspring?	Medical & administrative registers	• Large diverse total population, intergenerational sample • Prospective recording of data. • Low rate of loss to follow up. • Large availability of confounder data.	• Unmeasured confounding. • Exposure misclassification.
Linkage Disequilibrium score regression	Is there a shared genetic background between IBD and autism?	GWAS summary data	• Use of GWAS summary data instead of twin data or individual level data maximizes sample sizes and power. • Indicates genetic correlation due to linkage disequilibrium or pleiotropy.	• Cannot assess causality (since it assesses correlation).
Polygenic risk score analysis in the ALSPAC cohort	Is maternal genetic liability for IBD associated with childhood broad autistic traits?	GWAS summary data and individual level genotype and phenotype data	• Estimates the underlying common variant genetic liability for IBD in each genotyped mother of the cohort, regardless of diagnosis. This overcomes limitations of observational studies, such as measurement error in the exposure. • Can provide indication on potentially genetically transmitted vs in utero effects through the assessment of the maternal vs offspring underlying genetic liability for IBD. • Large birth cohort • Prospectively collected information	• Cannot decipher whether the identified associations are causal or due to pleiotropy. • Polygenic risk scores at lower p-value thresholds might not capture the phenotype adequately. • Attrition can influence association estimates.
Two-sample Mendelian randomization	Does genetic liability to IBD have a causal effect on autism?	GWAS summary data, exposure proxied by variants robustly associated with the exposure	• Using common variants as instruments for IBD, allows the assessment of causal effects. • Allows the assessment of reverse causation. • Allows the assessment of the influence of pleiotropy.	• Cannot decipher whether the identified causal effect is of parental origin. • Can be biased by dynastic effects and assortative mating.

5.2 Methods

5.2.1 Investigating associations between parental diagnoses of IBD and offspring autism- Swedish cohort study.

Individual-level data from 'Psychiatry Sweden', a comprehensive national register linkage, were used to investigate whether parental IBD diagnosis is associated with offspring autism diagnosis.

All children born in Sweden from 1-January-1987 to 31-December-2010 (n= 2,837,045) were eligible index persons, with follow-up to 31-December-2016. Exclusion criteria were: children born outside Sweden (n=292,023), not registered in the Medical Birth Register (n=74,240), resident in Sweden for <5 years (n=23,495), multiple pregnancy (n=67,309), adopted (n=2,425), known genetic/metabolic causes of neurodevelopmental conditions (e.g. trisomies) (n=7,873) or incomplete parental records (n=45,453)[275]. The study population included 2,324,227 offspring born to 1,282,494 mothers and 1,285,719 fathers (Figure 5.2). The Stockholm Regional Ethical Review Committee (DNR 2010/1185-31/5) approved the study.

Offspring autism was identified in the National Patient Register (NPR) using ICD-9 and ICD-10 codes (Appendix Table C4). Lifetime history of parental IBD, Crohn's disease (Crohn's) and ulcerative colitis (UC) were identified using ICD-9 and ICD-10 codes in the NPR (Appendix Figure C1**,** Appendix Table C4).

Using STATA/MP15, the odds ratios and 95% confidence intervals of the association of mother's and father's diagnosis of IBD (any IBD, Crohn's, or UC) with offspring autism were estimated, using generalised estimating logistic models with robust standard errors accounting for clustering of multiple children born to the same parents.

Model 1 was unadjusted. Model 2 was adjusted for parental age at delivery[276], migrant status[277], education level, family income quintile at birth[278], parents' history of psychiatric diagnosis prior to the birth of the child and offspring sex, birth year and birth order. Model 3 was additionally mutually adjusted for maternal and paternal IBD diagnoses to avoid bias from assortative mating[279]. As a sensitivity analysis, parental IBD diagnoses were restricted to those recorded prior to the birth of the

index person and investigated associations with offspring autism. Additionally, associations between any parental IBD diagnoses and offspring autism with and without intellectual disabilities (ID) were investigated separately, since these groups may have distinct genetic and environmental risk factors[280–283] and outcomes[284,285]. I led the formulation of the analysis plan for this study. However, I was unable to travel to Sweden due to COVID-19 travel restrictions, and therefore Dr Renee Gardner, based at the Karolinska Institutet in Stockholm conducted this part of the study.

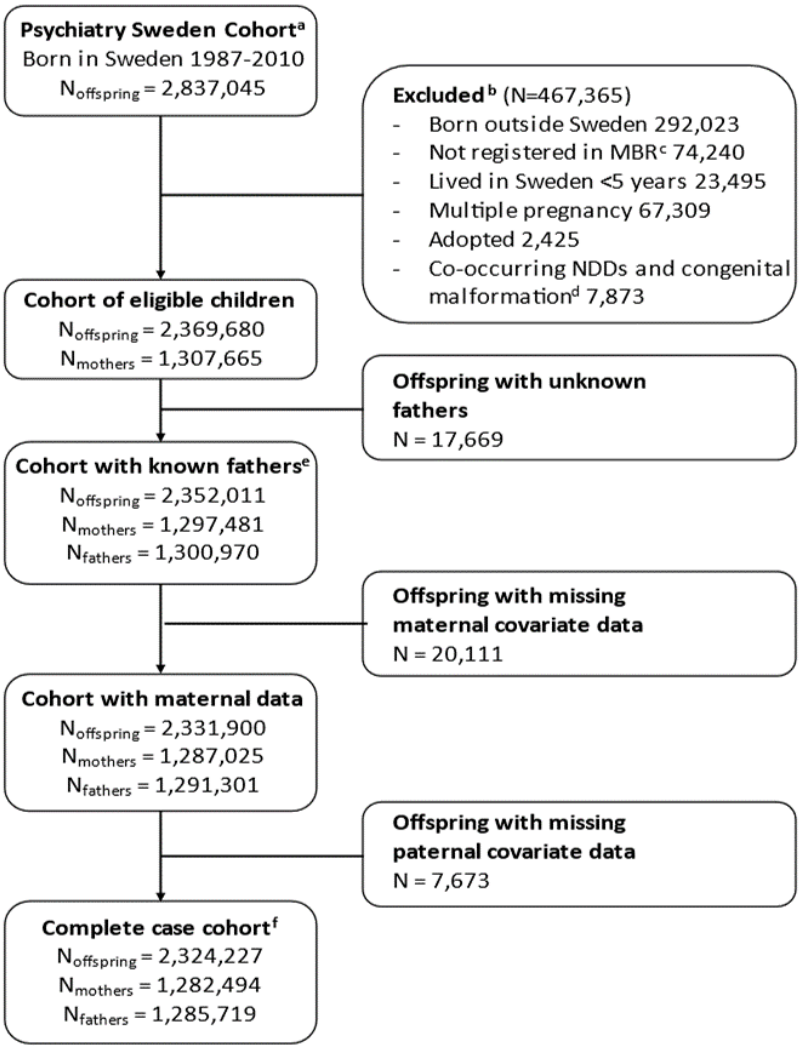

Figure 5.2 Study sample derivation for the Swedish cohort study.

[a] Children born before 1987 were excluded from the study population.
[b] Individuals were excluded stepwise with the criteria aligned to a previous study (Chen et al., 2020 - https://doi.org/10.1093/ije/dyaa212)
[c] Individuals without information from the Medical Birth Register (MBR) were excluded.
[d] Children with co-morbidities of congenital malformations (or inborn error of metabolism) documented in the MBR and neurodevelopmental disorders (NDDs), as NDDs may be attributable to the congenital condition.
[e] Those whose biological fathers were unknown were excluded.
[f] Those whose biological mothers or fathers lacked data on place of birth, age at delivery, education level, psychiatric history, or family income quintile were excluded.

5.2.2 Investigating genetic correlations- LD-Score regression

I used LD-score regression to estimate the genetic correlation between genetic liability to autism and IBD, Crohn's and UC.

LD-score regression allows the estimation of the genetic correlation between polygenic traits using GWAS summary statistics by capitalising on patterns of linkage disequilibrium among common genetic variants[194]. I used the latest available GWAS summary data on autism (N_{cases}= 18,381; $N_{controls}$= 27,969)[36], IBD (N_{cases}= 25,042; $N_{controls}$= 34,915)[286], Crohn's (N_{cases}= 12,194; $N_{controls}$= 28,072)[286] and UC (N_{cases}= 12,366; $N_{controls}$= 33,609)[286]. Detailed information on study samples and case definition can be found in the original publications.

I followed the suggested protocol for LD-score regression analyses (https://github.com/bulik/ldsc/wiki). Using the LDSC (LD Score) v1.0.1 software in Python, I estimated genetic correlations using pre-computed LD scores from the 1000 Genomes project European data[287] (from: https://data.broadinstitute.org/alkesgroup/LDSCORE/eur_w_ld_chr.tar.bz) with an unconstrained intercept term to account for any sample overlap, and population stratification.

5.2.3 Investigating associations between common variant genetic liability to IBD and childhood broad autistic traits- Polygenic Risk Score analysis in mothers and children of the ALSPAC cohort

Discovery Sample

I extracted common genetic variants, corresponding alleles, effect sizes and p-values in order to calculate polygenic risk scores (PRSs), from the GWAS summary data of IBD[286], UC[286] and Crohn's[286] described above.

Target Sample

A description of ALSPAC has been also provided in the methods section of Chapter 3. Briefly, ALSPAC is a UK prospective birth cohort study based in Bristol and surrounding areas, which recruited pregnant women with expected delivery dates from 1 April 1991 to 31 December 1992; 14,541 women were initially enrolled, with 14,062 children born, and 13,988 children alive at 1 year

of age. Detailed information on the cohort is available elsewhere[229,288]. A fully searchable study data dictionary is available at : http://www.bristol.ac.uk/alspac/researchers/our-data/. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

Genetic data

10,015 ALSPAC mothers were genotyped on the Illumina Human660W-quad genome-wide single nucleotide polymorphism (SNP) genotyping platform, and 9,912 ALSPAC children were genotyped on the Illumina HumanHap550-quad. After standard quality control[219] and excluding participants who had withdrawn consent, genetic data were available for 7,921 mothers and 7,977 children of European ancestry. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004).

Broad autistic traits- autism factor mean score

I used a measure of the broad autistic traits previously estimated in ALSPAC as the mean score of 7 factors derived from a factor analysis of 93 measures related to autism in ALSPAC[220]. The measure was available in 13,103 children and strongly predictive of the autism diagnosis measured independently via school records, record linkage and parental reports[220]. Other autism trait measures or diagnoses were not used as there were fewer genotyped mothers and children with these measures.

Calculation of Polygenic Risk Scores in ALSPAC and statistical analysis

I calculated using PLINK version 1.9, applying the method described by the Psychiatric Genomics Consortium (PGC)[227]. SNPs with mismatching alleles between the discovery and target dataset were removed. The MHC region was removed (25 Mb – 34 Mb), except for one SNP representing the strongest signal within the region. Using ALSPAC data as reference panel, SNPs were clumped with an r^2 of 0.25 and a physical distance threshold of 500 kB. The optimal p-value threshold for PRS is dependent on discovery and target sample sizes, as well as SNP inclusion parameters (e.g., r^2)[197,289]. For this reason, I calculated PRS for each participant across 13 p-value thresholds ($p<5e-8$ to $p<0.5$), standardised by subtracting the mean and dividing by the standard deviation. I defined PRS

corresponding to p-value threshold 0.05 as the primary exposure, based on a previous ALSPAC study[290]. This threshold has been found to have sufficient predictive ability for IBD and its subtypes[291]. I could not directly assess the predictive power and optimal p-value threshold of the PRSs in the target sample as there were few UC (n=12) and Crohn's cases (n=16).

After constructing PRS for IBD, UC and Crohn's in mothers and children, I performed linear regressions using STATA/MP 15 to examine associations with the standardised autism factor mean score in childhood. Analyses were adjusted for child's sex and the first 10 principal components of the ALSPAC genotype data to avoid population stratification bias[197]. Sample derivation and characteristics for the polygenic risk score analyses can be found in Figure 5.3.

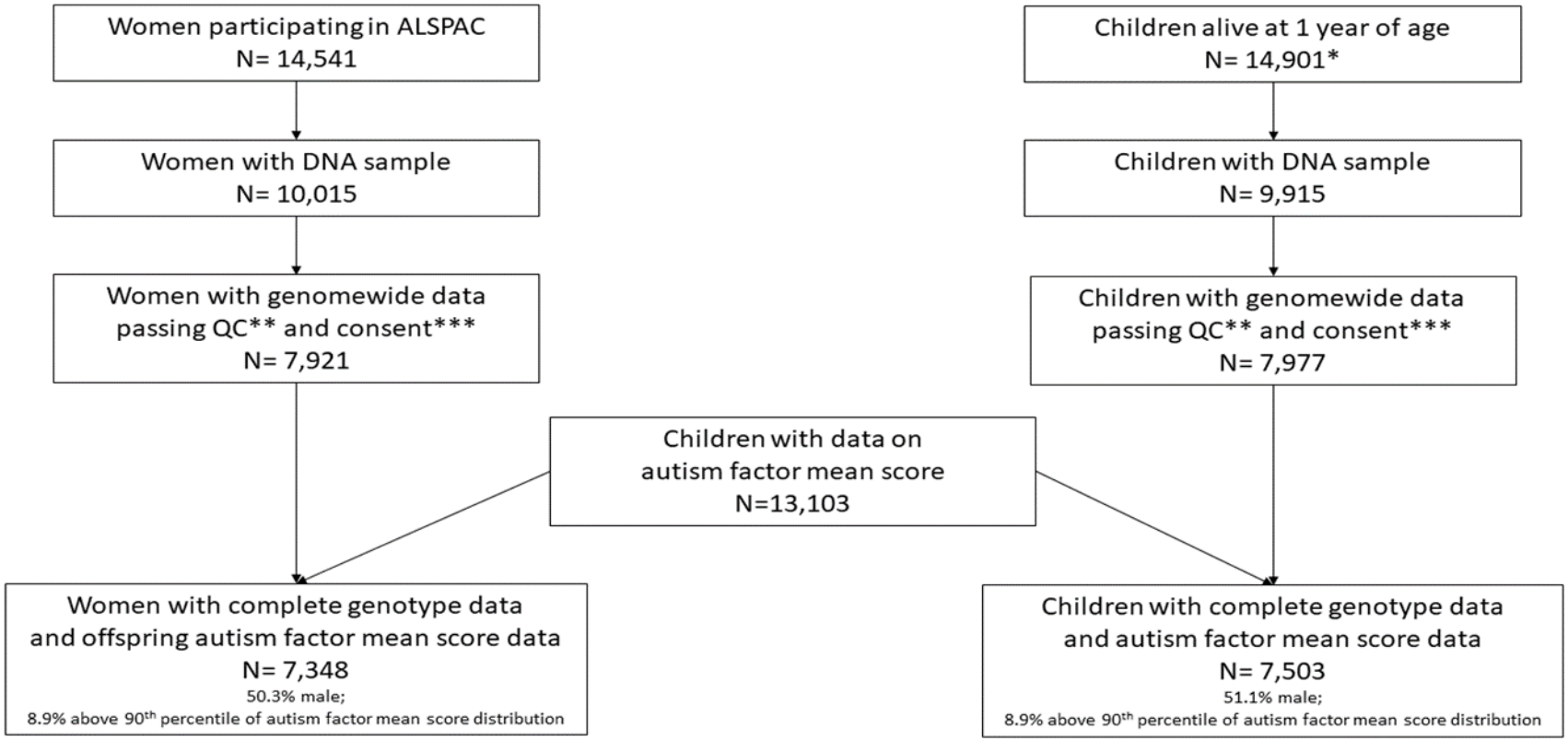

Figure 5.3 Study sample derivation and characteristics for the polygenic risk score analyses in the ALSPAC cohort.

*Although initial ALSPAC recruitment resulted in 13,988 children who were alive at 1 year of age, when the children were approximately 7 years old, the initial sample was bolstered with eligible children who did not join the study initially. 913 children were additionally enroled during three phases of recruitment. This resulted in 14,901 children alive at 1 year of age[229,288,373].
**Details on QC process can be found in Stergiakouli et al.,2014[219].
***Consent for biological samples has been collected in accordance with the Human Tissue Act (2004).

5.2.4 Investigating bidirectional causal links- Two-sample Mendelian randomisation

I performed two-sample Mendelian randomisation (MR) to assess bidirectional causal links between common variant genetic liability to autism and IBD and its subtypes, and vice versa. The method has been described in detail in Chapter 2 and in summary in Chapter 4. In the context of the present study, I applied two-sample MR.

Genetic instruments

Genetic instruments were extracted from the overlapping set of SNPs between the autism[36], IBD[286], UC[286], and Crohn's[286] GWASs. This ensured that all selected genetic instruments would be present in the outcome GWAS.

GWAS summary data were restricted to a common (overlapping) set of SNPs and then clumped in PLINK 1.90 using the 1000Genomes[287] phase 3 European ancestry reference panel, and an $r^2 = 0.01$, within a 10,000 kb window. Among the independent variants, instruments were defined using a genome-wide significance threshold of $p \leq 5 \times 10^{-08}$. The only exception was autism, as only two independent and genome-wide significant variants were identified. I therefore relaxed the p-value threshold to 5×10^{-07} to improve statistical power, as used previously [247]. Figure 5.4 illustrates the process of instrument definition, and Appendix Table C5 contains information on the genetic instruments used.

Harmonisation

I harmonised the alleles of the outcome on the exposure, to ensure SNP-exposure and SNP-outcome effects correspond to the same allele. Variants identified as palindromic were removed, as the effect allele frequencies in the IBD, UC, and Crohn's GWASs were not provided.

Inverse Variance Weighted MR

The primary MR analysis was the Inverse Variance Weighted (IVW) method which provides an overall causal effect estimate of the exposure on the outcome, estimated as a meta-analysis of the

ratios of the SNP-outcome effect to the SNP-exposure effect weighted by each SNP's relative precision[201].

Sensitivity Analyses to test robustness of causal effect estimates

I assessed the strength of the instruments by estimating the mean F statistic. As a rule of thumb, the IVW is unlikely to suffer from weak instrument bias if mean F>10[248].

I assessed the consistency of the IVW causal effect estimates using sensitivity analyses, including: MR Egger regression[201], Weighted Median[250] and Weighted Mode[204]. Details on these methods have been provided in Chapter 2 as well as in Chapter 4.

Sensitivity Analyses to test the consistency of the causal effect estimates in autism without intellectual disabilities (ID)

The autism GWAS used in the primary analyses included a proportion of autism cases with ID[36]. I tested the consistency of the causal effect estimates using GWAS summary data on a sub-sample of the iPSYCH cohort[292] excluding all intellectual disability cases (N_{cases}= 11,203; $N_{controls}$= 22,555). Appendix Figure C2 visualises the process of instrument definition, and Appendix Table C6 details on the instruments used.

Two-sample MR analyses were performed using the TwoSampleMR R package[253] in R version 3.5.1.

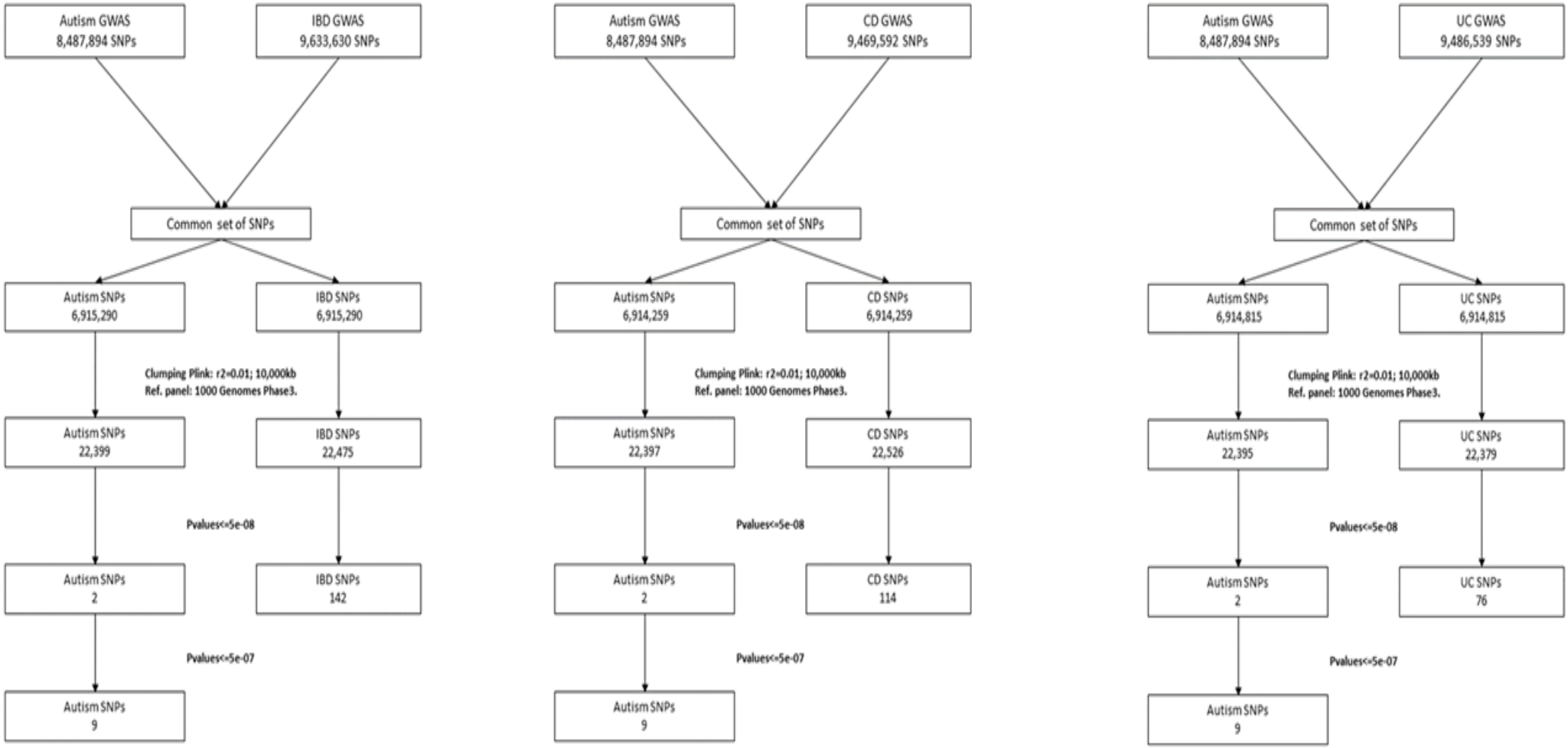

Figure 5.4 Genetic instrument extraction process for the MR analyses investigating the causal links between common variant genetic liability to autism, inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC).

5.3 Results

5.3.1 Associations between parental IBD diagnoses and offspring autism

The Swedish sample included 2,324,227 offspring born to 1,282,494 mothers and 1,285,719 fathers and was ascertained from "Psychiatry Sweden", a comprehensive national register linkage, the associations between parental IBD diagnosis and offspring autism were assessed. Cohort characteristics by exposure to maternal/paternal IBD diagnoses during index pregnancy, can be found in Appendix Tables C7 and C8 and details on the prevalence of each IBD subtype diagnosis in the cohort can be found in Appendix Figure C3.

Maternal IBD diagnosis was associated with offspring autism in crude and adjusted models (Any IBD diagnosis: OR_{MODEL3}= 1.32; 95% CIs: 1.25 to 1.40; Table 5.2). Similar results were observed in analyses of maternal UC and Crohn's diagnoses and offspring autism (Table 5.2), and in analyses restricted to maternal IBD diagnoses prior to the index person's birth (Any IBD diagnosis: OR_{MODEL3}= 1.20; 95% CIs: 1.09 to 1.32; Appendix Table C9). The paternal IBD associations with autism were weaker (OR_{MODEL3}= 1.09; 95% CIs 1.02 to 1.17) than the maternal associations (Table 5.2). Point estimates for associations of parental IBD diagnoses to autism without ID were higher than those for autism with ID, although confidence intervals overlapped (Appendix Table C10).

5.3.2 Genetic correlation between IBD and autism

There was no evidence of a genetic correlation between genetic liability to autism and IBD, UC, or Crohn's (Table 5.3). Heritability scores (z-scores: 8.34-11.75), chi-squares (1.20-1.53) and intercepts (1.01-1.12) satisfied the conditions to provide reliable LD-score regression estimates (Appendix Table C11).

5.3.3 Associations between polygenic risk for IBD, Crohn's and broad autistic traits in ALSPAC.

In a total sample size of 7,348 mothers with available genetic data and data on offspring broad autistic traits, there was evidence to suggest an association of maternal polygenic risk for UC and Crohn's with higher autism factor mean score in the offspring (UC: β_{PRS}= 0.02; 95%CIs: 0.003 to 0.05; p=

0.03; Crohn's: β_{PRS}= 0.03; 95%CIs: 0.01 to 0.05; p= 0.004). Similar results were found across other p-value thresholds (0.5- 0.05). The effect size of the association between maternal polygenic risk for IBD and autism factor mean score, was comparable to that of UC and Crohn's, although confidence intervals crossed the null (β_{PRS}= 0.02; 95%CIs: -0.004 to 0.04; p= 0.1; R^2= 0.06; Table 5.3, Figure 5.5, Appendix Table C12).

There was no evidence of associations between child's PRS for IBD, UC, Crohn's and autism mean factor score in children (IBD: β_{PRS}= 0.003; 95%CIs: -0.02 to 0.02; p= 0.79; R^2= 0.05; UC: β_{PRS}= 0.001; 95%CIs: -0.02 to 0.02; p= 0.89; R^2= 0.05; Crohn's: β_{PRS}= 0.007; 95%CIs: -0.01 to 0.03; p= 0.49; R^2= 0.05; Table 5.3, Figure 5.6, Appendix Table C13).

Table 5.2 Associations between maternal or paternal diagnosis of any inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease, other IBD and offspring diagnosis of autism.

Exposure	**n Autism/n total (% Autism)[a]**	**Model1[b] OR (95% CIs)**	**P value**	**Model2[c] OR (95% CIs)**	**P value**	**Model3[d] OR (95% CIs)**	**P value**
No maternal IBD	43,568/2,272,606 (1.92%)	Ref		Ref		Ref	
Any maternal IBD	1,361/51,621 (2.64%)	1.39 (1.31,1.47)	<0.001[e]	1.32 (1.24,1.40)	<0.001[e]	1.32 (1.25,1.40)	<0.001[e]
Maternal Crohn's Disease	422/17,832 (2.37%)	1.23 (1.09,1.40)	0.001[e]	1.19 (1.05,1.35)	0.006	1.20 (1.06,1.36)	0.004
Maternal Ulcerative Colitis	292/12,390 (2.36%)	1.24 (1.12,1.38)	<0.001[e]	1.22 (1.10,1.35)	<0.001[e]	1.22 (1.10,1.36)	0.001
Maternal Other IBD[f]	722/24,865 (2.90%)	1.53 (1.42,1.66)	<0.001[e]	1.42 (1.32,1.54)	<0.001[e]	1.43 (1.32,1.55)	<0.001[e]
Maternal Crohn's or Ulcerative Colitis[g]	639/26,756 (2.39%)	1.25 (1.15,1.35)	<0.001[e]	1.21 (1.11,1.32)	<0.001[e]	1.22 (1.12,1.32)	<0.001[e]
No paternal IBD	43,989/2,281,119 (1.93%)	Ref		Ref		Ref	
Any paternal IBD	940/43,108 (2.18%)	1.14 (1.06,1.22)	<0.001[e]	1.11 (1.03,1.18)	0.004	1.09 (1.02,1.17)	0.012
Paternal Crohn's Disease	346/18,290 (1.89%)	1.18 (1.04,1.35)	0.013	1.16 (1.02,1.33)	0.023	1.16 (1.01,1.32)	0.031
Paternal Ulcerative Colitis	254/11,274 (2.25%)	0.99 (0.88,1.10)	0.806	0.98 (0.87,1.09)	0.662	0.97 (0.86,1.08)	0.575
Paternal Other IBD[f]	407/16,958 (2.40%)	1.25 (1.12,1.38)	<0.001[e]	1.19 (1.07,1.32)	0.001[e]	1.17 (1.05,1.30)	0.003
Paternal Crohn's or Ulcerative Colitis[g]	533/26,150 (2.04%)	1.06 (0.97,1.16)	0.187	1.05 (0.96,1.15)	0.312	1.04 (0.95,1.14)	0.408

[a]The total numbers for those exposed to maternal or paternal Crohn's Disease, Ulcerative Colitis, or Other IBD do not sum to the total exposed to any IBD because some mothers or fathers received both a Crohn's Disease and an Ulcerative Colitis diagnosis Please see supplementary Figure S2 for details on the prevalence and overlap in diagnoses in the study sample.
[b] Crude models.
[c]Models adjusted for child's sex, year of birth, birth order, maternal/paternal age, migrant status, education level, family income and parental psychiatric history.
[d]Mutually adjusted models for maternal/paternal IBD diagnoses, child's sex, year of birth, birth order, maternal/paternal age, migrant status, education level, family income and parental psychiatric history.
[e] p-value is less than Bonferroni-corrected value of 0.0012, accounting for 42 models in Study 1. See Supplementary Table 20 for exact p-values.
[f]Excluding Crohn's and Ulcerative Colitis and including ICD-9 558 "Other and unspecified non-infectious gastroenteritis and colitis" and ICD-10 K52.3 "Indeterminate colitis" and K52.9 "Noninfective gastroenteritis and colitis". Please see supplementary methods S1 for details on the diagnostic codes.
[g] Including Crohn's and ulcerative colitis diagnoses and excluding ICD-9 558 "Other and unspecified non-infectious gastroenteritis and colitis" and ICD-10 K52.3 "Indeterminate colitis" and K52.9 "Noninfective gastroenteritis and colitis". Please see supplementary methods S1 for details on the diagnostic codes.
Odds ratios, 95% confidence intervals and p values calculated using generalised estimating logistic models with robust standard errors accounting for clustering of multiple children born to the same parents.

Table 5.3 LD-score regression coefficients (r_g), 95% confidence intervals (95% CIs) and p-values for the analyses investigating the genetic correlation between genetic liability to autism, Inflammatory Bowel Disease (IBD), ulcerative colitis and Crohn's disease.

Trait 1	**Trait 2**	**r_g (95% CIs)**	**P**
Autism	IBD	-0.0615 (-0.15, 0.02)	0.158
Autism	Ulcerative colitis	-0.0656 (-0.17, 0.04)	0.2064
Autism	Crohn's disease	-0.0403 (-0.13, 0.05)	0.3551

Table 5.4 Associations between child and maternal PRS for inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease at p-value threshold 0.05, and autism factor mean score in the children of the ALSPAC birth cohort.

	IBD PRS				**Ulcerative colitis PRS**				**Crohn's disease PRS**			
	Mother N= 7,348		Child N= 7,503		Mother N= 7,348		Child N= 7,503		Mother N= 7,348		Child N= 7,503	
	β (95% CIs)	**P**	**β (95% CIs)**	**P**	**β (95% CIs)**	**P**	**β (95% CIs)**	**P**	**β (95% CIs)**	**P**	**β (95% CIs)**	**P**
Autism factor mean score*	0.02 (-0.004, 0.04)	0.1	0.003 (-0.02, 0.02)	0.79	0.02 (0.003, 0.05)	0.03	0.001 (-0.02, 0.02)	0.89	0.03 (0.01, 0.05)	0.004	0.007 (-0.01, 0.03)	0.49

*Standardised score, with mean = 0, standard deviation = 1 and higher scores reflecting more autism related difficulties.

Figure 5.5 Associations between maternal polygenic risk (PRS) for inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease (Crohn's) at 13 p-value thresholds, and offspring autism factor mean score in the ALSPAC cohort.

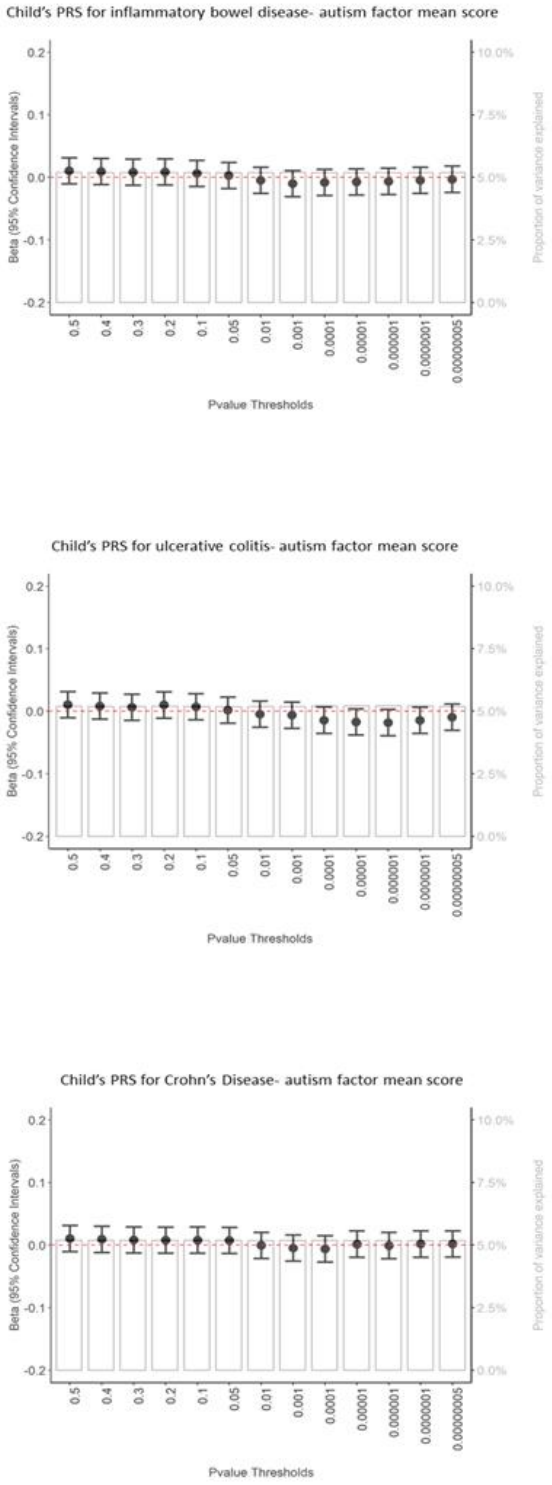

Figure 5.6 Associations between polygenic risk (PRS) for inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease (Crohn's) at 13 p-value thresholds, and autism factor mean score in children of the ALSPAC cohort.

5.3.4 Causal effects of common variant genetic liability to IBD on autism

The mean F statistics of the IBD, UC and Crohn's instruments were 67, 68 and 70, respectively, suggesting adequate strength. There was evidence of a causal effect of genetic liability to UC on risk of autism ($_{IVW}$OR= 1.04; 95% CIs: 1.01 to 1.07; p= 0.006). Evidence for the effect of genetic liability to IBD and Crohn's on autism risk was weaker, although the magnitude and direction of the effect estimates was comparable to the UC results (Table 5.5).

The magnitude and direction of causal effect estimates was consistent across all sensitivity analyses, and there was no evidence to suggest the influence of horizontal pleiotropy (Appendix Table C14). Results of analyses with instruments extracted from the autism GWAS excluding ID cases were comparable to the primary effect estimates (Appendix Table C15).

5.3.5 Causal effects of common variant genetic liability to autism on IBD

The mean F statistic of the autism instruments was 28, suggesting adequate strength. There was no evidence of a causal effect of genetic liability to autism on risk of IBD, UC or Crohn's (Table 5.5). The estimates were consistent across sensitivity analyses, with overlapping confidence intervals, and were unlikely to be influenced by horizontal pleiotropy (Appendix Table C16). Repeating the analyses with instruments extracted from the autism GWAS excluding all ID cases yielded similar results (Appendix Table C17).

Table 5.5Mendelian randomization Inverse Variance Weighted (IVW) estimates, 95% confidence intervals and p-values for the effect of common variant genetic liability to inflammatory bowel disease (IBD), Crohn's disease (Crohn's), ulcerative colitis (UC) on autism and vice versa.

Exposure	Outcome	OR (95% CIs)	P
Genetic liability to IBD	Autism	1.02 (1.0, 1.05)	0.1
Genetic liability to ulcerative colitis	Autism	1.04 (1.01, 1.07)	0.006
Genetic liability to Crohn's disease	Autism	1.01 (1.0, 1.04)	0.2
Genetic liability to autism	IBD	0.90 (0.73, 1.11)	0.32
Genetic liability to autism	Ulcerative colitis	0.95 (0.77, 1.18)	0.65
Genetic liability to autism	Crohn's disease	0.85 (0.63, 1.15)	0.29

5.4 Discussion

5.4.1 Summary of findings

Using four complementary approaches I investigated the associations between parental diagnoses and common variant genetic liability to IBD and offspring autism. Conducting a nationwide register-based cohort study in Sweden there was evidence of associations between parental diagnoses of IBD and offspring autism. Importantly, the maternal effect sizes were larger than paternal, without overlapping confidence intervals. PRS analyses in the ALSPAC birth cohort suggested associations between maternal common variant genetic liability to IBD and offspring autism, while two-sample MR studies provided evidence of a potentially causal effects of common variant genetic liability to IBD and its subtypes on autism risk. There was no evidence to suggest a genetic correlation between autism and IBD, as indicated by LD-score regression analyses.

5.4.2 Comparison to previous evidence

A number of studies so far have investigated the potential associations between parental autoimmune conditions and autism. Several parental autoimmune conditions have been previously identified to be linked to offspring autism, including rheumatoid arthritis[293] and psoriasis[294]. In the case of IBD, evidence from previous studies seems to be inconclusive. In contrast to studies so far, this is the first study to date to use four distinct study designs to triangulate findings.

Overall, the present findings suggesting larger maternal effect sizes than paternal in the registry-based study, in combination with the identified associations between maternal, but not child's, PRS for IBD and offspring autism factor mean score, could potentially indicate in-utero effects. This could be further supported considering that there was no evidence of a genetic correlation between autism and IBD. Specifically, based on liability-threshold models of inheritance[192,193,295,296] (and assuming that liability to IBD is normally distributed in the population), it could be hypothesised that liability to IBD will be expressed after a threshold has been exceeded, depending on a synergy of genetic variation, environmental factors and chance. Mothers below but close to the threshold, could be expected to express sub-phenotypic manifestations of IBD such as immunological alterations, micronutrient deficiencies, anaemia. These sub-phenotypic manifestations could influence fetal

development. In fact, several immune pathways have been implicated in both Crohn's and UC (which are strongly genetically correlated: r_g= 0.7; p= $2*10^{-47}$ [297]), including T-helper 1 (TH1), T-helper 2 (TH2) and T-helper 17 (TH17) cytokines[298], which are increasingly identified to be linked to perinatal complications[299–301] as well as autism [302–304]. Similarly, micronutrient malabsorption and anaemia during pregnancy have been found to be associated with offspring autism[305,306]. The availability of genotype and biospecimen data in autism family cohorts such as the Simons Simplex Collection (SSC) and the Simons Foundation Powering Autism Research (SPARK)[307,308] may allow the integration of genomic, immune, and gut microbiome profiling approaches to elucidate the potential aetiology and biological pathways underlying the identified associations.

5.4.3 Strengths and limitations

The use of four different designs to triangulate the findings is a notable strength of the present study[158]. The Swedish nationwide register-based cohort study of over 2 million parent-child pairs is the largest to date on parental IBD-offspring autism. In addition, the present study benefited from the longest to date follow-up period (1987-2016), as well as exposure and outcome ascertainment from both inpatient and outpatient specialist care. The ALSPAC cohort containing genotype data for over 7,000 mothers and children as well as broad autistic trait measures for over 13,000 children, is one of the richest resources for the investigation of the potential polygenic associations between maternal polygenic risk for IBD and offspring autism. Finally, in the MR analyses I used the largest GWAS data available for all conditions and conducted several sensitivity analyses to test the robustness of the findings.

Considering study limitations, in the Swedish registers the possibility of measurement error in IBD diagnoses cannot be excluded. However, this is likely to be non-differential in relation to the study outcome and would therefore bias the findings towards the null. Secondly, while PRSs were based on large GWAS samples, it was not possible for to investigate the variance explained by the PRSs in the target sample. However, based on previous studies[291,309], it could be expected that the PRSs potentially explain little variance in the phenotype, a limitation which could be overcome with future larger GWAS. Additionally, the autism mean factor score used in the present analyses, was derived

from individual measures that were not primarily purposed to assess autism. However, the score has been found to be predictive of a clinical autism diagnosis (measured independent of the variables contributing to the derivation of the mean factor score) and presents associations with autism PRS in ALSPAC, as suggested by previous studies[217,220].Thirdly, in two-sample MR analyses investigating the effects of genetic liability to autism on risk of IBD, I used a relaxed instrument inclusion p-value threshold. This could potentially result in including weak instruments and therefore bias the causal effect estimates. The F statistic of the autism instruments in the analyses suggested that weak instrument bias is unlikely. Fourth, using GWAS data I could only investigate the possible contribution of common variants acting under an additive model and not any contribution from rare variation which has been found to be implicated in autism[310,311]. Finally, an important consideration is that the present study has been conducted using samples and GWAS data of predominantly European ancestry individuals. Although a proportion of index children in the registry-based study had at least one parent of non-European descent (10%), the use of European ancestry summary and individual-level genetic data in LDSC, PRS and MR analyses, was unavoidable considering that the largest available GWAS on autism and IBD have been conducted in European ancestry samples. The increasing representation of ethnically diverse populations in biobanks and health registers will allow future studies to build on the present findings.

5.5 Conclusions and chapter summary

In conclusion, triangulation of evidence from a nationwide register-based cohort study, genetic correlation, polygenic risk score analyses and MR, suggest a potentially causal link between maternal diagnoses and common variant genetic liability to IBD, with offspring autism. These findings may suggest a causal role of maternal immune response on fetal development and therefore autism, although other pathways e.g., micronutrient malabsorption, cannot be excluded. In the last chapter of my thesis, I will describe how I interrogated further the present study findings by investigating whether cytokines implicated in IBD might have a causal role in autism but also schizophrenia, scrutinising therefore whether specific immunological pathways are shared between the two conditions. ♦

Chapter 6

Using Mendelian randomization and genetic colocalisation approaches to uncover shared immunological pathways underlying autism and schizophrenia.

This chapter closely resembles sections from the following preprint:

Dardani C, Robinson JW, Zheng J, Sadik A, Pagoni P, Stergiakouli E, Gardner RM, Havdahl A, Grove J, The iPSYCH Autism Spectrum Disorder Working Group, Davey Smith G, Sullivan SA, Leppert B, Jones HJ, Zammit S, Khandaker GM, Rai D. Immunological pathways underlying autism: Findings from Mendelian randomization and genetic colocalisation analyses. medRxiv; 2022; doi: https://www.medrxiv.org/content/10.1101/2022.02.16.22271031v1 (Currently under review *Biological Psychiatry*)

♦

6.1 Introduction

In Chapter 5, I found evidence suggesting a potentially causal link of maternal diagnoses and common variant genetic liability for inflammatory bowel disease (IBD) with offspring autism. There is currently increasing evidence from animal model, genomic and observational studies as well as clinical trials, suggesting a central role of $CD4^+$ T cell subsets and their cytokine networks in the onset and course of IBD[272,312]. $CD4^+$ T cells are types of T lymphocytes and are orchestrators of anti-viral, autoimmune, and anti-tumour responses[313–316]. Their involvement in these responses is largely induced through cytokines which drive the differentiation of naïve $CD4^+$ T cell into specific subsets, characterised by distinct cytokine products and functions[315–317]. Table 6.1 summarises the inductive and product cytokines for each subset, as well as their functions.

There is evidence suggesting that $CD4^+$ T cell subsets as well as their inductive and product cytokines might be implicated in psychosis and autism. In the case of psychosis, there is increasing evidence from case-control, population-based cohort and Mendelian randomization studies supporting a potentially causal role of T_{Reg} cell signature cytokines and particularly IL-6[94,152,318,319]. In the case of autism, evidence on the potential role of T_{Reg} cytokines is less consistent, although associations have been identified in animal and case-control studies between atypical levels of IL-6 and autism features [320,321]. Evidence is more consistent with regards to the potential role of T_H1 and T_H2 cytokines in autism as there are population-based case-control studies indicating associations between atypical

levels of T_H1 and T_H2 cytokines in neonatal blood spots as well as amniotic fluid and autism diagnosis later in life[303,322].

Despite available evidence on the potential links between specific $CD4^+$ T cell subset signature cytokines, autism, and psychosis, the question of whether the links are causal and represent shared immunological pathways for the two conditions has yet to be settled. In the case of autism, evidence so far has been based on observational studies which can be hampered by reverse causation and residual confounding, whereas in the case of psychosis, investigations have focused on a limited number of cytokines and predominantly IL6.

To address these gaps, I used GWAS summary data on autism[36] and schizophrenia[66], and conducted a study to investigate the causal influence of genetically proxied cytokines implicated in the differentiation and function of six major CD^+4 T cell subsets (T_H1, T_H2, T_H9, T_{FH}, T_H17, T_{Reg}) on both conditions.

(i) I firstly performed two-sample MR using single nucleotide polymorphisms (SNPs) associated with plasma cytokines (protein quantitative trait loci- pQTLs) as instruments[161–163,165] and assessed their causal effects on both conditions.

(ii) To gain insights into potential brain-specific effects, I additionally performed MR using SNPs associated with the expression of genes encoding the cytokines of interest in the brain cortex (expression quantitative trait loci- eQTLs) as instruments[323].

(iii) I complemented MR findings by performing genetic colocalisation analyses to identify shared causal variant(s) influencing levels/expression of the exposure (cytokine) and outcome risk (autism/schizophrenia), i.e. that there might be a shared underlying biological mechanism[207,210].

(iv) Finally, I assessed the possibility of bias due to reverse causation by performing Steiger filtering[324] and bidirectional MR analyses (common variant genetic liability to autism/schizophrenia → circulating cytokines).

Table 6.1 Summary of cytokines inducing naïve CD4+ T cell differentiation, the resulting six major CD4+ T cell subsets, their product cytokines and their functions*.

CD^+4 T cell subsets	**T_H1**	**T_H2**	**T_H9**	**T_{FH}**	**T_H17**	**T_{Reg}**
Inductive Cytokines	IL-2	IL-2	IL-2	IL-6	IL-6	IL-2
	IL-12	IL-4	IL-4	IL-21	IL-21	TGFβ
			TGFβ		IL-23	
					TGFβ	
Product Cytokines	IFN-γ	IL-4	IL-9	IL-21	IL-17A	IL-10
		IL-5			IL-17F	TGFβ
		IL-13			IL-22	
Subset associated functions	Macrophage activation	Eosinophil activation	Response in helminth infections	B cell activation	Neutrophil activation	Regulation of inflammatory response
	Inflammatory response against intracellular pathogens	Allergic and autoimmune response	Allergic and autoimmune response	Inflammatory response against extracellular pathogens	Inflammatory response against extracellular pathogens	Regulation of autoimmune response
			Anti-tumour immune response		Autoimmune response	Suppression of anti-tumour immune response

**The table summarises some of the main functions of the CD^+4 T cell subsets and does not imply that these are the only immune pathways and processes that they have been found to be implicated. A detailed description of each subset, signature cytokines and functions can be found in relevant publications*[315,316,325–328]*. IFN-γ: Interferon gamma; IL2-23: Interleukins 2-23; TGFβ: Transforming growth factor beta; T_H1: T helper 1; T_H2: T helper 2; T_H9: T helper 9; T_{FH}: T follicular helper; T_H17: T helper 17; T_{Reg}: Regulatory T cells.*

6.2 Methods

A summary of the analysis plan of the present study can be found in Figure 6.1.

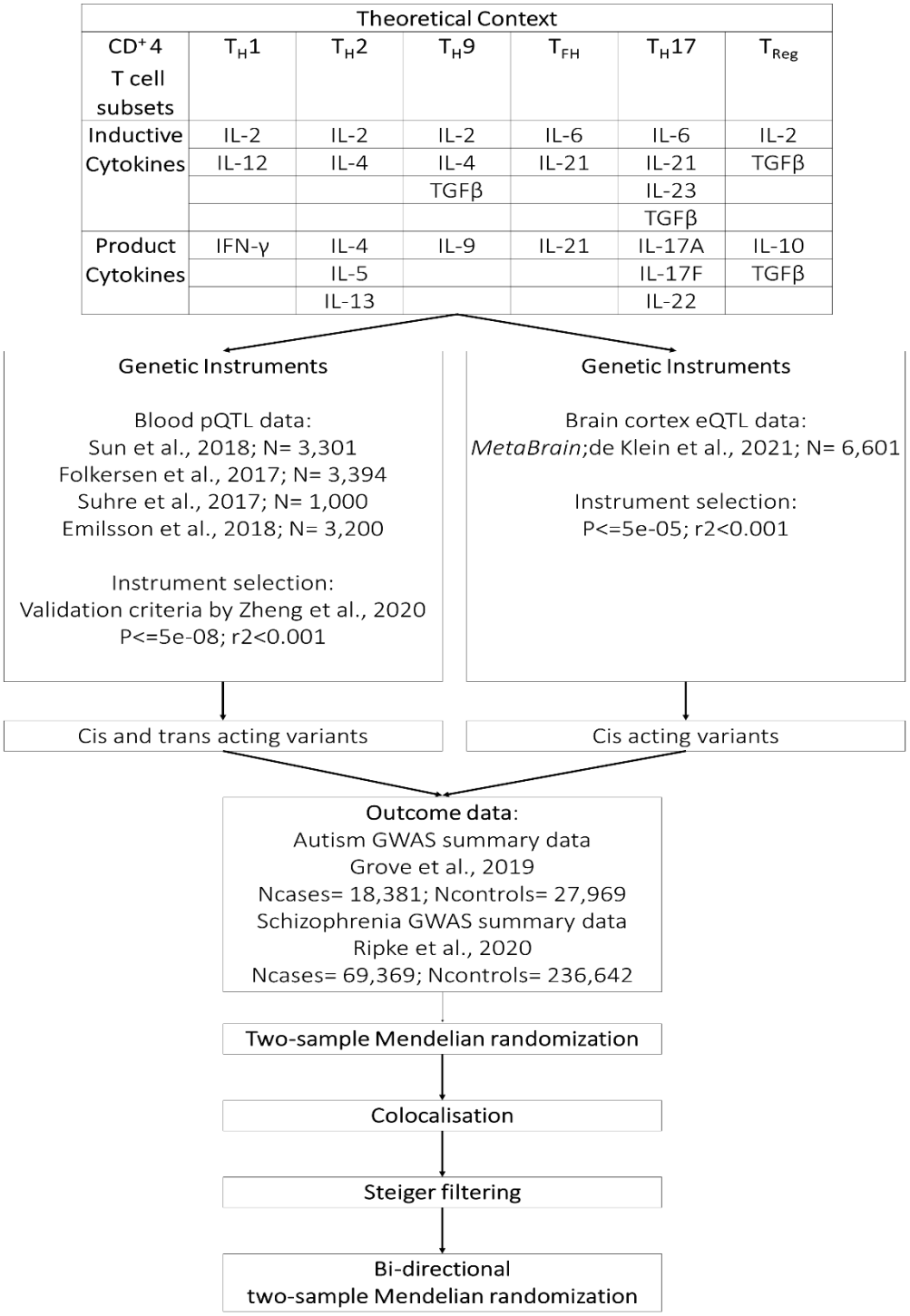

Figure 6.1 Summary of the analysis plan followed in the present study.

6.2.1 Data sources and instrument definition

Blood pQTL data

Plasma pQTL data for the 15 cytokines of interest (Table 6.1 for a summary of the cytokines) were available in four genome-wide association studies (GWAS): Sun et al, 2018 (N= 3,301)[161], Folkersen et al., 2017 (N= 3,394)[165], Suhre et al., 2017 (N= 1,000)[163], Emilsson et al., 2018 (N= 5,457)[162]. Details on participants, plasma protein measurements, and genotyping of each study, can be found in the original publications.

Instrument selection was based on previous work by Zheng et al.[329]. Specifically, Zheng et al. pooled pQTLs for 1,699 proteins from the above GWAS[161–165] and validated them in terms of their consistency (limited agreement of pQTL association estimates across GWAS might indicate artefactual associations and therefore potential violation of the MR assumption that the genetic instruments used are robustly associated with the exposure[167,198]) and their specificity (pQTLs associated with several proteins can indicate pleiotropy and therefore potential violation of the MR assumption that the genetic instruments should operate on the outcome entirely via the exposure[167,198]). Further details on the validation protocol can be found in the original publication. I considered this information important for the appraisal of the MR findings and therefore extracted 18 pQTLs that were independent (r^2<0.001; 10,000Kb) and robustly associated ($p \leq 5*10^{-08}$) with the cytokines of interest and their receptors from the work of Zheng et al[329]. The only exception were instruments for IL4 Receptor Subunit Alpha (IL-4RA) and IL17-F for which there was no information on their specificity and consistency in the work of Zheng et al.[329] and were therefore extracted from the Sun et al GWAS data using a $p<=5*10^{-08}$, r^2<0.001; 10,000 kb.

All instruments were categorised into cis-acting and trans-acting. Instruments were categorised as cis-acting when they located within proximity (±1Mb) to the cytokine-encoding gene, whereas instruments were categorised as trans-acting when they were located outside this window. SNPs acting in cis to the cytokine-encoding gene are more likely to influence mRNA and protein expression (thus being less pleiotropic), whereas trans-SNPs are likely to be pleiotropic due to their distance from the cytokine-encoding gene[330]. Table 6.2 provides details on the genetic instruments used in the study.

Table 6.2 Genetic instruments used in the MR analyses investigating the causal effects of genetically proxied plasma cytokines on autism and schizophrenia.

										VALIDATION CRITERIA BY ZHENG ET AL		
EXPOSURE	SNP	A1	A2	EAF	β	SE	P	CIS/TRANS	STUDY	SPECIFICITY	CONSISTENCY	Instrument Strength (F)
IL2	rs4241819	T	C	0.50721	0.1919	0.0247	$7*10^{-15}$	trans	Sun et al.	No	No	60
IL12B	rs4921484	C	T	0.678009	0.3123	0.0262	$7*10^{-33}$	cis	Sun et al.	Yes	Yes	142
IL12B	rs9815073	A	C	0.374252	0.2146	0.0277	$9*10^{-15}$	trans	Sun et al.	Yes	Yes	60
IL12RB1	rs376008	T	C	0.33501	-0.7569	0.039813	$6*10^{-69}$	cis	Suhre et al.	Yes	No	361
IL12RB2	rs12566098	G	C	0.688055	0.2568	0.0267	$6*10^{-22}$	cis	Sun et al.	Yes	Yes	93
IFNGR1	rs7080536	A	G	0.043842	0.6262	0.0617	$4*10^{-24}$	trans	Sun et al.	Yes	Yes	103
IL4RA	rs10418046	G	T	0.21727	-0.1694	0.0298	$1*10^{-08}$	trans	Sun et al.	No	No	32
IL5	rs704	A	G	0.466647	-0.2887	0.0242	$7*10^{-33}$	trans	Sun et al.	No	No	142
IL5RA	rs77400868	G	A	0.13908	0.5096	0.0362	$7*10^{-45}$	cis	Sun et al.	Yes	Yes	198
IL13RA1	rs4241818	C	T	0.513587	0.1924	0.0246	$5*10^{-15}$	trans	Sun et al.	No	No	61
TGFB1	rs1800470	A	G	0.621	0.259	0.024	$5*10^{-25}$	cis	Emilsson et al.	Yes	Yes	116
IL9	No instruments ($p<=5*10^{-08}$) available in datasets											
IL6R	rs4129267	T	C	0.36	0.81	0.023272	$2*10^{-265}$	cis	Folkersen et al.	Yes	No	1211
IL21	rs12368181	G	A	0.13305	-0.3688	0.0362	$2*10^{-24}$	trans	Sun et al.	No	No	104
IL23R	rs11581607	A	G	0.066948	-0.42	0.0491	$1*10^{-17}$	cis	Sun et al.	Yes	Yes	73
IL17RA	rs4819959	A	G	0.49643	0.9127	0.0195	$1*10^{-200}$	cis	Sun et al.	No	No	2190
IL17F	rs9274952	G	T	0.36485	0.1677	0.03	$2*10^{-08}$	trans	Sun et al.	No	No	31
IL22RA1	rs1065853	T	G	0.077779	-0.3498	0.0461	$3*10^{-14}$	trans	Sun et al.	No	No	58
IL10RB	rs2834167	A	G	0.732	0.16	0.028	$1*10^{-08}$	cis	Emilsson et al.	Yes	Yes	33

EAF: effect allele frequency

Brain cortex eQTL data

Brain-cortex eQTL data for the genes encoding the cytokines of interest were available in the largest meta-analysis of brain-derived eQTL datasets (*MetaBrain*), resulting in a size of 6,601 RNA-sequencing samples[323]. Details on the study datasets, samples and genotyping can be found in the original publication.

Cis-acting only eQTLs (±1Mb within the cytokine encoding gene region) were used for these analyses. This decision was based on the fact that the *MetaBrain* dataset has reported only the statistically significant trans-eQTLs, without information on the respective regions around them. This means that any genes with trans-acting SNPs are ineligible for subsequent colocalisation analyses (colocalisation analyses require information on the SNP-coverage of the extended region around the genetic instrument and details on the method can be found in section 6.2.3 below). I defined as instruments SNPs that were independent (r^2<0.001; 10,000 kb) and met a p-value threshold of $5*10^{-08}$. In cases that there were no instruments available for a cytokine of interest at this threshold, I used a relaxed p-value threshold of $5*10^{-05}$, in order to ensure that there would be at least one cis-acting eQTL for all the cytokine-encoding genes. In total, 19 eQTLs were extracted and details can be found in Table 6.3.

Schizophrenia GWAS data

I used the latest schizophrenia GWAS of 69,369 cases and 236,642 controls[66]. 255 genetic instruments were extracted using a p-threshold <=$5*10^{-08}$ and r^2<0.01 within a 10,000 kb window. Details on the instruments can be found in Appendix Table D1.

Autism GWAS data

In addition, I used the latest autism GWAS of 18,381 cases and 27,969 controls[36]. 10 independent (r^2<0.001; 10,000 kb) genetic instruments for autism were extracted using a relaxed p-threshold of $5*10^{-07}$, since the genome-wide significant threshold, p<=$5*10^{-08}$, yielded only two variants. Details on the instruments can be found in Appendix Table D2. I additionally used summary-level data on a sub-sample of the iPSYCH cohort[292] excluding all intellectual disability cases (cases= 11,203;

controls= 22,555) to test for any potential differences in the identified causal effects of genetically proxied cytokines across the two GWAS samples.

6.2.2 Two-sample Mendelian randomisation analyses

I assessed the strength of each instrument by estimating their F statistic. As a rule of thumb, an F>10 is indicative of adequate instrument strength[248]. SNP-exposure effect sizes and standard errors were extracted from the outcome GWAS (autism/schizophrenia), and their alleles were harmonised to ensure SNP-exposure and SNP-outcome effect sizes correspond to the same allele. The Wald ratio was used to generate causal effect estimates and the Taylor series expansion to approximate standard errors, as all exposures were instrumented by a single SNP[200,331]. The same process was followed using as an outcome the iPSYCH autism sub-sample excluding all intellectual disability cases. Despite the number of analyses, correction for multiple testing was not performed. This decision was made on the basis that the cytokines assessed in the present study are unlikely to be independent from each other (i.e., making difficult the definition of the number of independent tests conducted) and therefore, correction for multiple testing might be too stringent. Instead, results are presented and appraised in the context of their magnitude and consistency across analyses.

Table 6.3 Genetic instruments used in the MR analyses investigating brain-specific effects of genetically predicted expression of genes encoding cytokines on autism and schizophrenia.

EXPOSURE	SNP	ENSEMBL ID	CHR	BP[a]	A1	A2	β	SE	P	EAF	Instrument Strength (F)
IL2RA	rs12722497	ENSG00000134460.17	10	6095928	C	A	-0.36517	0.043232	$3*10^{-17}$	0.89	71
IL12A	rs1353248	ENSG00000168811.7	3	159623559	C	T	0.24656	0.029559	$7*10^{-17}$	0.70	70
IL12B	rs75259819	ENSG00000113302.4	5	158401932	A	G	-0.21666	0.049462	$1*10^{-05}$	0.92	19
IL12RB1	rs2644777	ENSG00000096996.16	19	18178616	A	C	0.25866	0.027514	$5*10^{-21}$	0.68	88
IL12RB2	rs72678518	ENSG00000081985.11	1	67771397	A	G	-0.27044	0.034361	$4*10^{-15}$	0.79	62
IFNGR1	rs4896249	ENSG00000027697.14	6	137594069	C	T	-0.32471	0.044829	$4*10^{-13}$	0.90	52
IFNGR2	rs9976971	ENSG00000159128.14	21	34768097	A	G	-0.1225	0.026135	$3*10^{-06}$	0.43	22
IL4	rs6879672	ENSG00000113520.11	5	132025947	A	G	-0.32098	0.029369	$8*10^{-28}$	0.25	119
IL4R	rs7205510	ENSG00000077238.14	16	27321398	G	A	0.191158	0.030116	$2*10^{-10}$	0.29	40
IL5	rs2070730	ENSG00000113525.10	5	131819800	G	A	-0.28132	0.027541	$2*10^{-24}$	0.69	104
IL5RA	rs6768065	ENSG00000091181.19	3	3110237	T	A	-0.13574	0.028282	$2*10^{-06}$	0.46	23
IL13	rs12652920	ENSG00000169194.9	5	131885240	G	C	0.180025	0.03224	$2*10^{-08}$	0.79	31
IL9	rs4487482	ENSG00000145839.2	5	135201771	A	G	0.232605	0.034617	$2*10^{-11}$	0.81	45
TGFB1	rs75520557	ENSG00000105329.10	19	40996988	A	G	0.267952	0.060981	$1*10^{-05}$	0.95	19
IL6	rs2905346	ENSG00000136244.12	7	22618248	G	A	-0.1225	0.027445	$8*10^{-06}$	0.49	20
IL21	rs35913539	ENSG00000103522.16	16	27479229	T	C	0.612885	0.033774	$1*10^{-73}$	0.84	329
IL17RA	rs2845391	ENSG00000177663.13	22	17526688	A	T	-0.50932	0.026428	$9*10^{-93}$	0.39	371
IL23A	rs59917308	ENSG00000110944.9	12	56658708	C	T	-0.43832	0.051091	$9*10^{-18}$	0.93	74
IL10RB	rs2834167	ENSG00000243646.10	21	34640788	A	G	-0.74472	0.027437	$3*10^{-162}$	0.73	737

a: coordinates in GRCh37
Ensembl ID: Gene id in Ensembl; CHR: chromosome; BP: position; EAF: effect allele frequency.

6.2.3 Genetic colocalisation analyses

Colocalisation approaches can complement MR approaches by elucidating a distinct aspect of the identified causal relationship between an exposure and an outcome[210]. Specifically, colocalisation allows the assessment of the hypothesis that any identified causal effects (from MR analyses) are driven by the same causal variant influencing both exposure and outcome, instead of distinct causal variants that are in linkage disequilibrium (LD) with each other[207]. This can be particularly important considering that evidence of shared causal variant for the exposure and the outcome might be suggestive of a shared underlying biological pathway[206,207,210]. In practice, the approach is harnessing SNP coverage within the same specified locus for two traits of interest and tests whether independent association signals for each trait at the specified locus are suggestive of a shared causal variant[207].

For each MR result providing evidence of causal effects, I tested for colocalisation between the genetically proxied exposure and autism/schizophrenia. I extracted regions of SNPs within ±500KB around the instrumented SNP and implemented the algorithm described by Zheng et al[329] to perform pairwise conditional and colocalisation (PWCoCo)[329] analyses, which assesses all conditionally independent signals in the exposure dataset region against all conditionally independent signals in the outcome data. Genotype data from mothers in the Avon Longitudinal Study of Parents and Children (ALSPAC)[229] cohort were used as the LD reference panel (N= 7,921; details on the ALSPAC cohort and available genotype data can be found in Chapters 3 and 5).

As discussed in Chapter 2, colocalisation assesses evidence on distinct hypotheses (H): H1: there is an association signal in the extracted genomic region of the exposure, but in the region of the outcome there is not; H2: there is an association signal in the extracted genomic region of the outcome, but in the region of the exposure there is not; H3: there are association signals in both exposure and outcome genomic regions but they are driven by two distinct causal variants; H4: there are association signals in both exposure and outcome genomic regions and they are driven by the same causal variant[207]. As suggested by the authors of the method, evidence of colocalisation in the context of the present study, was considered a probability of H4≥80%[207].

In the case of autism, as a post-hoc analysis to PWCoCo, I performed Linkage disequilibrium (LD) check[332]. The method was initially proposed to approximate colocalisation in cases of studies that sufficient SNP coverage in the region of interest was not available (for example in cases that for one of the traits of interest only the genome-wide significant hits were available/published, but not the full GWAS summary data to extract regions)[329]. In the context of the present study, the decision to perform LD check was based on the fact that the current autism GWAS yielded association signals in three only loci and therefore the autism dataset might be underpowered for colocalisation analyses[36] (assuming that these three loci are unlikely to be the only causal loci for autism and that future larger GWASs will reveal more information on the genetic architecture of autism). I assessed the LD between the instrumented SNP and the top 30 SNPs associated with autism in the test region (r^2>0.8 with any of the strongest 30 SNPs for autism in the region approximating colocalisation as suggested by the authors of the method[329]).

6.2.4 Examination of reverse causation

Steiger filtering

I performed Steiger filtering to assess whether causal effect estimates were influenced by reverse causation. The method assesses whether genetic instruments proxying for the exposure explain more variance in the outcome[324].

Bi-directional two-sample MR

I performed bi-directional two-sample MR to investigate the potential causal effects of common variant genetic liability to autism and schizophrenia on levels of plasma cytokines. Details on the genetic instrument extraction can be found in section 6.2.1 and in Appendix Tables D1 and D2. As outcome, I used GWAS summary data for each cytokine of interest from Sun et al[161]. The primary method of analysis was the Inverse Variance Weighted (IVW)[201]. The consistency of the IVW effect estimates was assessed using the MR Egger regression[201], the Weighted Median[250] and the Weighted Mode[204]- details on these methods have been provided in Chapter 2 as well as Chapter 4. Please note that bi-directional MR analyses could not be performed on the brain cortex eQTL data due to not having full genome-wide data for this dataset.

6.2.5 Software

Analyses were carried out using the computational facilities of the Advanced Computing Research Centre of the University of Bristol (http://www.bris.ac.uk/acrc/). Brain cortex cis-eQTLs were extracted using the Summary-data-based Mendelian Randomization (SMR) package version 1.03 (https://cnsgenomics.com/software/smr/). The TwoSampleMR R package was used to conduct two-sample MR analyses, Steiger filtering and to construct LD matrices for LD check analyses (https://github.com/MRCIEU/TwoSampleMR). The PWCoCo algorithm was implemented using the Pair-Wise Conditional analysis and Colocalisation analysis package version 0.3 (https://github.com/jwr-git/pwcoco).

6.3 Results

6.3.1 Causal effects of genetically proxied plasma cytokines on autism and schizophrenia

Using the autism GWAS summary data, I found evidence of a causal effect of genetically proxied Interferon Gamma Receptor-1 (IFNGR1: OR= 1.15; 95%CIs: 1.03-1.29; p= 0.02), Interleukin 4 Receptor Subunit Alpha (IL4RA: OR= 0.81; 95%CIs: 0.65-0.99; p= 0.04), Interleukin 5 Receptor Subunit Alpha (IL5RA: OR= 0.91; 95%CIs: 0.83-1; p= 0.05) and Interleukin 13 Receptor Subunit Alpha-1 (IL13RA1: OR= 1.16; 95%CIs: 1-1.34; p= 0.04) on autism. There was additionally weak evidence to suggest a causal effect of genetically proxied Interleukin 2 (IL2: OR= 1.14; 95%CIs: 0.99-1.32; p= 0.07). Results are detailed in Appendix Table D3 and summarised in Figure 6.2.

Using the autism GWAS summary data excluding intellectual disability cases, I found evidence of a causal effect of genetically proxied Interferon Gamma Receptor-1 (IFNGR1: OR= 1.18; 95%CIs: 1.03-1.35; p= 0.02), Interleukin 4 Receptor Subunit Alpha (IL4RA: OR= 0.77; 95%CIs: 0.6-0.99; p= 0.04), and Interleukin 12 Receptor Subunit Beta-1 (IL12RB1: OR= 1.06; 95%CIs: 1.01-1.11; p=0.02). Details can be found in Appendix Table D4 and Figure 6.2.

In the case of schizophrenia, there was evidence to suggest a causal effect of genetically proxied Interleukin 6 Receptor (IL6R: OR= 1.03; 95%CIs: 1.01-1.05; p= 0.01). Results are detailed in Appendix Table D5 and Figure 6.2.

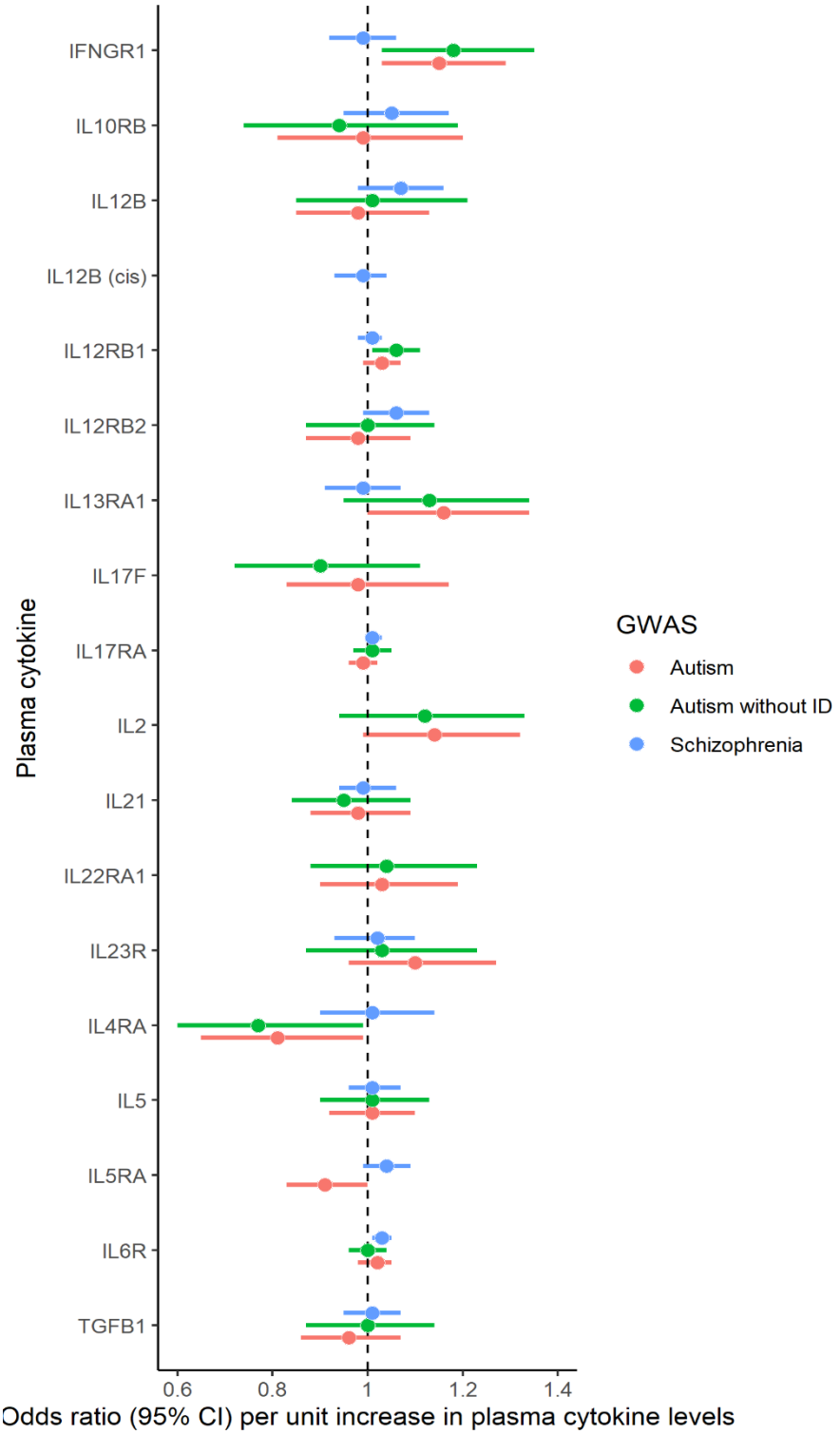

Figure 6.2 Forest plot of MR causal effect estimates and 95%CIs for autism, autism without intellectual disabilities and schizophrenia per unit change in plasma cytokine levels.

In some analyses the genetic instrument for the cytokine of interest was not available in the outcome data and therefore MR analyses could not be conducted. For example, the cis instrument for IL12B was available only in the schizophrenia GWAS, but not in the autism or autism without ID.

IFNGR1: Interferon Gamma Receptor-1; IL10RB: Interleukin 10 Receptor Subunit Beta; IL12B: Interleukin 12 Beta; IL12RB1: Interleukin 12 Receptor Subunit Beta-1; IL12RB2: Interleukin 12 Receptor Subunit Beta-2; IL13RA1: Interleukin 13 Receptor Subunit Alpha-1; IL17F: Interleukin 17 F; IL17RA: Interleukin 17 Receptor Alpha; IL21: Interleukin 21; IL22RA1: Interleukin 22 Receptor Subunit Alpha-1; IL23R: Interleukin 23 Receptor; IL2: Interleukin 2; IL4RA: Interleukin 4 receptor Subunit Alpha; IL5: Interleukin 5; IL6R: Interleukin 6 Receptor; TGFB1: Transforming Growth Factor Beta-1.

6.3.2 Effects of brain-expressed cytokine genes on autism and schizophrenia

There was evidence to suggest a causal effect of genetically predicted expression of IFNGR1 gene in brain cortex (OR= 1.22; 95%CIs: 1.05-1.42; p= 0.008), and IL23A gene (OR= 0.88; 95%CIs: 0.77-0.99; p= 0.04) on autism. Furthermore, there was weak evidence to suggest a causal effect of IL12RB1 gene (OR= 1.24; 95%CIs: 0.97-1.57; p= 0.08). A summary of the results can be found in Appendix Table D6 and Figure 6.3.

In the case of autism without intellectual disabilities, there was evidence to suggest a causal effect of genetically predicted expression of IL12RB1 gene (OR= 1.16; 95%CIs: 1.01-1.34; p= 0.04) and IL12B gene (OR= 1.36; 95%CIs: 1.01- 1.83; p= 0.04). Appendix Table D7 and Figure 6.3 summarise the results of the analyses.

Finally, with regards to schizophrenia, there was evidence consistent with a causal effect of genetically predicted expression of IL9 gene (OR= 1.15; 95%CIs: 1.04-1.28; p= 0.007) and some weaker for the IL4 (OR= 0.94; 95%CIs: 0.89-1; p= 0.4) and IL6 genes (OR= 0.87; 95%CIs: 0.76- 1; p= 0.06). A summary is available in Appendix Table D8 and Figure 6.3.

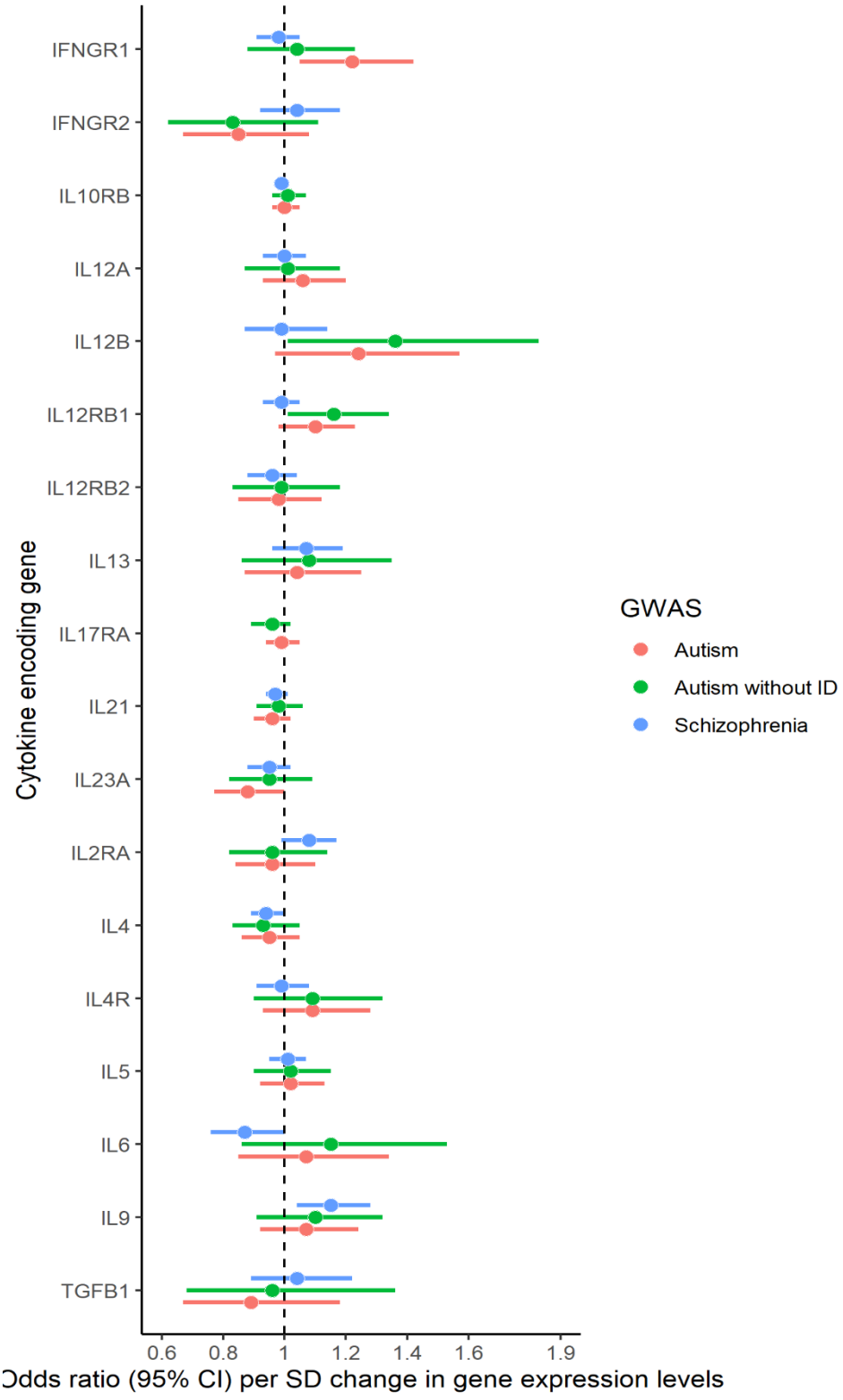

Figure 6.3 Forest plot of MR causal effect estimates and 95%CIs for autism, autism without intellectual disabilities and schizophrenia per standard deviation change in cytokine-encoding gene expression in the brain cortex.

SD: Standard deviation

6.3.3 Genetic colocalisation

None of the identified causal effects for autism and schizophrenia were supported by evidence of colocalisation (probability of H4 ranging from 1% to 37%). A summary of the results can be found in Table 6.4 and detailed results (H0-H4) can be found in Appendix Table D9.

However, in the case of autism LD Check analyses indicated that the lead brain cortex cis-eQTLs for IFNGR1 and IL23A were in strong LD with at least one of the autism lead variants in the respective regions (r^2>0.8; Table 6.4).

6.3.4 Analyses to assess bias due to reverse causation

Steiger filtering indicated that across all analyses the genetic variants explained more variance in the exposure rather than the outcome, and that therefore the MR causal effect estimates were unlikely to be influenced by reverse causation (Appendix Tables D3-D8).

There was no evidence to suggest a causal effect of common variant genetic liability to autism on plasma cytokine levels and there was some evidence to suggest an effect of common variant genetic liability to schizophrenia on levels of Interleukin 2 (IL2: β= 0.08; 95%CIs: 0.02-0.15; p= 0.01) (Appendix Tables D10 and D11).

Table 6.4 Colocalisation and LD Check results for each exposure with MR evidence of causal effects on autism and schizophrenia.

								Colocalization Analyses		**LD Check[a]**	
EXPOSURE	TISSUE	ENSEMBL_ID	LEAD_VARIANT	CHR	BP[b]	Exposure Data	Outcome data	NSNPs	H4[d]	Top Autism SNP	LD R2
IL12RB1	Blood	ENSG00000096996	rs376008	19	18189568	Suhre et al.[c]	Autism	No region data		rs273506	0.55
IFNGR1	Blood	ENSG00000027697	rs7080536	10	115348046	Sun et al.	Autism	2494	22%	rs2302373	0.22
IL4RA	Blood	ENSG00000077238	rs10418046	19	54327869	Sun et al.	Autism	3653	7%	rs11671984	0.77
IL5RA	Blood	ENSG00000091181	rs77400868	3	3150964	Sun et al.	Autism	4007	1%	rs4498029	0.06
IL13RA1	Blood	ENSG00000131724	rs4241818	4	187153786	Sun et al.	Autism	3409	5%	rs1039243	0.06
IL12B	Cortex	ENSG00000113302.4	rs75259819	5	158401932	Klein et al.	Autism	2204	6%	rs62378719	0.002
IL12RB1	Cortex	ENSG00000096996.16	rs2644777	19	18178616	Klein et al.	Autism	2394	8%	rs112461998	0.43
IFNGR1	Cortex	ENSG00000027697.14	rs4896249	6	137594069	Klein et al.	Autism	2645	37%	rs56061112	1
IL23A	Cortex	ENSG00000110944.9	rs59917308	12	56658708	Klein et al.	Autism	960	10%	rs75754909	1
IL6R	Blood	ENSG00000160712	rs4129267	1	154426264	Folkersen et al	Schizophrenia	1548	1%		
IL9	Cortex	ENSG00000145839.2	rs4487482	5	135201771	Klein et al.	Schizophrenia	2849	12%		
IL4	Cortex	ENSG00000113520.11	rs6879672	5	132025947	Klein et al.	Schizophrenia	1889	4%		
IL6	Cortex	ENSG00000136244.12	rs2905346	7	22618248	Klein et al.	Schizophrenia	3116	1%		

a: LDcheck analyses were performed only for colocalisation analyses using autism GWAS data.
b: Coordinates in GRCh37
c: No region data were available and therefore colocalisation analyses could not be performed.
d: Probability that the independent signals in the exposure and outcome regions are consistent with a shared causal variant.
ENSEMBL_ID: gene id in Ensembl; CHR: chromosome; BP: position; LD: linkage disequilibrium.

6.4 Discussion

6.4.1 Summary of findings

In the present study, I used MR and genetic colocalization approaches to investigate the causal influence of genetically proxied cytokines implicated in the differentiation and function of six major CD^+4 T cell subsets (T_H1, T_H2, T_H9, T_{FH}, T_H17, T_{Reg}) on autism and schizophrenia to elucidate potentially shared immunological mechanisms underlying both conditions. There was evidence consistent with a causal effect of genetically proxied T_H1 and T_H2 signature cytokines (IL4, IL5, IL13, IL2), and particularly IFGNR1 and IL12RB1 for which there was additional evidence to suggest brain-specific effects of their respective gene expression on autism. In the case of schizophrenia, previous MR findings suggesting a causal role of genetically proxied IL6R were replicated and there was additional evidence to suggest the possible causal influence of T_H9 cytokine encoding gene expression in the brain cortex (specifically IL4 and IL9).

6.4.2 Comparison to previous evidence

Autism

There is a substantial body of evidence suggesting a potential central role of T_H1 and T_H2 signature cytokines in autism. Specifically, in 1,100 neonatal dried blood spots from The Danish Newborn Screening Biobank, atypical levels of T_H1 and T_H2 cytokines (including IFN-γ, IL2, IL12, IL4, IL5) were found to be associated with autism later in life[303]. Additionally, in 1,029 amniotic fluid samples from a Danish historic birth cohort, atypical levels of IL4 and IL5 were found to be associated with autism and childhood psychiatric disorders[333], while elevated concentrations of IFN-γ, IL4 and IL5 in maternal serum during gestation, were associated with offspring autism and intellectual disabilities in the Early Markers for Autism study[334,335]. A similar pattern has been identified in peripheral blood of children with autism, characterised by atypical levels of IFN-γ, IL2, IL4, IL5 and IL13[336,337], as well as post-mortem brain tissue of adults with autism, characterised by increased levels of IFN-γ and an atypical IFN-γ/IL4 ratio[338]. By applying the principles of MR, the present study supports the existing evidence and indicates a potentially causal role of genetically proxied T_H1 and T_H2 signature cytokines on autism. Especially in the case of IL12RB1 and IL5RA, the SNPs instrumenting them

were cis-acting and specific to the proteins, minimising therefore the possibility of pleiotropic bias influencing the identified causal effects. Similarly, in the case of IFNGR1, the instrument showed specificity to the protein and consistency across pQTL studies.

Across all MR analyses, a consistent pattern was identified for IFNGR1 and IL12RB1. Specifically, elevated levels of genetically proxied IFGNR1 and IL12RB1 as well as increased genetically predicted expression of their respective genes in brain cortex were found to be associated with autism.

IL12RB1 (IL-12/23p40 subunit) is a common receptor for IL12 and IL23, which is promoting their signalling pathways[339]. However, IL12RB1 does not equally affect IL12 and IL23 signalling. Increasing evidence suggests that IL12RB1 signals drive naïve CD^+ 4 T cell differentiation to T_H1 (IL12 pathway) or instead to T_H17 (IL23 pathway), depending on the presence or absence of Interferon Regulatory Factor 1 (IRF1)[340]. IL12RB1 in combination with the presence of IRF1, drives naïve CD^+ 4 T cell differentiation to T_H1 and therefore production of IFN-γ, whereas in the absence of IRF1, drives differentiation towards T_H17[341]. This might be reflected in the present study findings in which I found evidence of an effect of increased genetically predicted expression of IL12RB1 and IFNGR1 in the brain cortex on autism but decreased genetically predicted expression of IL23A.

Interestingly, the effects of genetically predicted expression of IL12RB1 in the brain cortex were more pronounced on the autism sample without intellectual disability cases, whereas in the autism sample including intellectual disability cases the effect of IFNGR1 was more pronounced. IFN-γ signalling has been found to have a central role in brain function, influencing neurogenesis, synaptic plasticity and neurodegeneration[342]. Animal studies seem to indicate that excess IFN-γ signalling and production, drives neuronal cell death and synapse loss[343] while epidemiological studies seem to suggest associations between high circulating levels of IFN- γ and white matter damage in preterm infants[344]. This evidence might support the finding of a more pronounced effect of IFNGR1 expression in brain cortex on the autism sample including intellectual disability cases. However, given the sample sizes of the two autism GWASs, the possibility that the results reflect differences in power, cannot be excluded.

Schizophrenia

The finding of a causal effect of genetically proxied IL6R on schizophrenia is in line with amassing evidence indicating a causal role of the IL6R pathway in schizophrenia. Specifically, in over 3,000 participants of the ALSPAC birth cohort, IL6R genotype (captured by a functional common genetic variant associated with IL6R signalling), was found to be associated with risk of psychotic experiences at age 18[345]. In addition, previous MR studies using common genetic variants robustly associated with IL6R (from GWAS datasets different to the ones used in the present study) have identified causal effects on schizophrenia and yielded causal effect estimates comparable to the ones of the present study[152,346].

The present study adds to the existing evidence on the potential role of immune response in schizophrenia by identifying evidence consistent with a causal effect of genetically predicted expression of IL9 and IL4 genes in the brain cortex. IL4 and IL9 belong the T_H9 subset of $CD4^+$ T cells, with IL4 being the inductive and IL9 the product cytokine. The T_H9 $CD4^+$ T cell subset, has been increasingly recognised as having an important role in allergic conditions, particularly asthma[347], while recently it has been identified as a central promoter of antitumor response[347,348]. Little is currently known on the potential role of these cytokines in schizophrenia as well as brain function and neurodevelopment. Elevated levels of IL9 were found to be associated with multiple-episode schizophrenia in a small cross-sectional study of ~150 participants[349], while a causal effect of a trans IL9 genetic variant on schizophrenia risk was identified in a previous MR study[152]. Further research is necessary in order to elucidate the potential role of T_H9 cytokines in schizophrenia.

6.4.3 Strengths and limitations

The present study benefited from utilising a systematic approach for the selection of immune markers (based on CD4+ T cell subsets), as well as from the use of cis-acting genetic variants proxying for gene expression in the brain cortex. This allowed me to appraise the findings in the context of underlying immunological pathways and their mechanisms of action. Furthermore, I implemented a combination of MR and colocalisation approaches to strengthen causal inference and performed a series of sensitivity analyses to assess the possibility of reverse causation.

However, the present findings should be appraised in the context of their limitations. First and foremost, none of the identified MR effects were supported by robust evidence of colocalisation. This might suggest that the MR findings were confounded due to LD. Although, in the case of autism, there was some evidence suggestive of colocalisation based post-hoc LD check analyses, this evidence relied on the assumption that there are causal variants in the regions of interest which is difficult to ascertain given the possibility of the dataset being underpowered. Future larger GWASs are necessary to further elucidate the present LD-check findings. Second, some of the instruments used in the analyses were trans-acting, not specific to the cytokines of interest or consistent across studies and were selected using a relaxed p-value threshold. The inclusion of pleiotropic and weak instruments might have introduced bias in the causal effect estimates.[166,350] Third, although Steiger filtering suggested that the analyses were unlikely to be influenced by reverse causation, bi-directional MR analyses may have been underpowered considering the sample size of the outcome GWAS. Fourth, I assessed the contribution of common genetic variation and not rare, for which there is evidence of enrichment in immune-function gene sets in autism and schizophrenia[351,352]. Fifth, I did not have access to family and individual level data which could have allowed the assessment of the origins of the identified effects (parental vs individual) as well as the possibility of non-linear effects (which can be particularly relevant in the case of immune response[353,354]). Finally, analyses were conducted using summary data of European ancestry individuals, limiting therefore the generalisability of the present findings and replication across ancestries is necessary e.g., Zheng et al.,2021[332].

6.5 Conclusions and chapter summary

In conclusion, there was evidence consistent with a causal effect of genetically proxied T_H1 and T_H2 signature cytokines on autism. Particularly for IFGNR1 and IL12RB1, there was additional evidence to suggest brain-specific effects of their respective gene expression. In the case of schizophrenia, evidence on the causal role of the IL6R pathway was replicated, and there was evidence of brain-specific effects of genetically predicted T_H9 gene expression in the brain cortex. The findings appeared unlikely to be influenced by reverse causality. Based on the present findings there was no

evidence of shared immunological pathways underlying both autism and schizophrenia. However, only a small number of immune markers was assessed and further research is necessary in order to understand the role of immune response in both conditions.

♦

Chapter 7

Discussion

Among the aetiological models that have been proposed to explain the autism-psychosis co-occurrence, in the present thesis I assessed evidence on two possible models: causal pathways and shared risk factors.

7.1 Summary of thesis aims and methodological approaches

A summary of the thesis aims, research questions, methodological approaches and main findings is available in table 7.1

7.1.1 Causal pathways

I aimed at assessing the direct and indirect causal links between autism and psychosis. Using genotype and phenotype data from the ALSPAC birth cohort, I investigated the associations between autism polygenic risk as well as social and non-social autistic traits with psychotic experiences in adulthood. I assessed the potential confounding role of schizophrenia polygenic risk in the identified associations, and the potential mediating role of trauma in childhood. Furthermore, I applied two-sample MR and multivariable MR to assess the total and independent of IQ causal effects of genetic liability to autism as well as social and non-social autistic traits on psychotic experiences in adulthood and schizophrenia.

7.1.2 Shared risk factors

I aimed at determining whether shared immunological pathways underlie autism and psychosis. Firstly, I interrogated the potential causal role of the immune response in autism, by applying four distinct study designs and investigating the associations between parental diagnosis and genetic liability for inflammatory bowel disease and offspring autism. I used information on the central role of $CD4^+$ T cell subsets and signature cytokines in inflammatory bowel disease, to assess the causal effects of genetically proxied $CD4^+$ T cell signature cytokines in autism and schizophrenia by performing two-sample MR and genetic colocalisation analyses.

Table 7.1 Summary of thesis aims, research questions, methodological approaches and main findings.

Aim	Research Question	Chapter	Methodological approach	Data sources	Main findings
To assess the direct and indirect causal links between autism and psychosis.	Is autism liability (PRS/traits) associated with psychotic experiences in adulthood?	3	**Polygenic risk score analysis** and **multivariable regression** to investigate the associations between autism polygenic risk and psychotic experiences in adulthood.	Genotype and phenotype from the ALSPAC birth cohort.	Limited evidence to suggest an association between autism polygenic risk and psychotic experiences until ages 18/24 (OR= 0.98; 95%CIs: 0.9-1.08).
			Multivariable regression analysis to investigate the associations between social/non-social autistic traits and psychotic experiences in adulthood.		Evidence to suggest associations between broad autistic traits, particularly social communication difficulties, and distressing or frequent psychotic experiences until ages 18/24 (autism factor mean score crude OR= 1.20; 95%CIs: 1.04–1.38; SCDC crude OR=1.60; 95%CIs: 1.02–2.52).
			Multivariable regression analysis to assess the potential confounding influence of schizophrenia polygenic risk in any of the identified associations.		No evidence to suggest that schizophrenia polygenic risk confounds the associations between broad autistic traits, social communication difficulties and distressing or frequent psychotic experiences at ages 18/24(autism factor mean score adjusted OR= 1.17; 95%CIs: 1.01-1.32; SCDC adjusted OR= 1.69; 95%CIs: 1.08–2.64).
			Counterfactual mediation analysis to assess the potential mediating role of trauma in childhood in any of the identified associations.		A substantial proportion of the identified associations between broad autistic traits, social communication difficulties and psychotic experiences at ages 18/24 was mediated by traumatic experiences in childhood (autism factor mean score natural indirect effect OR= 1.05; 95%CIs: 1.02–1.07, proportion mediated: 28%; SCDC natural indirect effect OR= 1.11; 95%CIs: 1.05–1.18; proportion mediated: 38%).
	Does genetic liability to autism and social/non-social autistic traits have causal effects on psychotic experiences and schizophrenia?	4	**Two-sample MR** to estimate the total causal effects of genetic liability to autism and social/non-social autistic traits on psychotic experiences as well as schizophrenia.	GWAS summary-level data.	No evidence to suggest a causal effect of genetic liability to autism on psychotic experiences (IVW OR= 1.1; 95%CIs: 0.93-1.3) or schizophrenia (IVW OR= 1.06; 95%CIs: 0.96-1.17). Some evidence to suggest a potentially causal effect of genetic liability to social communication difficulties on psychotic experiences (IVW OR= 2.2; 95%CIs: 0.96-5.02).
			Multivariable two-sample MR to estimate the direct, independent of the potential pleiotropic influence of IQ, causal effects of genetic liability to autism and social/non-social autistic traits on psychotic experiences as well as schizophrenia.		IQ appeared to mask the causal effects of genetic liability to autism on schizophrenia, as there was evidence to suggest a direct, independent of IQ causal effect (IVW OR= 1.24; 95%CIs: 1.11-1.38).

Table 7.1. Continued from above.

Aim	Research Question	Chapter	Methodological approach	Data sources	Main findings
To determine whether shared immunological pathways underly autism and psychosis.	Is immune response causally implicated in autism?	5	**Multivariable regression analysis** to investigate the associations between parental diagnoses of inflammatory bowel disease and offspring autism.	Phenotype data from nationwide health registers in Sweden.	There was evidence to suggest associations between paternal and maternal diagnosis of inflammatory bowel disease and offspring autism (paternal diagnoses adjusted OR= 1.09; 95% CIs: 1.02-1.17; maternal diagnoses adjusted OR= 1.32; 95% CIs: 1.25-1.40).
			LD score regression analysis to assess the genetic correlation between inflammatory bowel disease and autism.	GWAS summary-level data.	No evidence to suggest a genetic correlation between inflammatory bowel disease and autism (rg= -0.06; 95%CIs: -0.15-0.02).
			Polygenic risk score analysis and **multivariable regression** to investigate the associations between maternal polygenic risk for inflammatory bowel disease and offspring autism.	Genotype and phenotype data from the ALSPAC birth cohort.	Evidence to suggest an association between maternal polygenic risk to inflammatory bowel disease subtypes and offspring autistic traits (ulcerative colitis β= 0.02; 95%CIs: 0.003-0.05; Crohn's disease β= 0.03; 95%CIs: 0.01 to 0.05).
			Two-sample MR to assess the causal effects of genetic liability to inflammatory bowel disease on autism.	GWAS summary-level data	Evidence to suggest a causal effect of genetic liability to ulcerative colitis on autism (IVW OR= 1.04; 95% CIs: 1.01-1.07).
	Are immunological markers causally implicated in autism, also causal for schizophrenia?	6	**Two-sample MR** analyses to assess the causal effects of genetically proxied immunological markers on autism and schizophrenia.	GWAS summary-level data	Evidence to suggest a causal effect of genetically proxied TH1 and TH2 cytokines in autism, while in contrast, there was evidence to suggest a causal effect of TH9 cytokines and IL6 (member of the TFH and TH17 cytokines).
			Genetic colocalisation analyses to assess whether any identified causal effects are consistent with a shared causal variant influencing levels of immunological markers as well as autism and/or schizophrenia.	GWAS summary-level data	None of the identified causal effects were supported by evidence of colocalisation (H4 ranging from 1% to 37%).

7.2 Direct and indirect causal links between autism and psychosis

Using genotype and phenotype data from the ALSPAC birth cohort in Chapter 2, I found limited evidence to suggest an association between autism polygenic risk and psychotic experiences in adulthood, but there was evidence to suggest associations between broad autistic traits, particularly social communication difficulties, and psychotic experiences in adulthood. The identified associations did not seem confounded by schizophrenia polygenic risk and were substantially mediated by trauma in childhood. Two-sample MR analyses in Chapter 3, utilising summary-level GWAS data, appeared to support the above findings, by providing limited evidence to suggest a causal effect of common variant genetic liability to autism on psychotic experiences, but a potentially causal role of genetic liability to social communication difficulties (although evidence was weak, potentially due to limited power in these analyses). Furthermore, there was evidence to suggest a direct, independent of IQ, effect of genetic liability to autism on schizophrenia. The present findings seem to be in support of the autism-psychosis aetiological models hypothesising that the two conditions co-occur because they are causally linked. Importantly, the findings emphasise that the relationships between the two conditions are complex, with genetic, phenotypic, as well as environmental factors playing a central role in their co-occurrence.

With regards to genetic factors, there was evidence for a central role of genetic liability to autism (over and beyond genetic liability to higher IQ) and genetic liability to social communication difficulties in risk of schizophrenia and psychotic experiences respectively. This can potentially imply, based on liability-threshold models of inheritance[191–193], that sub-phenotypic manifestations of autism and particularly its associated social autistic traits might confer risk for psychosis later in life. This was further supported by the observational findings in the ALSPAC cohort, suggesting that not only genetic liability, but also phenotypic expression of social communication difficulties is associated with psychotic experiences in adulthood. Social functioning appears to have a central role in psychosis risk. Difficulties in social functioning have been found to be predictive of conversion to psychosis in samples of adolescents and young adults at clinical high risk[236], while there is recent evidence from the population-based IMAGEN study, suggesting that difficulties in social functioning

are mediating the pathways between autism polygenic risk and psychotic experiences at age 18[142]. There is currently increasing interest into the potential efficacy of interventions targeting social functioning in order to aid prevention of transition to psychosis in individuals at clinical high risk[355].

However, it is important to note that it might be an overgeneralisation to conclude from the above findings that only the social sub-phenotypic autism manifestations might be causal for psychosis. The relationship between autism and psychosis seems to be more complex than this. Although genetic liability and phenotypic manifestations of social communication difficulties presented links with psychotic experiences, genetic liability to autism presented direct, independent of IQ, causal effects to schizophrenia. There are two possibilities to explain this, and they are not mutually exclusive. One possibility is that the identified causal links reflect the strong genetic correlations between autism and schizophrenia[36,66]. Another possibility is that schizophrenia risk might be influenced by a constellation of sub-phenotypic manifestations of genetic liability to autism, which extend beyond social features and are independent of IQ. Such sub-phenotypic manifestations could include structural and functional brain alterations as well as neurocognitive features. In line with this interpretation, there is recent evidence suggesting that autism polygenic risk is associated with brain functional alterations and difficulties in emotion recognition in schizophrenia cases, compared to general population controls[258].

With regards to environmental factors, the present thesis findings support a mediating role of traumatic experiences in childhood. Traumatic experiences appear to have central role in the emergence of mental health difficulties in the general population as well as autistic individuals. Specifically, trauma in childhood and adolescence has been associated with psychotic experiences at age 18 in the ALSPAC birth cohort[91], while bullying victimisation in childhood has been found to mediate the associations between autistic traits and psychotic experiences at age 14 in a Japanese population-based cohort (Tokyo Teen Cohort)[139], and depressive symptoms at age 18 in the ALSPAC birth cohort[285].

Overall, there is evidence to suggest direct and indirect links between autism and psychosis. Underlying genetic liability to autism, genetic liability as well as phenotypic expression of social

communication difficulties and experience of trauma in childhood appear to contribute to risk of psychotic experiences and schizophrenia in adulthood.

7.3 Shared immunological pathways underlying autism and psychosis

Utilising four distinct approaches, in Chapter 4, I assessed whether immune response is causally implicated in autism by investigating the associations between parental inflammatory bowel disease and offspring autism. Using data from nationwide health registers in Sweden, associations between parental diagnoses of inflammatory bowel disease and offspring autism were found. Using genotype and phenotype data from the ALSPAC birth cohort, I found evidence of an association between maternal polygenic risk for inflammatory bowel disease subtypes (ulcerative colitis and Crohn's disease) and offspring autistic traits. This was further supported by two-sample MR analyses suggesting a causal effect of genetic liability to ulcerative colitis on autism. In Chapter 5, I utilised information on CD4+ T cell subsets and their cytokine networks, which are implicated in the onset and course of inflammatory bowel disease, to investigate the causal effects of genetically proxied $CD4^+$ T cell subset (T_H1, T_H2, T_H9, T_{FH}, T_H17, T_{Reg}) signature cytokines on autism and schizophrenia. Using two-sample MR, I found evidence of a causal effect of genetically proxied T_H1 and T_H2 signature cytokines (IL4, IL5, IL13, IL2) on autism, and particularly IFGNR1 and IL12RB1 for which there was additional evidence to suggest brain-specific effects of their respective gene expression. In comparison, I found evidence of a causal effect of genetically proxied IL6R on schizophrenia, and there was additional evidence to suggest the possible causal influence of T_H9 cytokine encoding gene expression in the brain cortex (specifically IL4 and IL9).

The present findings implicate immunological pathways in both autism and schizophrenia but do not support the hypothesis that the immunological pathways investigated in the present thesis are shared for autism and psychosis. The hypothesis was predominantly based on evidence suggesting that maternal infections during pregnancy are associated with offspring autism as well as psychosis, and on evidence suggesting that autistic individuals and individuals with psychosis present some similarities in terms of their immune profiles, e.g., elevated levels of serum IL-6[130,264]. In the context of this hypothesis it has been proposed that shared phenotypic features between autism and psychosis

are a result of shared immune mechanisms implicated in both conditions and acting in utero, whereas distinct features are a result of genetic, epigenetic and immunomodulatory mechanisms (referring to mechanisms that respond to inflammation) specific to each condition[130,264]. The present thesis findings support the hypothesis that maternal immune response in utero might be causally implicated in autism- as suggested by evidence of associations between maternal polygenic risk for inflammatory bowel disease subtypes and offspring autistic traits. However, the immunological markers and respective pathways that were found to be causally implicated in autism appeared to be unique to the condition and not shared with schizophrenia- T_H1 and T_H2 signature cytokines in autism, T_H9 and IL6 in schizophrenia.

The importance of the present findings could rely on the fact that the identification of causal immunological markers unique to each condition, might imply distinct biological pathways and processes contributing to the phenotypic features of autism and schizophrenia. T_H1 and T_H2 signature cytokines have been found to be implicated in adverse pregnancy outcomes, including recurrent pregnancy losses, stillbirth and preeclampsia, as well as allergies and autoimmunity[299,316]. In contrast, T_H9 signature cytokines have been found to be implicated in antitumour response and allergic asthma, but their role in pregnancy is not clear yet[299,325]. However, it is important to note that it is currently debatable whether T_H9 signature cytokines form a distinct pathway to T_H2 or are part of the T_H2 pathway that have evolved to have some distinct functions[325]. This is based on evidence suggesting that the two subsets share two inductive cytokines, IL2 and IL4, and appear to be implicated in allergic response[325]. On this basis and considering that in the present thesis only a small number of immune markers was assessed, the possibility that there might be some shared immunological pathways between autism and schizophrenia, cannot be excluded.

Overall, based on the present findings, there was evidence to suggest that immune response in utero might be causally implicated in autism. Genetically proxied T_H1 and T_H2 signature cytokines appeared to have a causal effect on autism but not on schizophrenia, while genetically proxied T_H9 signature cytokines and IL-6 appeared to have a causal effect on schizophrenia, but not on autism.

This might indicate that potentially unique to each condition immunological pathways are implicated in their aetiology.

7.4 Strengths and limitations

Each of the studies presented in this thesis had strengths and limitations, which have been discussed in detail in the respective chapters. Here I will provide an overview of the key strengths and limitations that are relevant across all studies of the thesis.

7.4.1 Study designs and triangulation of evidence

A notable strength of this thesis is that for each aim, I applied a combination of distinct methodological approaches, utilising phenotype and genotype data, to strengthen causal inference.

For the first thesis aim, investigating the direct and indirect causal links between autism and psychosis (Chapters 2 and 3), I used traditional observational epidemiological approaches in combination with polygenic risk score analyses and two-sample MR. Similarly in Chapters 3 and 4 (second thesis aim) I applied a combination of observational approaches, LD score regression, polygenic risk score approaches, two-sample MR and genetic colocalisation analyses to investigate the potentially causal role of immune response in autism and identify whether autism and schizophrenia share immunological pathways.

Each approach was utilised with the intention to complement evidence provided by the other approaches and address potential sources of bias. For example, traditional observational approaches allowed the assessment of the influence of potential confounding factors such as schizophrenia polygenic risk in the associations between autistic traits and psychotic experiences in Chapter 2, and family psychiatric history in the associations between parental diagnoses of inflammatory bowel disease and offspring autism in Chapter 4. However, they can be hampered by measurement error in the exposure and residual confounding. For this reason, polygenic risk score approaches were employed, which refine the definition of the exposure[158] by capturing genetic liability (regardless of whether the phenotype has been expressed or not) and overcome residual confounding, assuming that genetic liability to a condition is unrelated to the confounders of the exposure-outcome associations.

On this basis, in Chapter 2, the associations between autism polygenic risk and psychotic experiences were assessed, and in Chapter 4, the associations between maternal polygenic risk for inflammatory bowel disease and offspring autistic traits were assessed. However, polygenic risk score approaches can be hampered by the influence of pleiotropy, which they cannot detect or account for. For this reason, two-sample MR analyses were employed, allowing the detection of pleiotropic bias through sensitivity analyses (e.g., MR Egger[201]) and the estimation of the independent effects of an exposure on an outcome, accounting for other genetically correlated traits, through multivariable MR[205]. This was the case in Chapter 3 in which I assessed the total and independent of IQ effects of genetic liability to autism and autistic traits on psychotic experiences and schizophrenia, as well as Chapter 4 in which I investigated the causal effects of generic liability to inflammatory bowel disease on autism.

Only exception and a limitation of the thesis is that triangulation was not possible for the evidence presented in Chapter 5. Two-sample MR was applied to assess the causal effects of genetically proxied immunological markers on autism and schizophrenia, overcoming limitations of observational approaches such as reverse causation and residual confounding, while genetic colocalisation was used to interrogate whether the identified relationships are driven by shared causal variant between immunological markers and autism/schizophrenia, or instead a result of the LD structure of the assessed loci[166,207]. These approaches, however, are not free from limitations. For example immunological markers in the present two-sample MR analyses were instrumented by a single SNP (which is the case in most analyses using transcriptomic and proteomic data) and therefore, did not allow the application of sensitivity analyses to detect and account for pleiotropy, while genetic colocalisation which was used as a complementary approach, requires well-powered GWASs. A potential approach to triangulate present findings would be to investigate the associations between the levels of the cytokines of interest in amniotic fluid or neonatal blood spots and autism/psychosis risk later in life. This approach has been previously applied for other investigations, such as to assess the associations between acute phase proteins, inflammatory cytokines and autism in the Danish Historic Birth cohort and the Stockholm Youth cohort[333,356]. During the design of the study presented in

Chapter 5 this possibility was considered, however, the vast majority of the markers of interest were not available in either cohort.

7.4.2 Sample sizes

An important consideration across all studies conducted in the present thesis is available sample sizes. The largest publicly available GWAS summary data were used for the calculation of polygenic risk scores as well as two-sample MR analyses. However, the sample sizes of the majority of these datasets are still relatively small, e.g., autism: Ncases/controls= 18,381/27,969; social communication difficulties: N= 5,421; psychotic experiences: Ncases/controls= 6,123/121,843. This implies that firstly, polygenic risk scores calculated based on these datasets might not capture adequately phenotypic variance (e.g., autism polygenic risk used as an exposure in Chapter 2) and similarly this might be the case for SNPs used as instruments in two-sample MR analyses (e.g., in Chapter 3). Secondly, the possibility of lack of statistical power to detect causal effects cannot be excluded. For example, this might have been the case in two-sample MR analyses in Chapter 4, investigating the causal effects of genetic liability to social communication difficulties on psychotic experiences and schizophrenia. Third, some of the analyses, although intended to be comparable, they are not, due to substantial differences in the sample sizes of the GWASs used. This was the case in Chapter 3 in which the outcomes were psychotic experiences (Ntotal= 127,966) and schizophrenia (Ntotal= 306,011), and in Chapter 5 in which the outcomes were autism (Ntotal= 46,350) and schizophrenia.

In the case of analyses using phenotypic data two approaches were followed to ensure adequate sample sizes and minimise bias due to attrition. Firstly, in Chapter 2, in combination to complete case analyses (maximum N with data on exposure, outcome, confounders = 3,707), I performed multiple imputation (maximum N= 13,105). Secondly, in Chapter 4, nationwide health registers were used, resulting in a sample size of 2,324,227 eligible index persons- one of the largest to date investigating the associations between parental autoimmune conditions and offspring autism.

A final important consideration with regards to samples used, is that despite attempts to use the largest possible sample sizes, their ethnic diversity was limited. All samples were based predominantly on individuals of European ancestry. This challenges substantially the generalisability of the findings

presented in the thesis, considering that genetic and environmental factors influencing the autism-psychosis co-occurrence across ancestries might be different[332,357].

7.4.3 Heterogeneity of autism and psychosis

Autism and psychosis are highly heterogeneous. With regards to the heterogeneity of autism, attempts were made across all studies of the thesis to address emerging evidence suggesting that autism with intellectual disabilities is distinct from autism without in terms of behavioural characteristics[358], genetic and environmental risk factors[281,282], and comorbid medical and mental health conditions[284,285]. For example, two-sample MR analyses in Chapters 3, 4 and 5, were conducted using an autism GWAS sample with and without intellectual disabilities and repeated using an autism GWAS sample without intellectual disabilities. In addition, I attempted to incorporate in my study designs evidence suggesting that the social and non-social features of autism are aetiologically distinct[41]. Therefore, I investigated their links to psychotic experiences in Chapter 2 and causal effects on psychotic experiences and schizophrenia in Chapter 3, separately.

However, a substantial limitation of the studies presented in the thesis, is that the heterogeneity of the psychosis spectrum was not addressed in the same way. Firstly, 'positive' (e.g., hallucinations, delusions) psychotic symptoms were assessed (Chapters 2 and 3). However, negative psychotic features (e.g., apathy) are also part of the psychosis spectrum and more importantly there is evidence suggesting that they present correlations and associations with autistic traits[106,107]. In the context of the present thesis, analyses with negative psychotic symptoms were not conducted. This decision was made because the largest available psychotic experiences in adulthood GWAS captures positive experiences only[87] and therefore triangulation of causal evidence would not be possible- this is particularly important considering that in an observational design this outcome may have substantial measurement error due to the close resemblance of some negative symptoms to features of autism (e.g., sociability[359]). Secondly, only the two extremes of the psychosis spectrum were investigated- psychotic experiences and schizophrenia, although it has been proposed that the psychosis spectrum includes conditions such as bipolar and major depressive disorder with psychotic features[3,74] (this could be relevant in Chapters 4 and 6).

7.5 Future directions

Despite using distinct methodological approaches to triangulate evidence, utilising large available sample sizes and incorporating in the study designs current conceptualisations of the autism and psychosis spectra, further research is necessary in order to develop our current understanding on whether causal links and/or shared immunological pathways underly the autism-psychosis co-occurrence.

Firstly, it is necessary to investigate the potential links between autism and psychosis in samples of mixed cognitive abilities, i.e., including also individuals with intellectual disabilities. The study conducted in Chapter 3, provided evidence suggesting that genetic liability to autism has causal effects on schizophrenia, over and beyond IQ. This emphasises the necessity to investigate the autism-psychosis co-occurrence in autistic individuals with intellectual disabilities. Recent meta-analytic evidence suggests that only a small proportion of studies in the field of autism, include participants with intellectual disabilities (less than 10% of participants in published autism studies appear to have intellectual disabilities)[52,360]. This implies that we currently know very little on the mental health outcomes of these individuals and it can be particularly important considering current challenges and limited availability of mental health assessment and intervention approaches for this population[259,260].

Secondly, the increasing availability of genotype and phenotype data across cohorts will enable investigations into the causal pathways linking autism and psychosis in diverse populations. For example, the Philadelphia Neurodevelopmental Cohort, is a population-based cohort of approximately 9,500 participants with available genotype and phenotype data (including autistic traits and psychotic experiences)[361,362]. The cohort is multi-ethnic, comprising of 66% participants of European ancestry and 26% of African American ancestry, and on this basis, it could be an appropriate population to investigate the potential polygenic and phenotypic associations between autism and psychosis.

Third, along with using multi-ethnic cohorts, there is a necessity for more and larger GWAS in populations of non-European ancestry[357]. Evidence from PRS and MR methods incorporating data from populations of different ancestries suggests that the efficacy of the methods can be substantially

improved. For example, incorporating multi-ethnic ancestry data in PRS for inflammatory bowel disease substantially improved prediction of the phenotype in the Mount Sinai BioMe Biobank and the UK Biobank[363], while investigating the causal effects of genetically proxied protein expression in populations of African and European ancestry, led to the identification of seven novel drug targets for five diseases including asthma, and stroke[332]. On this basis, it can be expected that utilising GWAS data from diverse ancestries can provide valuable insights into the polygenic associations and causal links between autism and psychosis.

Fourth, GWAS studies investigating the genetic determinants of distinct phenotypic features of autism and psychosis can be important towards gaining further understanding on the causal links and shared immunological pathways underlying the two conditions. For example, Pain et al. conducted a GWAS of distinct psychotic symptom domains in population-based samples of European ancestry adolescents[364], while there is an ongoing effort in the Norwegian Mother and Child cohort (MoBa) to conduct GWAS on social communication difficulties and repetitive behaviours[365]. Large sample sizes and phenotyping based on validated measures will be key determinants of future GWAS on distinct autism and psychosis features, and their release can aid towards understanding whether specific phenotypic expressions of the two conditions are causally linked and/or share immunological pathways.

Finally, the present thesis provided evidence that investigating the causal links between parental autoimmune conditions and offspring autism can be a fruitful approach towards uncovering underlying immunological pathways. Future extensions of this work including a range of autoimmune conditions (i.e., beyond inflammatory bowel disease) and incorporating methodological approaches allowing triangulation of evidence and investigating how risk is transmitted to the offspring (genetically transmitted risk vs in utero effects), is expected to further our current understanding on the potentially shared and distinct immunological pathways underlying autism and psychosis.

7.6 Conclusion

In this doctoral thesis, I aimed at assessing evidence on two aetiological models of the autism-psychosis co-occurrence proposing that the two conditions are causally linked and/or share immunological pathways.

Using traditional observational approaches, polygenic risk score and MR approaches, I found evidence suggesting that autism and psychosis might be causally linked. Autism common variation, phenotypic expression of social communication difficulties and traumatic experiences in childhood, were found to play a central role in co-occurrence of the two conditions. Although further research is necessary utilising diverse samples in terms of ethnicity and cognitive ability, as well as large GWAS samples on distinct phenotypic features of the two conditions, the present findings highlight that beyond genetic risk factors, phenotypic and environmental factors can explain their co-occurrence and should be considered in order to deliver targeted and effective interventions for autistic individuals.

With regards to shared immunological pathways underlying autism and psychosis, I found evidence to suggest that immune response is causally implicated in autism, by using four distinct study designs to investigate the causal links between maternal diagnosis and genetic liability to inflammatory bowel disease and offspring autism. However, MR and genetic colocalisation analyses suggested that the immunological pathways implicated in autism are likely to be distinct from the ones implicated in psychosis. This is only a first step towards understanding the causal contribution of immunological pathways in autism and psychosis. Future research in this area is expected to provide valuable insights into not only the immunological pathways that might underly their co-occurrence but more importantly on the aetiology of the two conditions.

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Appendix A

Table A1. Associations between autism polygenic risk score (PRS) at 13 p-value thresholds and psychotic experiences assessed at age 18 and/or 24.

p.threshold	OR	SE	P	95% CIs	
0.5	0.986413	0.046508	0.771706	0.899343	1.081913
0.4	0.984396	0.046446	0.738886	0.897446	1.07977
0.3	0.997801	0.046968	0.962704	0.909865	1.094237
0.2	0.994424	0.046732	0.905289	0.906923	1.090367
0.1	0.989412	0.046589	0.821159	0.902187	1.085071
0.05	0.982064	0.046184	0.700346	0.895592	1.076886
0.01	1.044534	0.048916	0.352173	0.952928	1.144946
0.001	1.013245	0.047316	0.778109	0.924626	1.110359
0.0001	1.066338	0.050569	0.175606	0.971691	1.170204
0.00001	1.00605	0.047458	0.898261	0.917204	1.103502
0.000001	1.03371	0.04882	0.482684	0.942319	1.133964
0.0000001	1.040374	0.049111	0.40176	0.948437	1.141223

Table A2. Associations between autism polygenic risk score (PRS) at 13 p-value thresholds and distressing or frequent psychotic experiences assessed at age 18 and/or 24.

p.threshold	OR	SE	P	95% CIs	
0.5	1.093295	0.069816	0.162481	0.964675	1.239065
0.4	1.090788	0.06973	0.174026	0.962335	1.236387
0.3	1.110382	0.070773	0.100434	0.979985	1.25813
0.2	1.094311	0.069664	0.156856	0.965947	1.239734
0.1	1.079415	0.068824	0.230705	0.952611	1.223098
0.05	1.064372	0.067807	0.327446	0.939436	1.205924
0.01	1.121847	0.071258	0.070275	0.990528	1.270576
0.001	1.089499	0.069135	0.17675	0.962085	1.233787
0.0001	1.122636	0.072319	0.072537	0.989476	1.273717
0.00001	1.028646	0.06587	0.659169	0.907317	1.1662
0.000001	1.011586	0.065099	0.857932	0.891713	1.147575
0.0000001	1.026585	0.065967	0.683047	0.905102	1.164373
0.00000005	1.026585	0.065967	0.683047	0.905102	1.164373

Table A3. Associations between autism polygenic risk score (PRS) at 13 p-value thresholds and psychotic experiences assessed at age 18 and/or 24, excluding tactile hallucinations.

p.threshold	OR	SE	P	95% CIs	
0.5	0.978839	0.048058	0.66311	0.889037	1.077713
0.4	0.978966	0.048094	0.665213	0.889099	1.077916
0.3	0.991053	0.048569	0.854496	0.900289	1.090968
0.2	0.9895	0.048411	0.82918	0.899023	1.089082
0.1	0.986129	0.048348	0.775722	0.89578	1.085591
0.05	0.969849	0.047498	0.5319	0.881083	1.067558
0.01	1.023088	0.049898	0.63979	0.929817	1.125714
0.001	0.996911	0.048517	0.949316	0.906215	1.096685
0.0001	1.049277	0.051865	0.33049	0.952392	1.156018
0.00001	0.994489	0.048888	0.9105	0.903141	1.095077
0.000001	1.016287	0.050105	0.743141	0.922679	1.119393
0.0000001	1.049453	0.051533	0.32562	0.953158	1.155476
0.00000005	1.049453	0.051533	0.32562	0.953158	1.155476

Table A4. Associations between autism polygenic risk score (PRS) at 13 p-value thresholds and distressing or frequent psychotic experiences assessed at age 18 and/or 24, excluding tactile hallucinations.

p.threshold	OR	SE	P	95% CIs	
0.5	1.052934	0.068856	0.430249	0.926269	1.196921
0.4	1.050061	0.068735	0.455512	0.923627	1.193802
0.3	1.06851	0.06973	0.309909	0.940221	1.214302
0.2	1.052052	0.068579	0.436313	0.925872	1.195429
0.1	1.03708	0.06774	0.577243	0.912459	1.178722
0.05	1.02379	0.066827	0.718704	0.900843	1.163516
0.01	1.076179	0.07003	0.259227	0.947315	1.222572
0.001	1.038967	0.067572	0.556693	0.914621	1.180217
0.0001	1.107556	0.07317	0.12203	0.973042	1.260665
0.00001	1.029564	0.067583	0.657149	0.905271	1.170922
0.000001	0.998549	0.066013	0.982471	0.877198	1.136687
0.0000001	1.01319	0.066908	0.842702	0.890185	1.153193
0.00000005	1.01319	0.066908	0.842702	0.890185	1.153193

Table A5. Associations between autistic traits and childhood traumatic experiences[1].

		Traumatic experiences between ages 5-11			
		Unadjusted		Adjusted[2]	
Exposure	n	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**
Autism mean factor score	5,438	1.41 (1.32–1.50)	<0.001	1.28 (1.20–1.38)	<0.001
Social communication difficulties	4,959	2.54 (2.08–3.11)	<0.001	2.20 (1.79–2.70)	<0.001
Repetitive behaviours	5,036	1.57 (1.25–1.98)	<0.001	1.35 (1.07–1.71)	0.013
Sociability	5,210	0.97 (0.82–1.16)	0.76	0.93 (0.78–1.11)	0.415
Pragmatic language	4,946	1.82 (1.50–2.22)	<0.001	1.57 (1.28–1.92)	<0.001

[1] Estimates based on observations with complete data on exposure, confounders, and childhood trauma.
[2] Adjusted for the following confounders: child sex, parity, major financial problems, maternal highest educational attainment, maternal anxiety, maternal depression, and child IQ.

Table A6. Summary of the characteristics for the sample with complete records across each analysis and the ALSPAC sample.

	Exposure in each analysis					
	Autism factor mean score	Social communication difficulties	Repetitive behaviours	Sociability	Pragmatic language	
Variable	Complete records[1] *n* = 3,707	Complete records[1] *n* = 3,384	Complete records[1] *n* =3,397	Complete records[1] *n* =3,536	Complete records[1] *n* = 3,409	Full sample[2] *n* = 14,868
Male sex, *n* (%)	1,649 (44%)	1,514 (45%)	1,529 (45%)	1,589 (45%)	1,518 (45%)	7,591 (51%)
Parity (<=1 child), *n* (%)	3,138 (85%)	2,861 (85%)	2,880 (85%)	3,000 (85%)	2,891 (85%)	10,295 (80%)
Maternal educational attainment (university degree), *n* (%)	761 (21%)	726 (21%)	711 (21%)	730 (21%)	723 (21%)	1,598 (13%)
Major financial problems (present), *n* (%)	462 (12%)	406 (12%)	404 (12%)	437 (12%)	411 (12%)	1,665 (15%)
Maternal depression during pregnancy (EPDS >= 12), *n* (%)	468 (13%)	410 (12%)	420(12%)	439 (12%)	426 (13%)	2,122 (18%)
Mother's age at delivery, mean (SD)	30 (4.4)	30 (4.3)	30 (4.4)	30 (4.4)	30 (4.4)	28 (4.9)
Maternal anxiety during pregnancy, mean (SD)	4.5 (3.3)	4.5 (3.3)	4.5 (3.3)	4.5 (3.3)	4.5 (3.3)	4.9 (3.6)
Total IQ score (WISC-III), mean (SD)	107 (16.1)	108 (15.9)	108 (16)	108 (16)	108 (16.1)	104 (16.5)
Psychotic experiences[3], *n* (%)	448 (12%)	404 (12%)	411 (12%)	429 (12%)	408 (12%)	770 (13%)
Traumatic experiences 5-11 years, *n* (%)	1,448 (40%)	1,322 (40%)	1,346 (40%)	1,382 (40%)	1,334 (40%)	3,658 (42%)
Autism factor mean score, *n* (%)[4]	268 (7%)	234 (7%)	241 (7%)	251 (7%)	249 (7%)	1,309 (10%)

SD, standard deviation; EPDS, Edinburgh Postnatal Depression Scale; IQ, Intelligence Quotient; WISC-III, Wechsler Intelligence Scale for Children third edition.
[1] Sample with complete data on exposure, outcome, confounders.
[2] ALSPAC children alive at 1 year and not withdrawn consent. Different completion rates across each variable.
[3] Psychotic experiences assessed at ages 18 and/or 24.
[4] The measure was dichotomised (worst 10th percentile) for the purposes of sample descriptive statistics.

Table A7. Predictors of being a complete case[1] across each analysis.

Exposure in each analysis										
	Autism factor mean score		Social communication difficulties		Repetitive behaviours		Sociability		Pragmatic language	
Predictor variable	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**
Sex (Female)	1.42 (1.32–1.53)	<0.001	1.39 (1.29–1.5)	<0.001	1.37 (1.27–1.48)	<0.001	1.38 (1.28–1.49)	<0.001	1.41 (1.30–1.52)	<0.001
Parity (>1 child)	0.63 (0.57–0.70)	<0.001	0.65 (0.58–0.72)	<0.001	0.63 (0.57–0.7)	<0.001	0.63 (0.56–0.69)	<0.001	0.63 (0.57–0.70)	<0.001
Maternal educational attainment (university degree)	2.42 (2.18–2.70)	<0.001	2.54 (2.28–2.83)	<0.001	2.42 (2.17–2.69)	<0.001	2.39 (2.15–2.66)	<0.001	2.49 (2.24–2.77)	<0.001
Major financial problems (present)	0.76 (0.67–0.85)	<0.001	0.72 (0.64–0.81)	<0.001	0.71 (0.63–0.8)	<0.001	0.75 (0.67–0.84)	<0.001	0.73 (0.64–0.82)	<0.001
Maternal depression during pregnancy (EPDS >= 12)	0.58 (0.52–0.64)	<0.001	0.55 (0.49–0.62)	<0.001	0.56 (0.50–0.63)	<0.001	0.56 (0.50–0.63)	<0.001	0.57 (0.51–0.64)	<0.001
Psychotic experiences (present)[2]	0.75 (0.64–0.87)	<0.001	0.75 (0.64–0.87)	<0.001	0.78 (0.67–0.9)	0.001	0.77 (0.66-0.90)	0.001	0.75 (0.65–0.88)	<0.001
Traumatic experiences 5-11 years	0.89 (0.82–0.97)	0.01	0.85 (0.78–0.93)	<0.001	0.87 (0.79–0.95)	0.002	0.87 (0.79–0.94)	0.001	0.86 (0.79–0.94)	0.001
Autism factor mean score (above worst 10th percentile)[3]	0.62 (0.54–0.72)	<0.001	0.59 (0.51–0.69)	<0.001	0.62 (0.53–0.71)	<0.001	0.61 (0.53–0.71)	<0.001	0.64 (0.55–0.74)	<0.001
Mother's age at delivery (per year increase)	1.10 (1.09–1.11)	<0.001	1.11 (1.09–1.12)	<0.001	1.10 (1.10–1.11)	<0.001	1.10 (1.09–1.11)	<0.001	1.10 (1.10–1.11)	<0.001
Maternal anxiety during pregnancy, (per point increase)	0.95 (0.94–0.96)	<0.001	0.95 (0.94–0.96)	<0.001	0.95 (0.94–0.96)	<0.001	0.95 (0.94–0.96)	<0.001	0.95 (0.94–0.96)	<0.001
Total IQ score (WISC-III), (per point increase)	1.03 (1.02–1.03)	<0.001	1.03 (1.02–1.03)	<0.001	1.03 (1.02–1.03)	<0.001	1.03 (1.02–1.03)	<0.001	1.03 (1.02–1.03)	<0.001

[1] Sample with complete data on exposure, outcome, and confounders.
[2] Psychotic experiences assessed at ages 18 and/or 24.
[3] The measure was dichotomised (worst 10th percentile) for the purposes of sample descriptive statistics.

Table A8. Association between autistic traits and psychotic experiences[1], adjusted for schizophrenia polygenic risk scores[2].

		Including tactile hallucinations								Excluding tactile hallucinations							
		Psychotic experiences				Psychotic experiences, distressing and/or frequent				Psychotic experiences				Psychotic experiences, distressing and/or frequent			
		Unadjusted		Adjusted[3]		Unadjusted		Adjusted[3]		Unadjusted		Adjusted[3]		Unadjusted		Adjusted[3]	
Exposure	**n**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Autism factor mean score	3,961	1.10 (0.99–1.22)	0.07	1.10 (0.99–1.22)	0.07	1.15 (1.01–1.32)	0.03	1.17 (1.01–1.32)	0.03	1.14 (1.02–1.26)	0.02	1.14 (1.02–1.26)	0.02	1.17 (1.02–1.33)	0.03	1.17 (1.02–1.34)	0.02
Social communication difficulties	3,299	1.47 (1.04–2.08)	0.03	1.47 (1.04–2.08)	0.03	1.68 (1.07–2.62)	0.02	1.69 (1.08–2.64)	0.02	1.46 (1.01–2.08)	0.05	1.45 (1.01–2.09)	0.05	1.59 (1.00-2.53)	0.05	1.6 (1.01–2.55)	0.05
Repetitive behaviour	3,293	0.80 (0.50–1.29)	0.37	0.81 (0.50–1.29)	0.37	1 (0.55–1.82)	0.99	1.01 (0.55–1.84)	0.98	0.85 (0.52–1.39)	0.52	0.86 (0.53–1.39)	0.53	0.96 (0.51–1.79)	0.89	0.97 (0.52–1.81)	0.91
Sociability	3,493	1.13 (0.83–1.54)	0.45	1.13 (0.83–1.54)	0.45	1.18 (0.78–1.79)	0.44	1.17 (0.77–1.78)	0.45	1.09 (0.79–1.51)	0.60	1.09 (0.79–1.51)	0.60	1.03 (0.66–1.61)	0.89	1.03 (0.66–1.61)	0.90
Pragmatic language	3,444	1.12 (0.79–1.59)	0.51	1.12 (0.79–1.59)	0.51	1.43 (0.92–2.21)	0.11	1.43 (0.93- 2.22)	0.11	1.23 (0.87–1.75)	0.24	1.24 (0.87–1.76)	0.24	1.52 (0.98–2.35)	0.06	1.52 (0.98–2.36)	0.06

[1] Psychotic experiences assessed at ages 18 and/or 24.
[2] Estimates based on observations with complete data on exposure, outcome, and schizophrenia polygenic risk scores.
[3] Adjusted for schizophrenia polygenic risk scores.

Table A9. Associations between autistic traits and psychotic experiences[1] using 100 imputed datasets.

		Including tactile hallucinations								Excluding tactile hallucinations							
		Psychotic experiences				Psychotic experiences, distressing and/or frequent				Psychotic experiences				Psychotic experiences, distressing and/or frequent			
		Unadjusted		Adjusted[2]		Unadjusted		Adjusted[2]		Unadjusted		Adjusted[2]		Unadjusted		Adjusted[2]	
Exposure	n	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	P	OR (95% CIs)	P
Autism factor mean score	13,105	1.11 (1.02–1.20)	0.02	1.06 (0.97–1.17)	0.20	1.15 (1.03–1.28)	0.01	1.11 (0.98–1.26)	0.07	1.13 (1.04–1.23)	0.005	1.08 (0.98–1.19)	0.13	1.14 (1.02–1.28)	0.02	1.09 (0.96–1.24)	0.16
Social communication difficulties	8,106	1.42 (1.05–1.92)	0.02	1.32 (0.97–1.08)	0.07	1.73 (1.18–2.54)	0.006	1.62 (1.09–2.41)	0.02	1.46 (1.07–1.99)	0.02	1.33 (0.97–1.83)	0.08	1.69 (1.14–2.51)	0.01	1.57 (1.04–2.37)	0.03
Repetitive behaviour	8,567	1.16 (0.81–1.64)	0.41	1.07 (0.75–1.53)	0.71	1.34 (0.85–2.11)	0.21	1.25 (0.79–2.00)	0.34	1.2 (0.83–1.73)	0.33	1.1 (0.75–1.60)	0.62	1.32 (0.82–2.13)	0.25	1.22 (0.75–2.01)	0.42
Sociability	10,037	1.20 (0.92–1.55)	0.17	1.16 (0.89–1.52)	0.26	1.27 (0.89–1.8)	0.19	1.23 (0.86–1.77)	0.26	1.17 (0.89–1.54)	0.27	1.13 (0.86–1.50)	0.38	1.14 (0.79–1.65)	0.48	1.10 (0.76–1.60)	0.61
Pragmatic language	8,104	1.16 (0.86–1.57)	0.32	1.07 (0.78–1.46)	0.68	1.26 (0.85–1.87)	0.24	1.14 (0.77–1.71)	0.53	1.23 (0.91–1.67)	0.17	1.11 (0.80–1.52)	0.54	1.34 (0.91–1.97)	0.14	1.20 (0.80–1.80)	0.38

[1]Psychotic experiences assessed at ages 18 and/or 24.

[2] Adjusted for child sex (male/female), parity (≤ 1 child versus ≥ 2 children), major financial problems in the family when the child was 8 months old (yes/no), maternal highest educational attainment, maternal age (at delivery), maternal Crown-Crisp anxiety scores (18 weeks gestation), maternal depression measured with the Edinburgh Postnatal Depression Scale (EPDS; 18 weeks gestation scores ≥ 13), and child IQ scores at age 8 assessed with the Wechsler Intelligence Scale for Children third edition (WISC-III).

Table A10. Mediation analyses results for the associations between autism factor mean score and social communication difficulties with psychotic experiences, excluding tactile hallucinations.

	Unadjusted		Adjusted[2]	
Estimate[1]	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**
Exposure: Autism mean factor score; Outcome: psychotic experiences measured at ages 18 and/or 24 (n = 3,577)				
Natural direct effect	1.11 (0.99–1.24)	0.08	1.07 (0.94–1.22)	0.28
Natural indirect effect	1.06 (1.03–1.08)	<0.001	1.04 (1.02–1.06)	<0.001
Total effect	1.17 (1.04–1.31)	0.01	1.11 (0.98–1.26)	0.11
Proportion mediated	38%		38%	
Exposure: Autism mean factor score; Outcome: psychotic experiences measured at ages 18 and/or 24 distressing/frequent (n = 3,577)				
Natural direct effect	1.12 (0.95–1.33)	0.18	1.10 (0.92–1.33)	0.29
Natural indirect effect	1.07 (1.04-1.1)	<0.001	1.05 (1.02–1.07)	<0.001
Total effect	1.21 (1.01–1.43)	0.03	1.16 (0.96–1.40)	0.12
Proportion mediated	40%		35%	
Exposure: Social communication difficulties; Outcome: psychotic experiences measured at ages 18 and/or 24 (n = 3,326)				
Natural direct effect	1.33 (0.93–1.89)	0.12	1.25 (0.88–1.78)	0.21
Natural indirect effect	1.14 (1.07–1.21)	<0.001	1.10 (1.04–1.17)	0.001
Total effect	1.51 (1.06–2.15)	0.02	1.38 (0.98–1.96)	0.07
Proportion mediated	36%		33%	
Exposure: Social communication difficulties; Outcome: psychotic experiences measured at ages 18 and/or 24 distressing/frequent (n = 3,326)				
Natural direct effect	1.45 (0.92–2.30)	0.11	1.43 (0.90–2.25)	0.13
Natural indirect effect	1.18 (1.09–1.28)	<0.001	1.15 (1.07–1.24)	<0.001
Total effect	1.72 (1.09–2.70)	0.02	1.64 (1.05–2.57)	0.03
Proportion mediated	37%		33%	

[1] Estimates based on observations with complete data on exposure, mediator, outcome, and confounders.
[2] Adjusted for the following confounders: child sex, parity, major financial problems, maternal highest educational attainment, maternal anxiety, maternal depression, and child IQ.

Table A11. Mediation analyses results for the associations between autism factor mean score and social communication difficulties with psychotic experiences adjusting for schizophrenia polygenic risk (PRS).

	Unadjusted		Adjusted[2]		Unadjusted		Adjusted[2]	
Estimate	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**
	Exposure: Autism mean factor score; Outcome: psychotic experiences measured at ages 18 and/or 24 (n = 3,503)				Exposure: Autism mean factor score; Outcome: psychotic experiences measured at ages 18 and/or 24 excluding tactile hallucinations (n = 3,503)			
Natural direct effect	1.04 (0.93–1.16)	0.47	1.04 (0.93–1.17)	0.46	1.08 (0.97–1.21)	0.15	1.09 (0.97–1.21)	0.14
Natural indirect effect	1.06 (1.03–2.13)	<0.001	1.06 (1.03–2.12)	<0.001	1.06 (1.04–1.08)	<0.001	1.06 (1.04–2.21)	<0.001
Total effect	1.10 (0.98–1.23)	0.09	1.10 (0.98–1.23)	0.09	1.15 (1.03–1.28)	0.02	1.15 (1.03–1.28)	0.01
Proportion mediated	61%		61%		45%		42%	
	Exposure: Autism mean factor score; Outcome: psychotic experiences measured at ages 18 and/or 24 distressing/frequent (n = 3,503)				Exposure: Autism mean factor score; Outcome: psychotic experiences measured at ages 18 and/or 24 distressing/frequent excluding tactile hallucinations (n = 3,503)			
Natural direct effect	1.08 (0.93–1.26)	0.33	1.09 (0.93–1.27)	0.30	1.09 (0.93–1.27)	0.27	1.10 (0.94–1.28)	0.25
Natural indirect effect	1.06 (1.03–2.43)	<0.001	1.06 (1.04–2.43)	<0.001	1.06 (1.03–1.09)	<0.001	1.06 (1.03–1.09)	<0.001
Total effect	1.15 (0.98–1.34)	0.08	1.15 (0.99–1.35)	0.07	1.16 (0.99–1.36)	0.06	1.17 (1.00–1.36)	0.06
Proportion mediated	45%		42%		42%		40%	
	Exposure: Social communication difficulties; Outcome: psychotic experiences measured at ages 18 and/or 24 (n = 3,195)				Exposure: Social communication difficulties; Outcome: psychotic experiences measured at ages 18 and/or 24 excluding tactile hallucinations (n = 3,195)			
Natural direct effect	1.28 (0.90–1.82)	0.16	1.28 (0.90–1.82)	0.16	1.24 (0.86–1.8)	0.24	1.25 (0.87–1.80)	0.23
Natural indirect effect	1.14 (1.08–1.21)	<0.001	1.14 (1.08–1.21)	<0.001	1.15 (1.08–1.22)	<0.001	1.15 (1.08–1.22)	<0.001
Total effect	1.40 (1.03–2.08)	0.04	1.40 (1.03–2.08)	0.03	1.43 (0.99–2.08)	0.06	1.44 (0.99–2.09)	0.06
Proportion mediated	39%		39%		44%		43%	
	Exposure: Social communication difficulties; Outcome: psychotic experiences measured at ages 18 and/or 24 distressing/frequent (n = 3,195)				Exposure: Social communication difficulties; Outcome: psychotic experiences measured at ages 18 and/or 24 distressing/frequent excluding tactile hallucinations (n = 3,195)			
Natural direct effect	1.40 (0.88–2.25)	0.16	1.42 (0.89–2.27)	0.15	1.33 (0.82–2.17)	0.25	1.34 (0.82–2.19)	0.24
Natural indirect effect	1.16 (1.08–1.25)	<0.001	1.16 (1.08–1.25)	<0.001	1.16 (1.08–1.25)	<0.001	1.16 (1.08–1.25)	<0.001
Total effect	1.63 (1.02–2.62)	0.04	1.65 (1.03–2.64)	0.04	1.55 (0.94–2.53)	0.08	1.56 (0.95–2.56)	0.08
Proportion mediated	36%		35%		39%		39%	

[1] Estimates based on observations with complete data on exposure, mediator, outcome, and confounders.
[2] Adjusted for the following confounders: child sex, parity, major financial problems, maternal highest educational attainment, maternal anxiety, maternal depression, and child IQ.

Table A12. Mediation analyses results for the associations between autism factor mean score and social communication difficulties with psychotic experiences[1] using imputed data.

	Including tactile hallucinations								Excluding tactile hallucinations							
	Psychotic experiences				Psychotic experiences, distressing and/or frequent				Psychotic experiences				Psychotic experiences, distressing and/or frequent			
	Unadjusted		Adjusted[2]		Unadjusted		Adjusted[2]		Unadjusted		Adjusted[2]		Unadjusted		Adjusted[2]	
Estimate	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**	**OR (95% CIs)**	**P**
Exposure: autism factor mean score (n = 13,105)																
Natural direct effect	1.08 (1.01–1.16)	0.02	1.02 (0.96–2.13)	0.55	1.15 (1.07–1.23)	<0.001	1.10 (0.96–1.26)	0.18	1.10 (1.02–1.17)	0.01	1.06 (0.95–1.17)	0.30	1.12 (1.05–1.21)	0.001	1.08 (0.94–1.24)	0.30
Natural indirect effect	1.06 (1.05–2.18)	<0.001	1.02 (1.01–1.29)	<0.001	1.09 (1.07–1.12)	<0.001	1.02 (1.01–1.48)	0.001	1.07 (1.05–2.24)	<0.001	1.02 (1.01–1.39)	<0.001	1.08 (1.06–2.57)	<0.001	1.03 (1.01–1.51)	0.001
Total effect	1.15 (1.07–1.23)	<0.001	1.03 (0.98–1.10)	0.26	1.26 (1.17–1.35)	<0.001	1.12 (0.98–1.29)	0.09	1.17 (1.09–1.25)	<0.001	1.08 (0.97–1.20)	0.15	1.21 (1.13–1.30)	<0.001	1.11 (0.96–1.27)	0.16
Proportion mediated	45%		51%		41%		18%		44%		26%		43%		29%	
Exposure: social communication difficulties (n = 8,106)																
Natural direct effect	1.13 (0.84–1.53)	0.43	1.13 (0.81–1.58)	0.47	1.16 (0.82–1.63)	0.41	1.41 (0.94–2.10)	0.10	1.16 (0.86–1.58)	0.33	1.16 (0.83–1.62)	0.39	1.14 (0.81–1.62)	0.45	1.38 (0.91–2.08)	0.13
Natural indirect effect	1.16 (1.11–1.21)	<0.001	1.10 (1.05–1.15)	<0.001	1.18 (1.12–1.24)	<0.001	1.14 (1.08–1.19)	<0.001	1.16 (1.11–1.22)	<0.001	1.10 (1.06–1.15)	<0.001	1.18 (1.12–1.25)	<0.001	1.14 (1.08–1.20)	<0.001
Total effect	1.31 (0.97–1.77)	0.08	1.24 (0.89–1.73)	0.20	1.36 (0.97–1.93)	0.08	1.60 (1.07–2.38)	0.022	1.35 (1.00–1.84)	0.05	1.28 (0.91–1.79)	0.15	1.35 (0.96–1.90)	0.08	1.58 (1.05–2.37)	0.03
Proportion mediated	58%		47%		57%		32%		54%		42%		59%		34%	

[1] Psychotic experiences measured at ages 18 and/or 24.
[2]Adjusted for child sex (male/female), parity (≤ 1 child versus ≥ 2 children), major financial problems in the family when the child was 8 months old (yes/no), maternal highest educational attainment, maternal age (at delivery), maternal Crown-Crisp anxiety scores (18 weeks gestation), maternal depression measured with the Edinburgh Postnatal Depression Scale (EPDS; 18 weeks gestation scores ≥ 13), and child IQ scores at age 8 assessed with the Wechsler Intelligence Scale for Children third edition (WISC-III).

Appendix B

Figure B1. Instrument definition process for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to autism and schizophrenia.

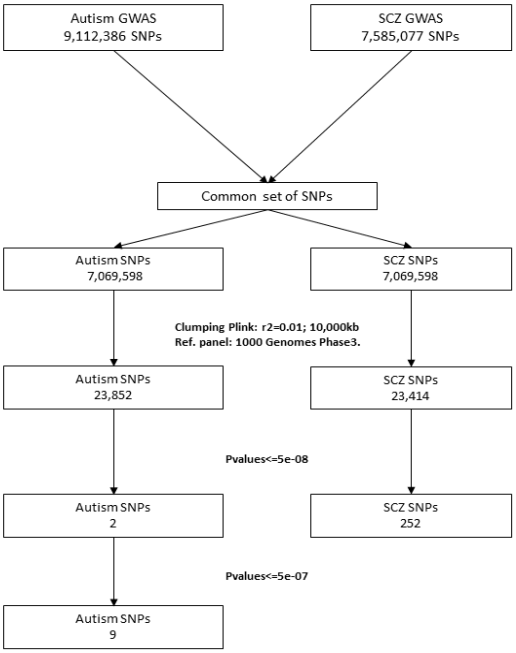


Figure B2. Instrument definition process for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to social communication difficulties and schizophrenia.

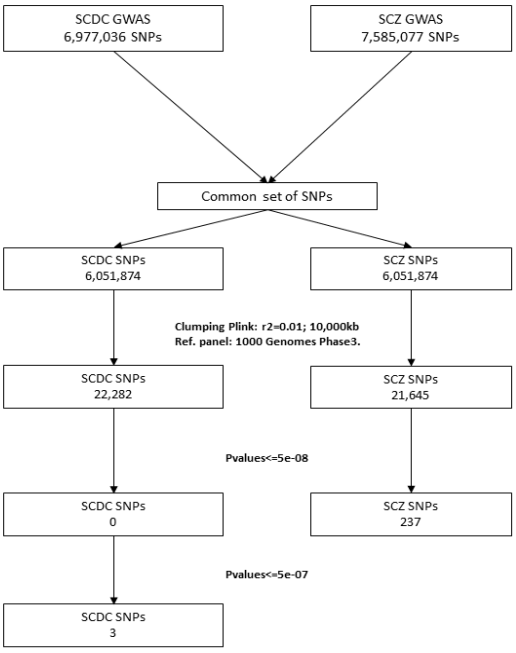


Figure B3. Instrument definition process for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to empathising and schizophrenia.

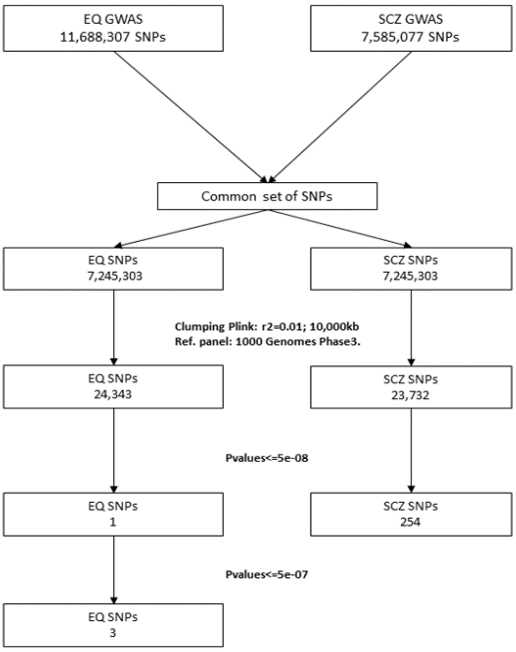


Figure B4. Instrument definition process for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to systemising and schizophrenia.

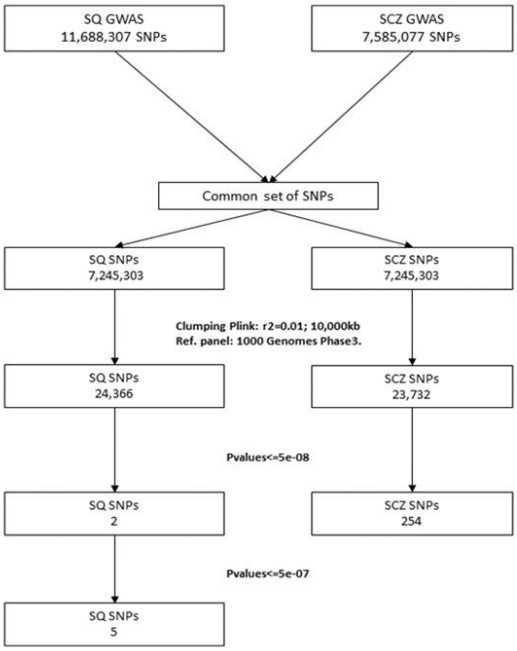


Figure B5. Instrument definition process for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to autism (excluding ID cases) and schizophrenia.

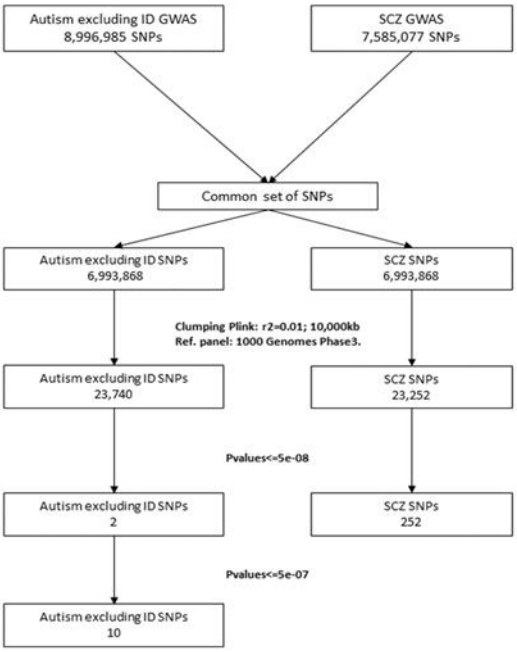


Figure B6. Instrument definition process for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to autism and psychotic experiences.

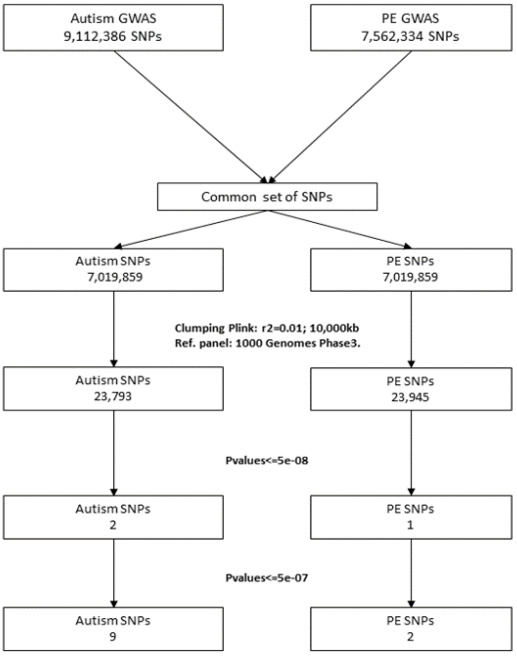


Figure B7. Instrument definition process for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to social communication difficulties and psychotic experiences.

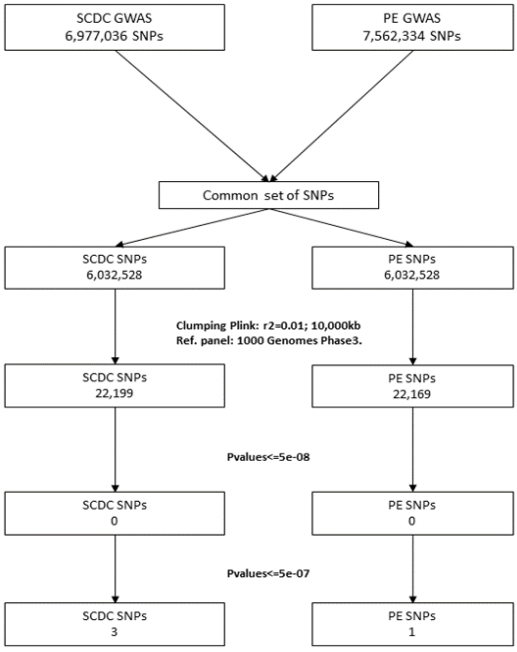


Figure B8. Instrument definition process for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to empathising and psychotic experiences.

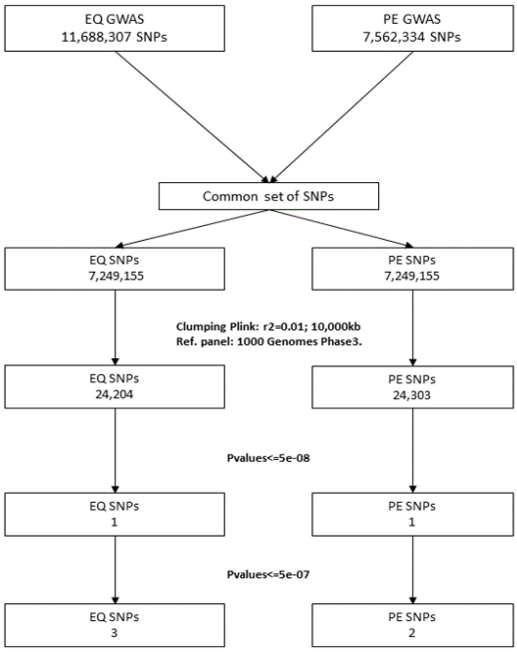


Figure B9. Instrument definition process for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to systemising and psychotic experiences.

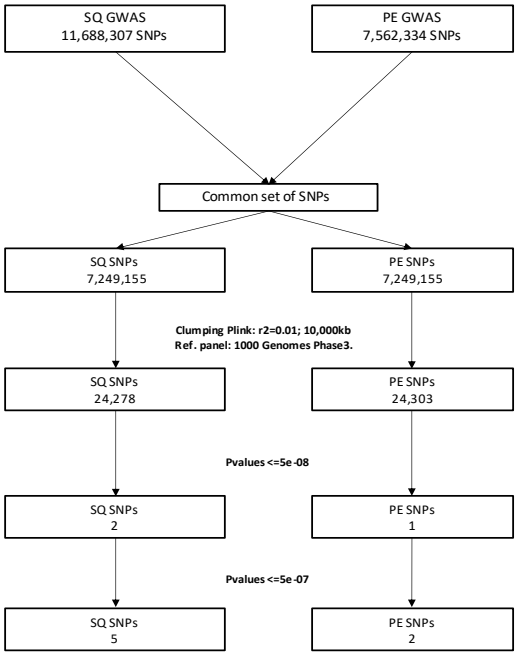


Figure B10. Instrument definition process for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to autism (excluding ID cases) and psychotic experiences.

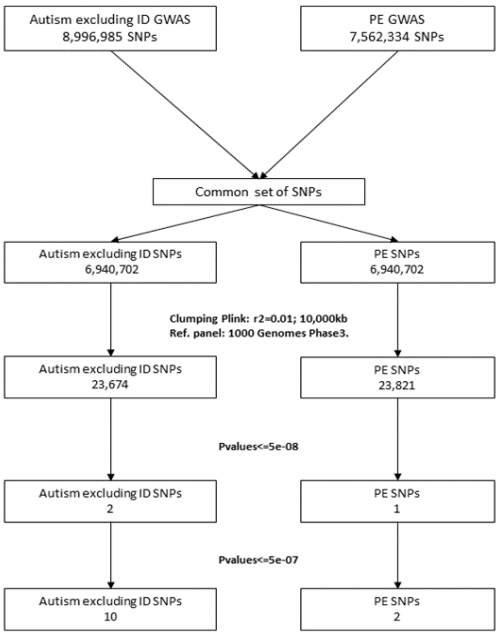


Table B9. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to autism and schizophrenia.

Autism instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs910805	20	21248116	A	G	-0.0957	0.016	2.04E-09
rs2224274	20	14760747	T	C	0.070999	0.0138	2.86E-07
rs325485	5	1.04E+08	A	G	0.072804	0.0143	3.25E-07
rs112635299	14	94838142	T	G	0.220997	0.0432	3.04E-07
rs10099100	8	10576775	C	G	0.084304	0.0147	1.07E-08
rs45595836	10	16691399	T	C	0.138996	0.0272	3.13E-07
rs2391769	1	96978961	A	G	-0.0769	0.0145	1.14E-07
rs6701243	1	99092784	A	C	0.073501	0.0144	3.07E-07
rs1452075	3	62481063	T	C	0.080704	0.0155	2.07E-07
Schizophrenia instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs7002992	8	1.04E+08	T	C	0.0484	0.0083	4.48E-09
rs6715366	2	2327295	G	A	-0.0551	0.0094	4.23E-09
rs77463171	16	66942206	C	T	-0.1465	0.0263	2.41E-08
rs113113059	6	43160375	T	C	0.061396	0.0092	2.29E-11
rs10873538	14	1.04E+08	T	G	-0.0632	0.0082	9.59E-15
rs61920311	12	14423294	A	C	0.046101	0.0082	1.75E-08
rs2532240	17	44265839	C	T	0.052099	0.0083	2.72E-10
rs6588168	1	66324118	C	T	-0.0489	0.0079	5.94E-10
rs12126806	1	2.01E+08	C	T	0.049904	0.009	2.89E-08
rs4915203	1	2E+08	A	G	0.050398	0.0085	3.30E-09
rs1658810	2	2.01E+08	C	T	0.080704	0.0096	3.54E-17
rs140001745	2	2.01E+08	T	C	0.106996	0.0155	5.13E-12
rs56335113	1	30427639	A	G	0.066602	0.0084	3.15E-15
rs581459	1	36375110	C	T	0.0743	0.0123	1.32E-09
rs1915019	8	89283689	A	G	0.057599	0.0092	3.43E-10
rs308697	3	1.61E+08	C	A	0.046903	0.0079	3.35E-09
rs13090130	3	1.62E+08	G	A	0.051396	0.0079	9.92E-11
rs2102949	12	1.24E+08	G	A	0.086003	0.0087	3.18E-23
rs75482067	12	1.23E+08	G	A	-0.0876	0.0148	3.06E-09
rs2649999	12	1.21E+08	T	C	0.049504	0.0082	1.28E-09
rs12311848	12	1.24E+08	A	G	-0.049	0.0087	1.65E-08
rs2686386	12	1.22E+08	C	T	0.054801	0.0096	1.26E-08
rs167924	3	1.07E+08	A	G	-0.0506	0.0089	1.33E-08
rs72943392	11	81178838	G	C	-0.0532	0.0094	1.44E-08
rs9975024	21	16439883	A	G	-0.0483	0.008	1.78E-09
rs75968099	3	36858583	C	T	-0.0582	0.0089	5.16E-11
rs1506297	3	30072307	T	C	0.051102	0.0091	1.98E-08
rs6538539	12	95195293	G	T	0.047704	0.0077	5.63E-10
rs7953300	12	92254654	G	T	-0.0449	0.0082	3.94E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs7575796	2	97746526	A	G	0.0969	0.0171	1.57E-08
rs7312697	12	29933069	T	C	-0.0533	0.0081	4.85E-11
rs28454198	4	80204001	G	C	0.0486	0.0081	1.88E-09
rs10086619	8	1.12E+08	A	G	-0.0691	0.0104	3.30E-11
rs4702	15	91426560	G	A	0.080298	0.0081	2.15E-23
rs11210892	1	44100084	G	A	0.0675	0.0081	1.18E-16
rs11136325	8	1.45E+08	G	A	0.053	0.009	3.30E-09
rs13262595	8	1.43E+08	A	G	0.069097	0.0079	2.21E-18
rs12301769	12	72231313	A	C	-0.08379	0.014	1.93E-09
rs2022265	6	84293271	A	G	0.048504	0.0077	3.74E-10
rs10985811	9	1.01E+08	T	C	-0.0545	0.0098	2.53E-08
rs4793888	17	55737740	G	A	-0.0609	0.0097	3.63E-10
rs2381411	9	36319928	T	C	-0.045	0.0079	1.28E-08
rs39967	5	57744788	T	C	-0.0604	0.0107	1.87E-08
rs12943566	17	2157774	A	G	-0.0525	0.0083	2.29E-10
rs3752827	17	1265325	T	A	0.052203	0.0084	6.33E-10
rs77502336	11	1.23E+08	G	C	-0.0545	0.0082	3.45E-11
rs1940171	11	1.25E+08	A	G	0.073501	0.0099	8.87E-14
rs10515678	5	1.52E+08	C	T	0.065703	0.0095	4.46E-12
rs11740474	5	1.54E+08	A	T	-0.0504	0.0086	4.46E-09
rs12652777	5	1.56E+08	T	C	0.045403	0.0079	1.06E-08
rs154433	16	58659808	G	A	0.047198	0.0084	2.38E-08
rs10957321	8	65605878	G	A	-0.0482	0.0077	4.18E-10
rs298216	8	65293195	C	G	-0.0727	0.0123	3.45E-09
rs6984242	8	60700469	G	A	0.052697	0.0078	1.50E-11
rs1454606	4	33642614	C	T	-0.0716	0.0108	2.90E-11
rs58120505	7	2029867	T	C	0.083302	0.0078	1.80E-26
rs11972718	7	8549187	C	G	-0.04949	0.0088	1.57E-08
rs17731	10	3821561	G	A	-0.0575	0.0079	3.76E-13
rs4766428	12	1.11E+08	C	T	-0.0721	0.0085	2.61E-17
rs2387414	19	51034243	G	C	-0.0515	0.0084	8.01E-10
rs2304205	19	50168927	A	C	0.070403	0.0092	2.38E-14
rs758749	19	57189718	C	T	-0.0615	0.0112	4.66E-08
rs9312586	4	1.77E+08	A	G	-0.0908	0.014	8.14E-11
rs41533650	4	1.77E+08	G	A	-0.0724	0.0097	8.69E-14
rs61405217	4	1.7E+08	C	T	0.052004	0.0079	5.39E-11
rs459391	21	22120508	T	C	0.056598	0.01	1.54E-08
rs6943762	7	86403263	T	C	0.103296	0.0124	6.30E-17
rs2252074	7	1.05E+08	T	G	-0.0603	0.0078	1.27E-14
rs1510136	4	1.44E+08	A	G	0.052602	0.0093	1.39E-08
rs61828917	1	1.74E+08	C	T	0.067603	0.011	7.95E-10
rs16851048	1	1.77E+08	T	C	-0.0676	0.0097	3.06E-12
rs12363019	11	24374545	T	A	-0.0516	0.0082	2.58E-10
rs10767734	11	28642381	C	T	0.050902	0.0082	5.62E-10

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs778371	2	2.34E+08	A	G	-0.0741	0.0089	1.10E-16
rs11647188	16	82648514	A	G	0.044495	0.0081	3.75E-08
rs11076631	16	89877975	A	G	0.052203	0.0088	2.59E-09
rs6919146	6	1.65E+08	T	G	-0.0488	0.0085	8.42E-09
rs2456020	15	78868398	C	T	0.068499	0.0088	5.35E-15
rs28521069	4	1.19E+08	C	T	-0.0457	0.0083	3.78E-08
rs10117	5	1.38E+08	G	A	0.055501	0.0082	9.54E-12
rs9687282	5	1.39E+08	T	G	-0.0486	0.0086	1.66E-08
rs28490262	3	80814042	G	C	0.053199	0.0086	6.68E-10
rs13195636	6	27509493	A	C	0.210504	0.0159	6.55E-40
rs356183	4	90626098	G	C	0.044304	0.008	3.37E-08
rs13230189	7	1.37E+08	C	T	0.071902	0.0081	1.04E-18
rs35792732	7	1.33E+08	C	T	0.060399	0.0106	1.08E-08
rs1593304	7	1.32E+08	A	G	-0.0642	0.0101	2.37E-10
rs10947452	6	33803752	T	C	-0.0448	0.0081	3.69E-08
rs9461856	6	33395199	G	A	-0.0639	0.0078	3.23E-16
rs3131295	6	32173257	G	A	0.0599	0.008	9.97E-14
rs11693094	2	1.86E+08	C	T	0.057297	0.0078	2.20E-13
rs12129573	1	73768366	C	A	-0.0681	0.0082	1.42E-16
rs1121296	1	72174197	T	C	0.047303	0.008	3.74E-09
rs11619756	13	44329004	G	A	0.047103	0.0082	7.97E-09
rs215483	4	23377121	G	A	-0.0507	0.0084	1.59E-09
rs4697446	4	24269622	G	T	-0.0446	0.0079	1.67E-08
rs7647398	3	1.81E+08	C	T	0.085003	0.01	2.21E-17
rs9882532	3	16865845	T	C	-0.05309	0.0087	8.57E-10
rs6577597	3	17871326	A	G	-0.0526	0.0085	5.52E-10
rs3739554	9	1.3E+08	A	G	-0.0576	0.0103	2.26E-08
rs5995756	22	40000313	T	C	0.056399	0.0084	2.38E-11
rs9607782	22	41587556	T	A	-0.0725	0.0097	7.10E-14
rs4822076	22	42364057	C	T	-0.0597	0.0089	1.94E-11
rs1451488	2	2E+08	A	G	-0.066	0.0079	6.72E-17
rs13032111	2	1.94E+08	T	G	0.043203	0.0077	2.15E-08
rs2914983	2	1.98E+08	A	G	0.062796	0.0081	1.10E-14
rs10190027	2	37190726	C	T	-0.04971	0.0089	2.57E-08
rs3770752	2	37576136	A	G	0.057401	0.0086	2.86E-11
rs6925079	6	64946311	T	C	-0.0448	0.0081	3.58E-08
rs6065094	20	37453194	A	G	-0.0634	0.0082	1.41E-14
rs13219424	6	1.28E+08	C	T	0.045996	0.0084	4.52E-08
rs60135207	3	71563777	G	T	0.049599	0.0087	1.27E-08
rs12991836	2	1.45E+08	A	C	-0.0584	0.008	2.72E-13
rs16825349	2	1.46E+08	A	G	-0.0704	0.0104	1.32E-11
rs10777187	12	89940502	T	C	0.050902	0.0092	2.82E-08
rs12713008	2	48503561	G	A	0.043002	0.0078	3.05E-08
rs500102	9	77358745	T	C	0.043299	0.0079	4.15E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs72761691	9	1.35E+08	A	C	-0.0664	0.0116	1.07E-08
rs79668541	10	1.05E+08	C	T	0.120703	0.0121	2.11E-23
rs1856507	6	73157926	C	A	0.050398	0.008	3.00E-10
rs9454727	6	70003389	A	G	0.054801	0.0098	1.93E-08
rs578470	12	50463325	T	C	-0.0462	0.0083	2.33E-08
rs61937595	12	57682956	C	T	0.121996	0.0158	1.32E-14
rs73292401	17	12875908	T	A	-0.0659	0.0103	1.82E-10
rs9891739	17	19942177	C	T	-0.045	0.008	2.18E-08
rs4073003	17	19148305	A	G	0.080603	0.0116	4.20E-12
rs8055219	16	13753384	G	A	-0.0672	0.0095	1.57E-12
rs252812	5	1.07E+08	A	G	0.053	0.0093	1.30E-08
rs35164357	5	1.09E+08	C	T	-0.0605	0.0096	2.59E-10
rs10861176	12	1.05E+08	G	A	-0.0504	0.0086	5.23E-09
rs3764002	12	1.09E+08	C	T	-0.0517	0.0086	1.65E-09
rs2455415	13	38860697	C	T	-0.04759	0.0081	3.43E-09
rs1924377	13	38362106	G	C	0.046903	0.0082	8.71E-09
rs55929115	3	1.18E+08	T	A	0.072004	0.013	3.21E-08
rs10035564	5	45252500	A	G	-0.06481	0.0081	1.65E-15
rs1540840	14	99733384	G	C	0.054999	0.009	1.04E-09
rs17194490	3	2547786	G	T	-0.0781	0.0116	1.85E-11
rs61857878	10	92789488	A	T	0.0599	0.0099	1.46E-09
rs2514218	11	1.13E+08	C	T	0.069899	0.009	6.46E-15
rs17644050	2	1.56E+08	G	C	-0.0538	0.0098	4.02E-08
rs79210963	7	24717969	T	C	-0.0863	0.0129	2.58E-11
rs7811417	7	21534152	T	C	0.048304	0.0081	2.17E-09
rs12285419	11	46343189	C	A	-0.0812	0.01	3.73E-16
rs634940	6	93077500	G	T	-0.0649	0.0098	2.88E-11
rs6925964	6	96475894	A	T	0.097499	0.0176	3.19E-08
rs9304548	18	27500959	C	A	0.060003	0.0089	1.90E-11
rs2710323	3	52815905	T	C	0.074597	0.0077	5.92E-22
rs11917680	3	50471408	G	T	0.056702	0.0091	4.17E-10
rs7432375	3	1.36E+08	G	A	0.063801	0.0082	5.32E-15
rs2238304	15	89843950	A	T	0.049599	0.0078	1.73E-10
rs4779050	15	83368738	T	G	0.049304	0.0079	4.18E-10
rs11638554	15	85148231	T	G	0.064504	0.0089	3.62E-13
rs6673880	1	2373168	A	G	-0.061	0.0086	1.32E-12
rs11121172	1	8418644	C	A	0.054602	0.0089	7.15E-10
rs11122119	1	6768856	C	A	-0.0453	0.0081	2.31E-08
rs9597388	13	56928696	G	A	0.066798	0.0101	3.24E-11
rs9569820	13	58702746	G	T	-0.0676	0.0109	6.56E-10
rs7938083	11	57493622	C	A	-0.0524	0.0087	1.60E-09
rs10069930	5	1.4E+08	T	A	0.048304	0.0079	9.43E-10
rs6479487	9	96237373	T	G	-0.0587	0.0103	1.37E-08
rs7609876	3	1.77E+08	T	C	-0.0512	0.0089	9.40E-09

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs2224086	1	1.15E+08	C	A	-0.0577	0.0103	2.09E-08
rs144821294	19	2155136	C	T	-0.138	0.0242	1.22E-08
rs72974269	2	2.25E+08	C	T	0.052099	0.0083	2.76E-10
rs35351411	15	61872197	A	C	-0.0573	0.0079	3.13E-13
rs3814883	16	29994922	C	T	0.060898	0.0079	8.82E-15
rs72723227	5	7245664	G	A	0.047999	0.0082	4.58E-09
rs1463209	12	39518293	C	T	0.047704	0.0081	3.34E-09
rs2190864	14	72416219	T	C	0.066097	0.008	1.12E-16
rs2206956	6	1.47E+08	G	A	-0.0462	0.0078	2.51E-09
rs9390083	6	1.44E+08	C	G	-0.05719	0.0103	2.95E-08
rs1858999	19	19497669	C	G	0.060502	0.0081	7.97E-14
rs72986630	19	11849736	C	T	-0.1117	0.0177	3.07E-10
rs322128	19	11402416	C	T	-0.0567	0.0095	2.08E-09
rs12431743	14	84673716	G	A	-0.0456	0.008	1.26E-08
rs9926049	16	9939960	C	A	-0.0556	0.0088	3.16E-10
rs8048039	16	4498486	A	T	0.049	0.0083	4.35E-09
rs10127983	1	1.54E+08	C	T	-0.0463	0.0084	3.11E-08
rs12138231	1	1.5E+08	T	A	-0.0671	0.0116	7.21E-09
rs7915131	10	64418656	C	T	0.042695	0.0078	4.94E-08
rs13107325	4	1.03E+08	C	T	-0.1587	0.0168	2.90E-21
rs6839635	4	1.04E+08	C	A	-0.0432	0.0079	3.87E-08
rs2153960	6	1.09E+08	G	A	0.051396	0.0084	9.22E-10
rs117799466	15	34659517	G	C	-0.0481	0.0087	3.86E-08
rs6504163	17	61545779	C	T	-0.0492	0.0082	1.87E-09
rs6732355	2	1.05E+08	C	A	-0.0587	0.0094	4.36E-10
rs2119242	10	21344773	G	A	-0.0602	0.0106	1.34E-08
rs11807834	1	2.3E+08	G	A	-0.053	0.0093	1.12E-08
rs11587347	1	2.39E+08	C	G	-0.1028	0.0139	1.50E-13
rs61833239	1	2.44E+08	T	G	-0.0843	0.0122	5.22E-12
rs10148671	14	29469373	T	C	-0.0479	0.0083	6.82E-09
rs6482437	10	18726326	A	C	-0.10471	0.0135	1.05E-14
rs115325222	5	88854539	A	G	0.090398	0.0151	1.93E-09
rs6969410	7	1.1E+08	T	G	0.055501	0.0083	1.90E-11
rs38752	7	1.11E+08	T	G	0.060003	0.0081	1.08E-13
rs1589726	7	79348201	C	T	0.077896	0.0137	1.20E-08
rs10238960	7	70773271	C	T	-0.0482	0.0084	7.65E-09
rs2944821	7	71795998	G	C	0.047799	0.008	1.90E-09
rs7701440	5	60620980	T	C	-0.0638	0.008	1.86E-15
rs73229090	8	27442127	C	A	0.102602	0.0142	4.34E-13
rs3808581	8	26250047	G	A	-0.06699	0.0097	3.82E-12
rs2717003	2	58143438	A	G	-0.07529	0.008	2.76E-21
rs12969453	18	52751708	A	G	0.054299	0.0078	3.53E-12
rs715170	18	53795514	C	T	0.064701	0.009	7.40E-13
rs4632195	18	50746748	C	T	-0.0498	0.0084	2.73E-09

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs9636107	18	53200117	A	G	-0.0609	0.0081	5.72E-14
rs17571951	14	30017039	T	C	-0.0645	0.0105	7.89E-10
rs12883788	14	33303540	C	T	-0.0543	0.0079	8.43E-12
rs8104557	19	31030189	T	C	-0.0604	0.011	3.76E-08
rs3810450	19	36530562	T	C	0.092497	0.016	8.27E-09
rs505061	9	22767164	C	A	-0.0499	0.0077	1.03E-10
rs9545047	13	79859456	A	C	0.053797	0.0081	3.05E-11
rs58950470	11	65383755	G	T	-0.0493	0.0086	1.10E-08
rs6546857	2	73837955	A	G	-0.0603	0.0101	2.80E-09
rs11897811	2	76267139	C	T	-0.0575	0.0102	1.49E-08
rs999494	2	73157395	C	T	0.057599	0.0101	1.04E-08
rs1198588	1	98552832	A	T	-0.0964	0.0103	7.88E-21
rs59519965	1	97168334	G	T	-0.0582	0.0098	3.36E-09
rs72728416	1	97834691	A	G	-0.0598	0.0087	4.99E-12
rs337718	18	69774278	T	C	0.0492	0.0084	4.39E-09
rs6588355	1	50113591	T	C	0.049504	0.009	3.65E-08
rs56205728	15	40567237	G	A	-0.0575	0.0093	5.43E-10
rs2929278	15	44250313	C	T	0.061904	0.0091	8.50E-12
rs9287971	2	1.75E+08	G	A	-0.0458	0.0083	3.82E-08
rs62184960	2	1.73E+08	C	T	0.069797	0.0122	1.08E-08
rs6430492	2	1.35E+08	G	A	0.057703	0.0094	6.72E-10
rs331395	5	91006918	C	G	-0.0549	0.009	1.27E-09
rs4672366	2	60389362	A	T	0.049799	0.0087	1.07E-08
rs10503253	8	4180844	C	A	-0.0602	0.0091	4.37E-11
rs72980087	18	77632194	G	A	-0.0644	0.0079	4.06E-16
rs7238071	18	77579812	A	G	-0.0629	0.0084	9.29E-14
rs4937935	11	1.35E+08	A	T	-0.0539	0.0081	2.30E-11
rs1440480	11	1.34E+08	A	G	0.057504	0.0086	2.52E-11
rs10894308	11	1.31E+08	G	A	0.047704	0.0079	1.36E-09
rs4936215	11	1.34E+08	A	G	0.082796	0.0104	1.86E-15
rs1939514	11	1.33E+08	T	C	0.055198	0.0077	1.06E-12
rs79445414	8	33863561	T	C	-0.1235	0.0222	2.63E-08
rs7816998	8	38257506	G	A	0.057797	0.0092	3.11E-10
rs35045093	7	1.28E+08	A	C	0.056598	0.0103	3.36E-08
rs61786047	1	29032580	G	A	0.078802	0.0135	4.91E-09
rs6010045	22	51103091	T	C	-0.0477	0.0085	1.82E-08
rs704364	3	63874734	A	G	0.050303	0.0082	8.41E-10
rs9813516	3	60293004	G	A	-0.0513	0.0084	1.25E-09
rs498591	9	14509105	A	T	-0.0679	0.0111	9.59E-10
rs2890914	9	10239181	A	G	-0.0432	0.0077	2.31E-08
rs10774034	12	2330458	C	T	-0.08329	0.0085	7.10E-23
rs12712510	2	22749726	T	C	0.051501	0.0084	9.34E-10
rs141216273	2	25599172	C	A	-0.1247	0.0228	4.49E-08
rs12474906	2	28033538	A	C	0.056796	0.0095	2.20E-09

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs2909457	2	1.63E+08	G	A	0.045805	0.0083	3.09E-08
rs35734242	4	706700	T	C	-0.0499	0.008	3.93E-10
rs11696755	20	48105317	T	C	-0.0653	0.0104	2.99E-10

Table B10. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to autism and psychotic experiences.

Autism instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs910805	20	21248116	A	G	-0.0957	0.016	2.04E-09
rs2224274	20	14760747	T	C	0.070999	0.0138	2.86E-07
rs325485	5	1.04E+08	A	G	0.072804	0.0143	3.25E-07
rs112635299	14	94838142	T	G	0.220997	0.0432	3.04E-07
rs10099100	8	10576775	C	G	0.084304	0.0147	1.07E-08
rs45595836	10	16691399	T	C	0.138996	0.0272	3.13E-07
rs2391769	1	96978961	A	G	-0.0769	0.0145	1.14E-07
rs6701243	1	99092784	A	C	0.073501	0.0144	3.07E-07
rs1452075	3	62481063	T	C	0.080704	0.0155	2.07E-07

Table B11. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to autism and schizophrenia (European ancestry only- Ripke et al., 2014).

Autism instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs910805	20	21248116	A	G	-0.0957	0.016	2.04E-09
rs111931861	7	1.05E+08	A	G	-0.2169	0.0409	1.12E-07
rs2224274	20	14760747	T	C	0.070999	0.0138	2.86E-07
rs325485	5	1.04E+08	A	G	0.072804	0.0143	3.25E-07
rs112635299	14	94838142	T	G	0.220997	0.0432	3.04E-07
rs10099100	8	10576775	C	G	0.084304	0.0147	1.07E-08
rs45595836	10	16691399	T	C	0.138996	0.0272	3.13E-07
rs2391769	1	96978961	A	G	-0.0769	0.0145	1.14E-07
rs6701243	1	99092784	A	C	0.073501	0.0144	3.07E-07
rs1452075	3	62481063	T	C	0.080704	0.0155	2.07E-07
Schizophrenia instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs4648845	1	2387101	T	C	0.067201	0.0119	1.74E-08
rs7893279	10	18745105	T	G	0.1124	0.0175	1.24E-10
rs301797	1	8487323	A	C	0.066097	0.0116	1.2E-08
rs11191419	10	1.05E+08	A	T	-0.1016	0.0118	6.69E-18
rs1498232	1	30433951	T	C	0.072004	0.0118	1.21E-09
rs11210892	1	44100084	A	G	-0.0678	0.0115	3.42E-09
rs35998080	1	73278615	T	G	0.069004	0.0112	6.95E-10
rs1702294	1	98501984	T	C	-0.1184	0.0138	1.03E-17
rs11027857	11	24403620	A	G	0.063998	0.0109	3.67E-09
rs35324223	11	46402852	A	G	-0.09199	0.0145	2.04E-10
rs2514218	11	1.13E+08	T	C	-0.07221	0.0116	4.64E-10
rs55661361	11	1.25E+08	A	G	-0.07881	0.0116	1.04E-11
rs10791097	11	1.31E+08	T	G	0.0766	0.0109	2.05E-12
rs75059851	11	1.34E+08	A	G	0.091302	0.0136	2.18E-11
rs12062861	1	1.5E+08	A	G	-0.0911	0.0149	9.66E-10
rs1024582	12	2402246	A	G	0.098904	0.0115	6.27E-18
rs679087	12	29917265	A	C	-0.0642	0.0116	3.28E-08
rs12826178	12	57622371	T	G	-0.16821	0.0244	5.7E-12
rs4766428	12	1.11E+08	T	C	0.069395	0.0112	6.12E-10
rs1615350	12	1.24E+08	T	C	-0.0851	0.0123	4.26E-12
rs10803138	1	2.44E+08	A	G	-0.07221	0.0126	1.13E-08
rs77149735	1	2.44E+08	A	G	0.284502	0.0485	4.4E-09
rs1191551	14	30000405	T	G	0.071697	0.0131	4.21E-08
rs67981189	14	71472226	A	G	-0.0698	0.0118	3.75E-09
rs2332700	14	72417326	C	G	0.0771	0.0125	7.38E-10
rs2693698	14	99719219	A	G	-0.06171	0.0111	2.99E-08
rs12887734	14	1.04E+08	T	G	0.088304	0.0121	3.72E-13
rs2414718	15	61863133	A	G	0.069797	0.011	1.98E-10
rs28681284	15	78908565	T	C	-0.1016	0.0141	6.35E-13

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs783540	15	83254708	A	G	-0.0599	0.011	4.77E-08
rs12902973	15	85105982	C	G	-0.0791	0.0122	8.83E-11
rs4702	15	91426560	A	G	-0.08051	0.0115	2.62E-12
rs9922678	16	9946319	A	G	0.068397	0.0118	6.18E-09
rs8055219	16	13753384	A	G	0.076998	0.0127	1.45E-09
rs12691307	16	29939877	A	G	0.071902	0.0113	2.03E-10
rs12932476	16	63709630	C	G	0.059702	0.0109	4.62E-08
rs4523957	17	2208899	T	G	0.069703	0.0115	1.4E-09
rs11658257	17	17956459	C	G	-0.0662	0.0115	8.34E-09
rs11874716	18	52750688	T	G	0.067201	0.011	1.01E-09
rs9636107	18	53200117	A	G	-0.0796	0.0108	2.17E-13
rs9966779	18	53620456	T	C	-0.1329	0.0231	8.56E-09
rs715170	18	53795514	T	C	-0.0669	0.0122	4.65E-08
rs72986630	19	11849736	T	C	0.1459	0.0266	4.12E-08
rs2905426	19	19478022	T	G	-0.0677	0.0115	4.07E-09
rs2053079	19	30987423	A	G	-0.0718	0.0127	1.74E-08
rs2103655	20	37425958	A	G	0.0766	0.0119	1.24E-10
rs1509378	2	22754466	A	G	0.0692	0.0119	5.39E-09
rs11682175	2	57987593	T	C	-0.0735	0.0109	1.58E-11
rs6430095	2	1.46E+08	A	G	0.0798	0.0145	3.4E-08
rs76355118	2	1.49E+08	A	G	-0.1544	0.0278	2.78E-08
rs2909457	2	1.63E+08	A	G	-0.0597	0.0109	4.25E-08
rs11693094	2	1.86E+08	T	C	-0.0736	0.011	2.17E-11
rs59979824	2	1.94E+08	A	C	-0.071	0.0119	2.73E-09
rs281768	2	2.01E+08	A	T	0.104198	0.0137	2.64E-14
rs6434928	2	1.98E+08	A	G	-0.0787	0.0116	1.17E-11
rs5995756	22	40000313	T	C	0.072497	0.0109	2.91E-11
rs9607782	22	41587556	A	T	0.088697	0.0128	3.98E-12
rs28733092	22	42537115	T	C	0.070999	0.0121	4.36E-09
rs11685299	2	2.25E+08	A	C	-0.0662	0.0117	1.49E-08
rs7601312	2	2.29E+08	A	G	-0.059	0.0108	4.68E-08
rs6704768	2	2.34E+08	A	G	-0.0766	0.0109	2.06E-12
rs17194490	3	2547786	T	G	0.0966	0.0148	6.38E-11
rs75968099	3	36858583	T	C	0.080104	0.0114	2.31E-12
rs2535627	3	52845105	T	C	0.070403	0.0109	1.17E-10
rs832190	3	63842629	T	C	-0.0699	0.0113	5.73E-10
rs6439649	3	1.36E+08	T	G	0.070999	0.0111	1.37E-10
rs34796896	3	1.81E+08	A	G	-0.0822	0.0135	1.23E-09
rs215411	4	23423603	A	T	0.0692	0.0115	1.68E-09
rs35225200	4	1.03E+08	A	C	-0.14479	0.0203	9.56E-13
rs1106568	4	1.77E+08	A	G	-0.0694	0.0125	2.85E-08
rs17073903	4	1.84E+08	A	G	-0.08141	0.0148	3.92E-08
rs4391122	5	60598543	A	G	-0.078	0.0109	8.9E-13
rs16867576	5	88746331	A	G	0.095801	0.017	1.61E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs3849046	5	1.38E+08	T	C	0.062496	0.0109	1.04E-08
rs111294930	5	1.52E+08	A	G	0.087699	0.0143	9.29E-10
rs76091702	5	1.52E+08	T	C	0.129299	0.0236	4.49E-08
rs11740474	5	1.54E+08	A	T	-0.06269	0.0112	2E-08
rs13437595	6	29763308	T	C	0.262203	0.0392	2.19E-11
rs13217619	6	28306671	T	C	0.219698	0.0195	1.44E-29
rs115296342	6	32503526	A	C	0.090398	0.0135	1.9E-11
rs9274390	6	32632660	T	G	0.160604	0.0183	1.54E-18
rs9461856	6	33395199	A	G	0.074996	0.0109	6.52E-12
rs1339227	6	73155701	T	C	-0.0633	0.0114	3.06E-08
rs3798869	6	84328660	A	G	-0.0668	0.011	1.09E-09
rs117074560	6	96459651	T	C	-0.1566	0.0277	1.66E-08
rs58120505	7	2029867	T	C	0.082197	0.0111	1.26E-13
rs12704290	7	86427626	A	G	-0.10611	0.0168	2.59E-10
rs6466055	7	1.05E+08	A	C	0.068798	0.0114	1.59E-09
rs13240464	7	1.11E+08	T	C	0.080704	0.0116	3.12E-12
rs7801375	7	1.32E+08	A	G	-0.083	0.015	2.88E-08
rs17529963	7	1.37E+08	T	C	0.0629	0.0114	3.24E-08
rs10108725	8	4191202	T	C	0.073204	0.0133	3.32E-08
rs73191547	8	10033425	A	T	-0.0669	0.0115	6.13E-09
rs17687067	8	17036201	A	C	-0.0763	0.0139	4.49E-08
rs73229090	8	27442127	A	C	-0.0995	0.0177	1.95E-08
rs13261481	8	60701801	T	G	0.062402	0.011	1.66E-08
rs7819570	8	89588626	T	G	0.076498	0.014	4.47E-08
rs36068923	8	1.11E+08	A	G	-0.0835	0.0134	4.14E-10
rs4129585	8	1.43E+08	A	C	0.079301	0.0109	3.61E-13
rs11139497	9	84739941	A	T	0.0656	0.0118	2.65E-08

Table B12. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to social communication difficulties and schizophrenia.

Social Communication difficulties instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**β**	**SE**	**P**
rs13212953	6	39130740	A	G	0.053738	0.010458	2.87E-07
rs79594111	12	97986384	C	A	0.079381	0.015108	1.54E-07
rs4802272	19	46235950	G	A	-0.02388	0.004718	4.28E-07
Schizophrenia instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs7002992	8	1.04E+08	T	C	0.0484	0.0083	4.48E-09
rs6715366	2	2327295	G	A	-0.0551	0.0094	4.23E-09
rs77463171	16	66942206	C	T	-0.1465	0.0263	2.41E-08
rs113113059	6	43160375	T	C	0.061396	0.0092	2.29E-11
rs722637	14	1.04E+08	A	C	-0.0629	0.0081	9.64E-15
rs17426174	17	43830938	G	C	0.062796	0.0108	5.47E-09
rs6588168	1	66324118	C	T	-0.0489	0.0079	5.94E-10
rs12126806	1	2.01E+08	C	T	0.049904	0.009	2.89E-08
rs4915203	1	2E+08	A	G	0.050398	0.0085	3.30E-09
rs1658810	2	2.01E+08	C	T	0.080704	0.0096	3.54E-17
rs140001745	2	2.01E+08	T	C	0.106996	0.0155	5.13E-12
rs56335113	1	30427639	A	G	0.066602	0.0084	3.15E-15
rs581459	1	36375110	C	T	0.0743	0.0123	1.32E-09
rs1915019	8	89283689	A	G	0.057599	0.0092	3.43E-10
rs308697	3	1.61E+08	C	A	0.046903	0.0079	3.35E-09
rs13090130	3	1.62E+08	G	A	0.051396	0.0079	9.92E-11
rs2102949	12	1.24E+08	G	A	0.086003	0.0087	3.18E-23
rs75482067	12	1.23E+08	G	A	-0.0876	0.0148	3.06E-09
rs12311848	12	1.24E+08	A	G	-0.049	0.0087	1.65E-08
rs2686386	12	1.22E+08	C	T	0.054801	0.0096	1.26E-08
rs167924	3	1.07E+08	A	G	-0.0506	0.0089	1.33E-08
rs72943392	11	81178838	G	C	-0.0532	0.0094	1.44E-08
rs9975024	21	16439883	A	G	-0.0483	0.008	1.78E-09
rs75968099	3	36858583	C	T	-0.0582	0.0089	5.16E-11
rs1506297	3	30072307	T	C	0.051102	0.0091	1.98E-08
rs6538539	12	95195293	G	T	0.047704	0.0077	5.63E-10
rs7953300	12	92254654	G	T	-0.0449	0.0082	3.94E-08
rs7312697	12	29933069	T	C	-0.0533	0.0081	4.85E-11
rs28454198	4	80204001	G	C	0.0486	0.0081	1.88E-09
rs10086619	8	1.12E+08	A	G	-0.0691	0.0104	3.30E-11
rs4702	15	91426560	G	A	0.080298	0.0081	2.15E-23
rs11210892	1	44100084	G	A	0.0675	0.0081	1.18E-16
rs13262595	8	1.43E+08	A	G	0.069097	0.0079	2.21E-18
rs13252406	8	1.45E+08	T	C	0.050398	0.0087	6.19E-09
rs12301769	12	72231313	A	C	-0.08379	0.014	1.93E-09

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs2022265	6	84293271	A	G	0.048504	0.0077	3.74E-10
rs10985811	9	1.01E+08	T	C	-0.0545	0.0098	2.53E-08
rs4793888	17	55737740	G	A	-0.0609	0.0097	3.63E-10
rs39967	5	57744788	T	C	-0.0604	0.0107	1.87E-08
rs7207904	17	1267857	G	A	0.047704	0.0079	1.65E-09
rs12943566	17	2157774	A	G	-0.0525	0.0083	2.29E-10
rs77502336	11	1.23E+08	G	C	-0.0545	0.0082	3.45E-11
rs1940171	11	1.25E+08	A	G	0.073501	0.0099	8.87E-14
rs10515678	5	1.52E+08	C	T	0.065703	0.0095	4.46E-12
rs11740474	5	1.54E+08	A	T	-0.0504	0.0086	4.46E-09
rs12652777	5	1.56E+08	T	C	0.045403	0.0079	1.06E-08
rs154433	16	58659808	G	A	0.047198	0.0084	2.38E-08
rs10957321	8	65605878	G	A	-0.0482	0.0077	4.18E-10
rs298216	8	65293195	C	G	-0.0727	0.0123	3.45E-09
rs6984242	8	60700469	G	A	0.052697	0.0078	1.50E-11
rs1454606	4	33642614	C	T	-0.0716	0.0108	2.90E-11
rs58120505	7	2029867	T	C	0.083302	0.0078	1.80E-26
rs11972718	7	8549187	C	G	-0.04949	0.0088	1.57E-08
rs17731	10	3821561	G	A	-0.0575	0.0079	3.76E-13
rs28555214	12	1.11E+08	A	C	0.064598	0.0083	9.89E-15
rs2304205	19	50168927	A	C	0.070403	0.0092	2.38E-14
rs9312586	4	1.77E+08	A	G	-0.0908	0.014	8.14E-11
rs41533650	4	1.77E+08	G	A	-0.0724	0.0097	8.69E-14
rs61405217	4	1.7E+08	C	T	0.052004	0.0079	5.39E-11
rs459391	21	22120508	T	C	0.056598	0.01	1.54E-08
rs6943762	7	86403263	T	C	0.103296	0.0124	6.30E-17
rs2252074	7	1.05E+08	T	G	-0.0603	0.0078	1.27E-14
rs1510136	4	1.44E+08	A	G	0.052602	0.0093	1.39E-08
rs61828917	1	1.74E+08	C	T	0.067603	0.011	7.95E-10
rs16851048	1	1.77E+08	T	C	-0.0676	0.0097	3.06E-12
rs12363019	11	24374545	T	A	-0.0516	0.0082	2.58E-10
rs10767734	11	28642381	C	T	0.050902	0.0082	5.62E-10
rs778371	2	2.34E+08	A	G	-0.0741	0.0089	1.10E-16
rs11647188	16	82648514	A	G	0.044495	0.0081	3.75E-08
rs11076631	16	89877975	A	G	0.052203	0.0088	2.59E-09
rs9459170	6	1.65E+08	T	C	0.055302	0.0098	1.43E-08
rs2456020	15	78868398	C	T	0.068499	0.0088	5.35E-15
rs28521069	4	1.19E+08	C	T	-0.0457	0.0083	3.78E-08
rs10117	5	1.38E+08	G	A	0.055501	0.0082	9.54E-12
rs9687282	5	1.39E+08	T	G	-0.0486	0.0086	1.66E-08
rs28490262	3	80814042	G	C	0.053199	0.0086	6.68E-10
rs13195636	6	27509493	A	C	0.210504	0.0159	6.55E-40
rs13230189	7	1.37E+08	C	T	0.071902	0.0081	1.04E-18
rs35531336	7	1.33E+08	A	G	0.073501	0.013	1.46E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs1593304	7	1.32E+08	A	G	-0.0642	0.0101	2.37E-10
rs10947452	6	33803752	T	C	-0.0448	0.0081	3.69E-08
rs9461856	6	33395199	G	A	-0.0639	0.0078	3.23E-16
rs11693094	2	1.86E+08	C	T	0.057297	0.0078	2.20E-13
rs12129573	1	73768366	C	A	-0.0681	0.0082	1.42E-16
rs1121296	1	72174197	T	C	0.047303	0.008	3.74E-09
rs11619756	13	44329004	G	A	0.047103	0.0082	7.97E-09
rs215483	4	23377121	G	A	-0.0507	0.0084	1.59E-09
rs4697446	4	24269622	G	T	-0.0446	0.0079	1.67E-08
rs7647398	3	1.81E+08	C	T	0.085003	0.01	2.21E-17
rs9882532	3	16865845	T	C	-0.05309	0.0087	8.57E-10
rs6577597	3	17871326	A	G	-0.0526	0.0085	5.52E-10
rs3739554	9	1.3E+08	A	G	-0.0576	0.0103	2.26E-08
rs5995756	22	40000313	T	C	0.056399	0.0084	2.38E-11
rs9607782	22	41587556	T	A	-0.0725	0.0097	7.10E-14
rs4822076	22	42364057	C	T	-0.0597	0.0089	1.94E-11
rs1451488	2	2E+08	A	G	-0.066	0.0079	6.72E-17
rs13032111	2	1.94E+08	T	G	0.043203	0.0077	2.15E-08
rs2914983	2	1.98E+08	A	G	0.062796	0.0081	1.10E-14
rs9636429	2	37215607	G	A	-0.0547	0.009	1.10E-09
rs12712532	2	37558211	T	A	0.049999	0.0079	2.75E-10
rs6925079	6	64946311	T	C	-0.0448	0.0081	3.58E-08
rs6065094	20	37453194	A	G	-0.0634	0.0082	1.41E-14
rs13219424	6	1.28E+08	C	T	0.045996	0.0084	4.52E-08
rs60135207	3	71563777	G	T	0.049599	0.0087	1.27E-08
rs12991836	2	1.45E+08	A	C	-0.0584	0.008	2.72E-13
rs16825349	2	1.46E+08	A	G	-0.0704	0.0104	1.32E-11
rs12713008	2	48503561	G	A	0.043002	0.0078	3.05E-08
rs500102	9	77358745	T	C	0.043299	0.0079	4.15E-08
rs61363285	9	1.35E+08	T	C	-0.0646	0.0116	2.86E-08
rs79668541	10	1.05E+08	C	T	0.120703	0.0121	2.11E-23
rs1856507	6	73157926	C	A	0.050398	0.008	3.00E-10
rs9454727	6	70003389	A	G	0.054801	0.0098	1.93E-08
rs324017	12	57487814	A	C	-0.0563	0.0084	2.21E-11
rs578470	12	50463325	T	C	-0.0462	0.0083	2.33E-08
rs73292401	17	12875908	T	A	-0.0659	0.0103	1.82E-10
rs9891739	17	19942177	C	T	-0.045	0.008	2.18E-08
rs4073003	17	19148305	A	G	0.080603	0.0116	4.20E-12
rs8055219	16	13753384	G	A	-0.0672	0.0095	1.57E-12
rs252812	5	1.07E+08	A	G	0.053	0.0093	1.30E-08
rs35164357	5	1.09E+08	C	T	-0.0605	0.0096	2.59E-10
rs10861176	12	1.05E+08	G	A	-0.0504	0.0086	5.23E-09
rs3764002	12	1.09E+08	C	T	-0.0517	0.0086	1.65E-09
rs7133857	12	1.04E+08	G	A	0.0482	0.0085	1.18E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs2088911	13	38844439	G	A	0.044495	0.0079	2.12E-08
rs12853617	13	38317781	T	C	0.045996	0.0081	1.43E-08
rs55929115	3	1.18E+08	T	A	0.072004	0.013	3.21E-08
rs10035564	5	45252500	A	G	-0.06481	0.0081	1.65E-15
rs17194490	3	2547786	G	T	-0.0781	0.0116	1.85E-11
rs2514218	11	1.13E+08	C	T	0.069899	0.009	6.46E-15
rs17644050	2	1.56E+08	G	C	-0.0538	0.0098	4.02E-08
rs79210963	7	24717969	T	C	-0.0863	0.0129	2.58E-11
rs7811417	7	21534152	T	C	0.048304	0.0081	2.17E-09
rs12285419	11	46343189	C	A	-0.0812	0.01	3.73E-16
rs634940	6	93077500	G	T	-0.0649	0.0098	2.88E-11
rs6925964	6	96475894	A	T	0.097499	0.0176	3.19E-08
rs72901550	18	27478326	G	C	-0.0536	0.0096	2.81E-08
rs2710323	3	52815905	T	C	0.074597	0.0077	5.92E-22
rs11917680	3	50471408	G	T	0.056702	0.0091	4.17E-10
rs7432375	3	1.36E+08	G	A	0.063801	0.0082	5.32E-15
rs2238304	15	89843950	A	T	0.049599	0.0078	1.73E-10
rs4779050	15	83368738	T	G	0.049304	0.0079	4.18E-10
rs11638554	15	85148231	T	G	0.064504	0.0089	3.62E-13
rs10910078	1	2390588	T	C	-0.0526	0.0085	5.78E-10
rs11121172	1	8418644	C	A	0.054602	0.0089	7.15E-10
rs11122119	1	6768856	C	A	-0.0453	0.0081	2.31E-08
rs9597388	13	56928696	G	A	0.066798	0.0101	3.24E-11
rs9569820	13	58702746	G	T	-0.0676	0.0109	6.56E-10
rs7938083	11	57493622	C	A	-0.0524	0.0087	1.60E-09
rs10069930	5	1.4E+08	T	A	0.048304	0.0079	9.43E-10
rs6479487	9	96237373	T	G	-0.0587	0.0103	1.37E-08
rs7609876	3	1.77E+08	T	C	-0.0512	0.0089	9.40E-09
rs144821294	19	2155136	C	T	-0.138	0.0242	1.22E-08
rs72974269	2	2.25E+08	C	T	0.052099	0.0083	2.76E-10
rs35351411	15	61872197	A	C	-0.0573	0.0079	3.13E-13
rs9925915	16	29993686	G	C	0.059297	0.0078	2.43E-14
rs1463209	12	39518293	C	T	0.047704	0.0081	3.34E-09
rs2190864	14	72416219	T	C	0.066097	0.008	1.12E-16
rs2206956	6	1.47E+08	G	A	-0.0462	0.0078	2.51E-09
rs9390083	6	1.44E+08	C	G	-0.05719	0.0103	2.95E-08
rs2905432	19	19484295	G	A	0.059598	0.008	1.08E-13
rs322128	19	11402416	C	T	-0.0567	0.0095	2.08E-09
rs12431743	14	84673716	G	A	-0.0456	0.008	1.26E-08
rs12446640	16	4494549	A	G	0.047103	0.0085	3.31E-08
rs9926049	16	9939960	C	A	-0.0556	0.0088	3.16E-10
rs10127983	1	1.54E+08	C	T	-0.0463	0.0084	3.11E-08
rs12138231	1	1.5E+08	T	A	-0.0671	0.0116	7.21E-09
rs7915131	10	64418656	C	T	0.042695	0.0078	4.94E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs13107325	4	1.03E+08	C	T	-0.1587	0.0168	2.90E-21
rs6839635	4	1.04E+08	C	A	-0.0432	0.0079	3.87E-08
rs2153960	6	1.09E+08	G	A	0.051396	0.0084	9.22E-10
rs6504163	17	61545779	C	T	-0.0492	0.0082	1.87E-09
rs6732355	2	1.05E+08	C	A	-0.0587	0.0094	4.36E-10
rs2119242	10	21344773	G	A	-0.0602	0.0106	1.34E-08
rs11587347	1	2.39E+08	C	G	-0.1028	0.0139	1.50E-13
rs2220276	1	2.44E+08	A	T	-0.0505	0.0082	6.09E-10
rs10148671	14	29469373	T	C	-0.0479	0.0083	6.82E-09
rs6482437	10	18726326	A	C	-0.10471	0.0135	1.05E-14
rs16867576	5	88746331	A	G	0.076998	0.0129	2.12E-09
rs6969410	7	1.1E+08	T	G	0.055501	0.0083	1.90E-11
rs38752	7	1.11E+08	T	G	0.060003	0.0081	1.08E-13
rs1589726	7	79348201	C	T	0.077896	0.0137	1.20E-08
rs10238960	7	70773271	C	T	-0.0482	0.0084	7.65E-09
rs2944821	7	71795998	G	C	0.047799	0.008	1.90E-09
rs7701440	5	60620980	T	C	-0.0638	0.008	1.86E-15
rs73229090	8	27442127	C	A	0.102602	0.0142	4.34E-13
rs3808581	8	26250047	G	A	-0.06699	0.0097	3.82E-12
rs2717003	2	58143438	A	G	-0.07529	0.008	2.76E-21
rs12969453	18	52751708	A	G	0.054299	0.0078	3.53E-12
rs715170	18	53795514	C	T	0.064701	0.009	7.40E-13
rs4632195	18	50746748	C	T	-0.0498	0.0084	2.73E-09
rs9636107	18	53200117	A	G	-0.0609	0.0081	5.72E-14
rs17571951	14	30017039	T	C	-0.0645	0.0105	7.89E-10
rs12883788	14	33303540	C	T	-0.0543	0.0079	8.43E-12
rs8104557	19	31030189	T	C	-0.0604	0.011	3.76E-08
rs3810450	19	36530562	T	C	0.092497	0.016	8.27E-09
rs505061	9	22767164	C	A	-0.0499	0.0077	1.03E-10
rs9545047	13	79859456	A	C	0.053797	0.0081	3.05E-11
rs58950470	11	65383755	G	T	-0.0493	0.0086	1.10E-08
rs6546857	2	73837955	A	G	-0.0603	0.0101	2.80E-09
rs11897811	2	76267139	C	T	-0.0575	0.0102	1.49E-08
rs999494	2	73157395	C	T	0.057599	0.0101	1.04E-08
rs1198588	1	98552832	A	T	-0.0964	0.0103	7.88E-21
rs59519965	1	97168334	G	T	-0.0582	0.0098	3.36E-09
rs72728416	1	97834691	A	G	-0.0598	0.0087	4.99E-12
rs337718	18	69774278	T	C	0.0492	0.0084	4.39E-09
rs6588355	1	50113591	T	C	0.049504	0.009	3.65E-08
rs2412823	15	44227270	C	T	0.056305	0.0084	2.46E-11
rs55927878	15	40573201	G	A	-0.0493	0.0089	2.92E-08
rs9287971	2	1.75E+08	G	A	-0.0458	0.0083	3.82E-08
rs62184960	2	1.73E+08	C	T	0.069797	0.0122	1.08E-08
rs6430492	2	1.35E+08	G	A	0.057703	0.0094	6.72E-10

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs331395	5	91006918	C	G	-0.0549	0.009	1.27E-09
rs7582445	2	60495874	A	C	0.045604	0.0081	1.70E-08
rs10503253	8	4180844	C	A	-0.0602	0.0091	4.37E-11
rs72980087	18	77632194	G	A	-0.0644	0.0079	4.06E-16
rs7238071	18	77579812	A	G	-0.0629	0.0084	9.29E-14
rs4937935	11	1.35E+08	A	T	-0.0539	0.0081	2.30E-11
rs10894308	11	1.31E+08	G	A	0.047704	0.0079	1.36E-09
rs893949	11	1.34E+08	C	T	0.052896	0.0079	2.74E-11
rs1939514	11	1.33E+08	T	C	0.055198	0.0077	1.06E-12
rs11223661	11	1.34E+08	G	T	0.078996	0.0105	5.01E-14
rs79445414	8	33863561	T	C	-0.1235	0.0222	2.63E-08
rs7816998	8	38257506	G	A	0.057797	0.0092	3.11E-10
rs35045093	7	1.28E+08	A	C	0.056598	0.0103	3.36E-08
rs61786047	1	29032580	G	A	0.078802	0.0135	4.91E-09
rs6010045	22	51103091	T	C	-0.0477	0.0085	1.82E-08
rs704364	3	63874734	A	G	0.050303	0.0082	8.41E-10
rs9813516	3	60293004	G	A	-0.0513	0.0084	1.25E-09
rs498591	9	14509105	A	T	-0.0679	0.0111	9.59E-10
rs2890914	9	10239181	A	G	-0.0432	0.0077	2.31E-08
rs10774034	12	2330458	C	T	-0.08329	0.0085	7.10E-23
rs13414801	2	28290347	T	C	-0.0469	0.0081	6.30E-09
rs12712510	2	22749726	T	C	0.051501	0.0084	9.34E-10
rs141216273	2	25599172	C	A	-0.1247	0.0228	4.49E-08
rs2909457	2	1.63E+08	G	A	0.045805	0.0083	3.09E-08
rs35734242	4	706700	T	C	-0.0499	0.008	3.93E-10
rs11696755	20	48105317	T	C	-0.0653	0.0104	2.99E-10

Table B13. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to social communication difficulites and psychotic experiences.

Social Communication difficulties instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**β**	**SE**	**P**
rs13212953	6	39130740	A	G	0.053738	0.010458	2.87E-07
rs79594111	12	97986384	C	A	0.079381	0.015108	1.54E-07
rs4802272	19	46235950	G	A	-0.02388	0.004718	4.28E-07

Table B14. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to social communication difficulties and schizophrenia (European ancestry only- Ripke et al., 2014).

Social Communication difficulties instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**β**	**SE**	**P**
rs13212953	6	39130740	A	G	0.053738	0.010458	2.87E-07
rs79594111	12	97986384	C	A	0.079381	0.015108	1.54E-07
rs4802272	19	46235950	G	A	-0.02388	0.004718	4.28E-07
Schizophrenia instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs7893279	10	18745105	T	G	0.1124	0.0175	1.24E-10
rs301797	1	8487323	A	C	0.066097	0.0116	1.2E-08
rs11191419	10	1.05E+08	A	T	-0.1016	0.0118	6.69E-18
rs1498232	1	30433951	T	C	0.072004	0.0118	1.21E-09
rs11210892	1	44100084	A	G	-0.0678	0.0115	3.42E-09
rs35998080	1	73278615	T	G	0.069004	0.0112	6.95E-10
rs1702294	1	98501984	T	C	-0.1184	0.0138	1.03E-17
rs11027857	11	24403620	A	G	0.063998	0.0109	3.67E-09
rs35324223	11	46402852	A	G	-0.09199	0.0145	2.04E-10
rs2514218	11	1.13E+08	T	C	-0.07221	0.0116	4.64E-10
rs55661361	11	1.25E+08	A	G	-0.07881	0.0116	1.04E-11
rs10791097	11	1.31E+08	T	G	0.0766	0.0109	2.05E-12
rs75059851	11	1.34E+08	A	G	0.091302	0.0136	2.18E-11
rs12062861	1	1.5E+08	A	G	-0.0911	0.0149	9.66E-10
rs1024582	12	2402246	A	G	0.098904	0.0115	6.27E-18
rs73115999	12	57778221	T	C	-0.1985	0.0351	1.54E-08
rs10860964	12	1.04E+08	T	C	0.063003	0.0112	1.86E-08
rs1615350	12	1.24E+08	T	C	-0.0851	0.0123	4.26E-12
rs10803138	1	2.44E+08	A	G	-0.07221	0.0126	1.13E-08
rs1191551	14	30000405	T	G	0.071697	0.0131	4.21E-08
rs67981189	14	71472226	A	G	-0.0698	0.0118	3.75E-09
rs2332700	14	72417326	C	G	0.0771	0.0125	7.38E-10
rs2693698	14	99719219	A	G	-0.06171	0.0111	2.99E-08
rs12887734	14	1.04E+08	T	G	0.088304	0.0121	3.72E-13
rs2414718	15	61863133	A	G	0.069797	0.011	1.98E-10
rs8042374	15	78908032	A	G	0.089704	0.0128	2.91E-12
rs783540	15	83254708	A	G	-0.0599	0.011	4.77E-08
rs12902973	15	85105982	C	G	-0.0791	0.0122	8.83E-11
rs4702	15	91426560	A	G	-0.08051	0.0115	2.62E-12
rs9922678	16	9946319	A	G	0.068397	0.0118	6.18E-09
rs8055219	16	13753384	A	G	0.076998	0.0127	1.45E-09
rs12691307	16	29939877	A	G	0.071902	0.0113	2.03E-10
rs12932476	16	63709630	C	G	0.059702	0.0109	4.62E-08
rs216189	17	2187401	A	G	0.0662	0.0115	8.79E-09
rs11658257	17	17956459	C	G	-0.0662	0.0115	8.34E-09

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs11874716	18	52750688	T	G	0.067201	0.011	1.01E-09
rs9636107	18	53200117	A	G	-0.0796	0.0108	2.17E-13
rs9966779	18	53620456	T	C	-0.1329	0.0231	8.56E-09
rs715170	18	53795514	T	C	-0.0669	0.0122	4.65E-08
rs2905426	19	19478022	T	G	-0.0677	0.0115	4.07E-09
rs2053079	19	30987423	A	G	-0.0718	0.0127	1.74E-08
rs2103655	20	37425958	A	G	0.0766	0.0119	1.24E-10
rs10199182	2	22747124	A	T	0.060003	0.0109	3.82E-08
rs11682175	2	57987593	T	C	-0.0735	0.0109	1.58E-11
rs6430095	2	1.46E+08	A	G	0.0798	0.0145	3.4E-08
rs76355118	2	1.49E+08	A	G	-0.1544	0.0278	2.78E-08
rs2909457	2	1.63E+08	A	G	-0.0597	0.0109	4.25E-08
rs11693094	2	1.86E+08	T	C	-0.0736	0.011	2.17E-11
rs6716963	2	1.94E+08	A	G	0.062796	0.0113	3.05E-08
rs281768	2	2.01E+08	A	T	0.104198	0.0137	2.64E-14
rs6434928	2	1.98E+08	A	G	-0.0787	0.0116	1.17E-11
rs5995756	22	40000313	T	C	0.072497	0.0109	2.91E-11
rs9607782	22	41587556	A	T	0.088697	0.0128	3.98E-12
rs1058167	22	42538029	A	G	-0.0668	0.0118	1.32E-08
rs11685299	2	2.25E+08	A	C	-0.0662	0.0117	1.49E-08
rs7601312	2	2.29E+08	A	G	-0.059	0.0108	4.68E-08
rs6704768	2	2.34E+08	A	G	-0.0766	0.0109	2.06E-12
rs17194490	3	2547786	T	G	0.0966	0.0148	6.38E-11
rs75968099	3	36858583	T	C	0.080104	0.0114	2.31E-12
rs2535627	3	52845105	T	C	0.070403	0.0109	1.17E-10
rs832190	3	63842629	T	C	-0.0699	0.0113	5.73E-10
rs6439649	3	1.36E+08	T	G	0.070999	0.0111	1.37E-10
rs34796896	3	1.81E+08	A	G	-0.0822	0.0135	1.23E-09
rs215411	4	23423603	A	T	0.0692	0.0115	1.68E-09
rs13107325	4	1.03E+08	T	C	0.151897	0.0215	1.54E-12
rs1106568	4	1.77E+08	A	G	-0.0694	0.0125	2.85E-08
rs17073903	4	1.84E+08	A	G	-0.08141	0.0148	3.92E-08
rs7701440	5	60620980	T	C	-0.0765	0.0108	1.66E-12
rs16867576	5	88746331	A	G	0.095801	0.017	1.61E-08
rs3849046	5	1.38E+08	T	C	0.062496	0.0109	1.04E-08
rs13176930	5	1.53E+08	A	T	-0.0697	0.0115	1.27E-09
rs11740474	5	1.54E+08	A	T	-0.06269	0.0112	2E-08
rs13437595	6	29763308	T	C	0.262203	0.0392	2.19E-11
rs13217619	6	28306671	T	C	0.219698	0.0195	1.44E-29
rs9270965	6	32573471	A	G	0.071697	0.0125	9.84E-09
rs9461856	6	33395199	A	G	0.074996	0.0109	6.52E-12
rs1339227	6	73155701	T	C	-0.0633	0.0114	3.06E-08
rs3798869	6	84328660	A	G	-0.0668	0.011	1.09E-09
rs117074560	6	96459651	T	C	-0.1566	0.0277	1.66E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs58120505	7	2029867	T	C	0.082197	0.0111	1.26E-13
rs12704290	7	86427626	A	G	-0.10611	0.0168	2.59E-10
rs6466055	7	1.05E+08	A	C	0.068798	0.0114	1.59E-09
rs13240464	7	1.11E+08	T	C	0.080704	0.0116	3.12E-12
rs7801375	7	1.32E+08	A	G	-0.083	0.015	2.88E-08
rs17529963	7	1.37E+08	T	C	0.0629	0.0114	3.24E-08
rs10108725	8	4191202	T	C	0.073204	0.0133	3.32E-08
rs73191547	8	10033425	A	T	-0.0669	0.0115	6.13E-09
rs73229090	8	27442127	A	C	-0.0995	0.0177	1.95E-08
rs13261481	8	60701801	T	G	0.062402	0.011	1.66E-08
rs7819570	8	89588626	T	G	0.076498	0.014	4.47E-08
rs36068923	8	1.11E+08	A	G	-0.0835	0.0134	4.14E-10
rs4129585	8	1.43E+08	A	C	0.079301	0.0109	3.61E-13
rs11139497	9	84739941	A	T	0.0656	0.0118	2.65E-08

Table B15. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to empathising and schizophrenia.

Empathy instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**β**	**SE**	**P**
rs2420485	chr10	1.21E+08	G	C	-0.48262	0.095075	3.85E-07
rs1141090	chr11	13033155	C	A	0.434924	0.085494	3.64E-07
rs4882760	chr12	1.29E+08	T	A	-0.509	0.092905	4.29E-08
Schizophrenia instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs7002992	8	1.04E+08	T	C	0.0484	0.0083	4.48E-09
rs6715366	2	2327295	G	A	-0.0551	0.0094	4.23E-09
rs77463171	16	66942206	C	T	-0.1465	0.0263	2.41E-08
rs113113059	6	43160375	T	C	0.061396	0.0092	2.29E-11
rs10873538	14	1.04E+08	T	G	-0.0632	0.0082	9.59E-15
rs61920311	12	14423294	A	C	0.046101	0.0082	1.75E-08
rs2532240	17	44265839	C	T	0.052099	0.0083	2.72E-10
rs55938136	17	43798360	A	G	0.0615	0.0108	1.23E-08
rs6588168	1	66324118	C	T	-0.0489	0.0079	5.94E-10
rs12126806	1	2.01E+08	C	T	0.049904	0.009	2.89E-08
rs4915203	1	2E+08	A	G	0.050398	0.0085	3.3E-09
rs1658810	2	2.01E+08	C	T	0.080704	0.0096	3.54E-17
rs140001745	2	2.01E+08	T	C	0.106996	0.0155	5.13E-12
rs56335113	1	30427639	A	G	0.066602	0.0084	3.15E-15
rs581459	1	36375110	C	T	0.0743	0.0123	1.32E-09
rs1915019	8	89283689	A	G	0.057599	0.0092	3.43E-10
rs308697	3	1.61E+08	C	A	0.046903	0.0079	3.35E-09
rs13090130	3	1.62E+08	G	A	0.051396	0.0079	9.92E-11
rs2102949	12	1.24E+08	G	A	0.086003	0.0087	3.18E-23
rs75482067	12	1.23E+08	G	A	-0.0876	0.0148	3.06E-09
rs2649999	12	1.21E+08	T	C	0.049504	0.0082	1.28E-09
rs12311848	12	1.24E+08	A	G	-0.049	0.0087	1.65E-08
rs2686386	12	1.22E+08	C	T	0.054801	0.0096	1.26E-08
rs167924	3	1.07E+08	A	G	-0.0506	0.0089	1.33E-08
rs72943392	11	81178838	G	C	-0.0532	0.0094	1.44E-08
rs9975024	21	16439883	A	G	-0.0483	0.008	1.78E-09
rs75968099	3	36858583	C	T	-0.0582	0.0089	5.16E-11
rs1506297	3	30072307	T	C	0.051102	0.0091	1.98E-08
rs6538539	12	95195293	G	T	0.047704	0.0077	5.63E-10
rs7953300	12	92254654	G	T	-0.0449	0.0082	3.94E-08
rs7312697	12	29933069	T	C	-0.0533	0.0081	4.85E-11
rs28454198	4	80204001	G	C	0.0486	0.0081	1.88E-09
rs10086619	8	1.12E+08	A	G	-0.0691	0.0104	3.3E-11
rs4702	15	91426560	G	A	0.080298	0.0081	2.15E-23
rs11210892	1	44100084	G	A	0.0675	0.0081	1.18E-16

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs11136325	8	1.45E+08	G	A	0.053	0.009	3.3E-09
rs13262595	8	1.43E+08	A	G	0.069097	0.0079	2.21E-18
rs12301769	12	72231313	A	C	-0.08379	0.014	1.93E-09
rs2022265	6	84293271	A	G	0.048504	0.0077	3.74E-10
rs10985811	9	1.01E+08	T	C	-0.0545	0.0098	2.53E-08
rs4793888	17	55737740	G	A	-0.0609	0.0097	3.63E-10
rs2381411	9	36319928	T	C	-0.045	0.0079	1.28E-08
rs39967	5	57744788	T	C	-0.0604	0.0107	1.87E-08
rs12943566	17	2157774	A	G	-0.0525	0.0083	2.29E-10
rs3752827	17	1265325	T	A	0.052203	0.0084	6.33E-10
rs77502336	11	1.23E+08	G	C	-0.0545	0.0082	3.45E-11
rs1940171	11	1.25E+08	A	G	0.073501	0.0099	8.87E-14
rs10515678	5	1.52E+08	C	T	0.065703	0.0095	4.46E-12
rs11740474	5	1.54E+08	A	T	-0.0504	0.0086	4.46E-09
rs12652777	5	1.56E+08	T	C	0.045403	0.0079	1.06E-08
rs154433	16	58659808	G	A	0.047198	0.0084	2.38E-08
rs10957321	8	65605878	G	A	-0.0482	0.0077	4.18E-10
rs298216	8	65293195	C	G	-0.0727	0.0123	3.45E-09
rs6984242	8	60700469	G	A	0.052697	0.0078	1.5E-11
rs1454606	4	33642614	C	T	-0.0716	0.0108	2.9E-11
rs58120505	7	2029867	T	C	0.083302	0.0078	1.8E-26
rs11972718	7	8549187	C	G	-0.04949	0.0088	1.57E-08
rs17731	10	3821561	G	A	-0.0575	0.0079	3.76E-13
rs4766428	12	1.11E+08	C	T	-0.0721	0.0085	2.61E-17
rs2387414	19	51034243	G	C	-0.0515	0.0084	8.01E-10
rs2304205	19	50168927	A	C	0.070403	0.0092	2.38E-14
rs758749	19	57189718	C	T	-0.0615	0.0112	4.66E-08
rs9312586	4	1.77E+08	A	G	-0.0908	0.014	8.14E-11
rs41533650	4	1.77E+08	G	A	-0.0724	0.0097	8.69E-14
rs61405217	4	1.7E+08	C	T	0.052004	0.0079	5.39E-11
rs459391	21	22120508	T	C	0.056598	0.01	1.54E-08
rs6943762	7	86403263	T	C	0.103296	0.0124	6.3E-17
rs2252074	7	1.05E+08	T	G	-0.0603	0.0078	1.27E-14
rs1510136	4	1.44E+08	A	G	0.052602	0.0093	1.39E-08
rs61828917	1	1.74E+08	C	T	0.067603	0.011	7.95E-10
rs16851048	1	1.77E+08	T	C	-0.0676	0.0097	3.06E-12
rs12363019	11	24374545	T	A	-0.0516	0.0082	2.58E-10
rs10767734	11	28642381	C	T	0.050902	0.0082	5.62E-10
rs778371	2	2.34E+08	A	G	-0.0741	0.0089	1.1E-16
rs11647188	16	82648514	A	G	0.044495	0.0081	3.75E-08
rs11076631	16	89877975	A	G	0.052203	0.0088	2.59E-09
rs6919146	6	1.65E+08	T	G	-0.0488	0.0085	8.42E-09
rs2456020	15	78868398	C	T	0.068499	0.0088	5.35E-15
rs28521069	4	1.19E+08	C	T	-0.0457	0.0083	3.78E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs10117	5	1.38E+08	G	A	0.055501	0.0082	9.54E-12
rs9687282	5	1.39E+08	T	G	-0.0486	0.0086	1.66E-08
rs28490262	3	80814042	G	C	0.053199	0.0086	6.68E-10
rs13195636	6	27509493	A	C	0.210504	0.0159	6.55E-40
rs356183	4	90626098	G	C	0.044304	0.008	3.37E-08
rs13230189	7	1.37E+08	C	T	0.071902	0.0081	1.04E-18
rs35792732	7	1.33E+08	C	T	0.060399	0.0106	1.08E-08
rs1593304	7	1.32E+08	A	G	-0.0642	0.0101	2.37E-10
rs10947452	6	33803752	T	C	-0.0448	0.0081	3.69E-08
rs9461856	6	33395199	G	A	-0.0639	0.0078	3.23E-16
rs3131295	6	32173257	G	A	0.0599	0.008	9.97E-14
rs11693094	2	1.86E+08	C	T	0.057297	0.0078	2.2E-13
rs12129573	1	73768366	C	A	-0.0681	0.0082	1.42E-16
rs1121296	1	72174197	T	C	0.047303	0.008	3.74E-09
rs11619756	13	44329004	G	A	0.047103	0.0082	7.97E-09
rs215483	4	23377121	G	A	-0.0507	0.0084	1.59E-09
rs4697446	4	24269622	G	T	-0.0446	0.0079	1.67E-08
rs7647398	3	1.81E+08	C	T	0.085003	0.01	2.21E-17
rs9882532	3	16865845	T	C	-0.05309	0.0087	8.57E-10
rs6577597	3	17871326	A	G	-0.0526	0.0085	5.52E-10
rs3739554	9	1.3E+08	A	G	-0.0576	0.0103	2.26E-08
rs5995756	22	40000313	T	C	0.056399	0.0084	2.38E-11
rs9607782	22	41587556	T	A	-0.0725	0.0097	7.1E-14
rs4822076	22	42364057	C	T	-0.0597	0.0089	1.94E-11
rs1451488	2	2E+08	A	G	-0.066	0.0079	6.72E-17
rs13032111	2	1.94E+08	T	G	0.043203	0.0077	2.15E-08
rs2914983	2	1.98E+08	A	G	0.062796	0.0081	1.1E-14
rs10190027	2	37190726	C	T	-0.04971	0.0089	2.57E-08
rs3770752	2	37576136	A	G	0.057401	0.0086	2.86E-11
rs6925079	6	64946311	T	C	-0.0448	0.0081	3.58E-08
rs6065094	20	37453194	A	G	-0.0634	0.0082	1.41E-14
rs13219424	6	1.28E+08	C	T	0.045996	0.0084	4.52E-08
rs60135207	3	71563777	G	T	0.049599	0.0087	1.27E-08
rs12991836	2	1.45E+08	A	C	-0.0584	0.008	2.72E-13
rs16825349	2	1.46E+08	A	G	-0.0704	0.0104	1.32E-11
rs10777187	12	89940502	T	C	0.050902	0.0092	2.82E-08
rs12713008	2	48503561	G	A	0.043002	0.0078	3.05E-08
rs500102	9	77358745	T	C	0.043299	0.0079	4.15E-08
rs72761691	9	1.35E+08	A	C	-0.0664	0.0116	1.07E-08
rs2078266	9	1.38E+08	A	G	0.0618	0.0113	4.86E-08
rs79668541	10	1.05E+08	C	T	0.120703	0.0121	2.11E-23
rs79780963	10	1.05E+08	C	T	0.118396	0.0122	2.53E-22
rs1856507	6	73157926	C	A	0.050398	0.008	3E-10
rs9454727	6	70003389	A	G	0.054801	0.0098	1.93E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs578470	12	50463325	T	C	-0.0462	0.0083	2.33E-08
rs61937595	12	57682956	C	T	0.121996	0.0158	1.32E-14
rs73292401	17	12875908	T	A	-0.0659	0.0103	1.82E-10
rs9891739	17	19942177	C	T	-0.045	0.008	2.18E-08
rs4073003	17	19148305	A	G	0.080603	0.0116	4.2E-12
rs8055219	16	13753384	G	A	-0.0672	0.0095	1.57E-12
rs252812	5	1.07E+08	A	G	0.053	0.0093	1.3E-08
rs35164357	5	1.09E+08	C	T	-0.0605	0.0096	2.59E-10
rs10861176	12	1.05E+08	G	A	-0.0504	0.0086	5.23E-09
rs3764002	12	1.09E+08	C	T	-0.0517	0.0086	1.65E-09
rs2455415	13	38860697	C	T	-0.04759	0.0081	3.43E-09
rs1924377	13	38362106	G	C	0.046903	0.0082	8.71E-09
rs55929115	3	1.18E+08	T	A	0.072004	0.013	3.21E-08
rs10035564	5	45252500	A	G	-0.06481	0.0081	1.65E-15
rs1540840	14	99733384	G	C	0.054999	0.009	1.04E-09
rs17194490	3	2547786	G	T	-0.0781	0.0116	1.85E-11
rs61857878	10	92789488	A	T	0.0599	0.0099	1.46E-09
rs2514218	11	1.13E+08	C	T	0.069899	0.009	6.46E-15
rs17644050	2	1.56E+08	G	C	-0.0538	0.0098	4.02E-08
rs79210963	7	24717969	T	C	-0.0863	0.0129	2.58E-11
rs7811417	7	21534152	T	C	0.048304	0.0081	2.17E-09
rs12285419	11	46343189	C	A	-0.0812	0.01	3.73E-16
rs634940	6	93077500	G	T	-0.0649	0.0098	2.88E-11
rs6925964	6	96475894	A	T	0.097499	0.0176	3.19E-08
rs9304548	18	27500959	C	A	0.060003	0.0089	1.9E-11
rs2710323	3	52815905	T	C	0.074597	0.0077	5.92E-22
rs11917680	3	50471408	G	T	0.056702	0.0091	4.17E-10
rs7432375	3	1.36E+08	G	A	0.063801	0.0082	5.32E-15
rs2238304	15	89843950	A	T	0.049599	0.0078	1.73E-10
rs4779050	15	83368738	T	G	0.049304	0.0079	4.18E-10
rs11638554	15	85148231	T	G	0.064504	0.0089	3.62E-13
rs6673880	1	2373168	A	G	-0.061	0.0086	1.32E-12
rs11121172	1	8418644	C	A	0.054602	0.0089	7.15E-10
rs11122119	1	6768856	C	A	-0.0453	0.0081	2.31E-08
rs9597388	13	56928696	G	A	0.066798	0.0101	3.24E-11
rs9569820	13	58702746	G	T	-0.0676	0.0109	6.56E-10
rs7938083	11	57493622	C	A	-0.0524	0.0087	1.6E-09
rs10069930	5	1.4E+08	T	A	0.048304	0.0079	9.43E-10
rs6479487	9	96237373	T	G	-0.0587	0.0103	1.37E-08
rs7609876	3	1.77E+08	T	C	-0.0512	0.0089	9.4E-09
rs2224086	1	1.15E+08	C	A	-0.0577	0.0103	2.09E-08
rs144821294	19	2155136	C	T	-0.138	0.0242	1.22E-08
rs72974269	2	2.25E+08	C	T	0.052099	0.0083	2.76E-10
rs35351411	15	61872197	A	C	-0.0573	0.0079	3.13E-13

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs3814883	16	29994922	C	T	0.060898	0.0079	8.82E-15
rs72723227	5	7245664	G	A	0.047999	0.0082	4.58E-09
rs1463209	12	39518293	C	T	0.047704	0.0081	3.34E-09
rs2190864	14	72416219	T	C	0.066097	0.008	1.12E-16
rs2206956	6	1.47E+08	G	A	-0.0462	0.0078	2.51E-09
rs9390083	6	1.44E+08	C	G	-0.05719	0.0103	2.95E-08
rs1858999	19	19497669	C	G	0.060502	0.0081	7.97E-14
rs72986630	19	11849736	C	T	-0.1117	0.0177	3.07E-10
rs322128	19	11402416	C	T	-0.0567	0.0095	2.08E-09
rs12431743	14	84673716	G	A	-0.0456	0.008	1.26E-08
rs9926049	16	9939960	C	A	-0.0556	0.0088	3.16E-10
rs8048039	16	4498486	A	T	0.049	0.0083	4.35E-09
rs10127983	1	1.54E+08	C	T	-0.0463	0.0084	3.11E-08
rs12138231	1	1.5E+08	T	A	-0.0671	0.0116	7.21E-09
rs7915131	10	64418656	C	T	0.042695	0.0078	4.94E-08
rs13107325	4	1.03E+08	C	T	-0.1587	0.0168	2.9E-21
rs6839635	4	1.04E+08	C	A	-0.0432	0.0079	3.87E-08
rs2153960	6	1.09E+08	G	A	0.051396	0.0084	9.22E-10
rs117799466	15	34659517	G	C	-0.0481	0.0087	3.86E-08
rs6504163	17	61545779	C	T	-0.0492	0.0082	1.87E-09
rs6732355	2	1.05E+08	C	A	-0.0587	0.0094	4.36E-10
rs2119242	10	21344773	G	A	-0.0602	0.0106	1.34E-08
rs11807834	1	2.3E+08	G	A	-0.053	0.0093	1.12E-08
rs11587347	1	2.39E+08	C	G	-0.1028	0.0139	1.5E-13
rs145071536	1	2.44E+08	T	C	-0.0817	0.0119	5.76E-12
rs10148671	14	29469373	T	C	-0.0479	0.0083	6.82E-09
rs6482437	10	18726326	A	C	-0.10471	0.0135	1.05E-14
rs115325222	5	88854539	A	G	0.090398	0.0151	1.93E-09
rs6969410	7	1.1E+08	T	G	0.055501	0.0083	1.9E-11
rs38752	7	1.11E+08	T	G	0.060003	0.0081	1.08E-13
rs1589726	7	79348201	C	T	0.077896	0.0137	1.2E-08
rs10238960	7	70773271	C	T	-0.0482	0.0084	7.65E-09
rs2944821	7	71795998	G	C	0.047799	0.008	1.9E-09
rs7701440	5	60620980	T	C	-0.0638	0.008	1.86E-15
rs73229090	8	27442127	C	A	0.102602	0.0142	4.34E-13
rs3808581	8	26250047	G	A	-0.06699	0.0097	3.82E-12
rs2717003	2	58143438	A	G	-0.07529	0.008	2.76E-21
rs12969453	18	52751708	A	G	0.054299	0.0078	3.53E-12
rs715170	18	53795514	C	T	0.064701	0.009	7.4E-13
rs4632195	18	50746748	C	T	-0.0498	0.0084	2.73E-09
rs9636107	18	53200117	A	G	-0.0609	0.0081	5.72E-14
rs17571951	14	30017039	T	C	-0.0645	0.0105	7.89E-10
rs12883788	14	33303540	C	T	-0.0543	0.0079	8.43E-12
rs8104557	19	31030189	T	C	-0.0604	0.011	3.76E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs3810450	19	36530562	T	C	0.092497	0.016	8.27E-09
rs505061	9	22767164	C	A	-0.0499	0.0077	1.03E-10
rs9545047	13	79859456	A	C	0.053797	0.0081	3.05E-11
rs58950470	11	65383755	G	T	-0.0493	0.0086	1.1E-08
rs6546857	2	73837955	A	G	-0.0603	0.0101	2.8E-09
rs11897811	2	76267139	C	T	-0.0575	0.0102	1.49E-08
rs999494	2	73157395	C	T	0.057599	0.0101	1.04E-08
rs1198588	1	98552832	A	T	-0.0964	0.0103	7.88E-21
rs59519965	1	97168334	G	T	-0.0582	0.0098	3.36E-09
rs72728416	1	97834691	A	G	-0.0598	0.0087	4.99E-12
rs337718	18	69774278	T	C	0.0492	0.0084	4.39E-09
rs6588355	1	50113591	T	C	0.049504	0.009	3.65E-08
rs56205728	15	40567237	G	A	-0.0575	0.0093	5.43E-10
rs2929278	15	44250313	C	T	0.061904	0.0091	8.5E-12
rs9287971	2	1.75E+08	G	A	-0.0458	0.0083	3.82E-08
rs62184960	2	1.73E+08	C	T	0.069797	0.0122	1.08E-08
rs6430492	2	1.35E+08	G	A	0.057703	0.0094	6.72E-10
rs331395	5	91006918	C	G	-0.0549	0.009	1.27E-09
rs4672366	2	60389362	A	T	0.049799	0.0087	1.07E-08
rs10503253	8	4180844	C	A	-0.0602	0.0091	4.37E-11
rs72980087	18	77632194	G	A	-0.0644	0.0079	4.06E-16
rs7238071	18	77579812	A	G	-0.0629	0.0084	9.29E-14
rs4937935	11	1.35E+08	A	T	-0.0539	0.0081	2.3E-11
rs1440480	11	1.34E+08	A	G	0.057504	0.0086	2.52E-11
rs10894308	11	1.31E+08	G	A	0.047704	0.0079	1.36E-09
rs4936215	11	1.34E+08	A	G	0.082796	0.0104	1.86E-15
rs1939514	11	1.33E+08	T	C	0.055198	0.0077	1.06E-12
rs79445414	8	33863561	T	C	-0.1235	0.0222	2.63E-08
rs7816998	8	38257506	G	A	0.057797	0.0092	3.11E-10
rs35045093	7	1.28E+08	A	C	0.056598	0.0103	3.36E-08
rs61786047	1	29032580	G	A	0.078802	0.0135	4.91E-09
rs6010045	22	51103091	T	C	-0.0477	0.0085	1.82E-08
rs704364	3	63874734	A	G	0.050303	0.0082	8.41E-10
rs9813516	3	60293004	G	A	-0.0513	0.0084	1.25E-09
rs498591	9	14509105	A	T	-0.0679	0.0111	9.59E-10
rs2890914	9	10239181	A	G	-0.0432	0.0077	2.31E-08
rs10774034	12	2330458	C	T	-0.08329	0.0085	7.1E-23
rs12712510	2	22749726	T	C	0.051501	0.0084	9.34E-10
rs141216273	2	25599172	C	A	-0.1247	0.0228	4.49E-08
rs12474906	2	28033538	A	C	0.056796	0.0095	2.2E-09
rs2909457	2	1.63E+08	G	A	0.045805	0.0083	3.09E-08
rs35734242	4	706700	T	C	-0.0499	0.008	3.93E-10
rs11696755	20	48105317	T	C	-0.0653	0.0104	2.99E-10

Table B16. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to empathising and psychotic experiences.

Empathy instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**β**	**SE**	**P**
rs2420485	chr10	1.21E+08	G	C	-0.48262	0.095075	3.85E-07
rs1141090	chr11	13033155	C	A	0.434924	0.085494	3.64E-07
rs4882760	chr12	1.29E+08	T	A	-0.509	0.092905	4.29E-08

Table B17. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to empathising and schizophrenia (European ancestry only- Ripke et al., 2014).

Empathy instruments							
SNP	**CHR**	**BP**	**A2**	**A1**	**β**	**SE**	**P**
rs189163756	chr2	1.43E+08	A	C	-1.33045	0.251402	1.21E-07
rs147499660	chr10	1.21E+08	A	G	-0.4868	0.095768	3.72E-07
rs1141090	chr11	13033155	A	C	0.434924	0.085494	3.64E-07
rs4882760	chr12	1.29E+08	A	T	-0.509	0.092905	4.29E-08
Schizophrenia instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs4648845	1	2387101	T	C	0.067201	0.0119	1.74E-08
rs7893279	10	18745105	T	G	0.1124	0.0175	1.24E-10
rs301797	1	8487323	A	C	0.066097	0.0116	1.20E-08
rs11191419	10	1.05E+08	A	T	-0.1016	0.0118	6.69E-18
rs79780963	10	1.05E+08	T	C	-0.1597	0.0195	2.79E-16
rs1498232	1	30433951	T	C	0.072004	0.0118	1.21E-09
rs11210892	1	44100084	A	G	-0.0678	0.0115	3.42E-09
rs35998080	1	73278615	T	G	0.069004	0.0112	6.95E-10
rs1702294	1	98501984	T	C	-0.1184	0.0138	1.03E-17
rs11027857	11	24403620	A	G	0.063998	0.0109	3.67E-09
rs35324223	11	46402852	A	G	-0.09199	0.0145	2.04E-10
rs2514218	11	1.13E+08	T	C	-0.07221	0.0116	4.64E-10
rs55661361	11	1.25E+08	A	G	-0.07881	0.0116	1.04E-11
rs10791097	11	1.31E+08	T	G	0.0766	0.0109	2.05E-12
rs75059851	11	1.34E+08	A	G	0.091302	0.0136	2.18E-11
rs12062861	1	1.5E+08	A	G	-0.0911	0.0149	9.66E-10
rs1024582	12	2402246	A	G	0.098904	0.0115	6.27E-18
rs679087	12	29917265	A	C	-0.0642	0.0116	3.28E-08
rs12826178	12	57622371	T	G	-0.16821	0.0244	5.70E-12
rs4766428	12	1.11E+08	T	C	0.069395	0.0112	6.12E-10
rs1615350	12	1.24E+08	T	C	-0.0851	0.0123	4.26E-12
rs10803138	1	2.44E+08	A	G	-0.07221	0.0126	1.13E-08
rs1191551	14	30000405	T	G	0.071697	0.0131	4.21E-08
rs67981189	14	71472226	A	G	-0.0698	0.0118	3.75E-09
rs2332700	14	72417326	C	G	0.0771	0.0125	7.38E-10
rs2693698	14	99719219	A	G	-0.06171	0.0111	2.99E-08
rs12887734	14	1.04E+08	T	G	0.088304	0.0121	3.72E-13
rs2414718	15	61863133	A	G	0.069797	0.011	1.98E-10
rs28681284	15	78908565	T	C	-0.1016	0.0141	6.35E-13
rs783540	15	83254708	A	G	-0.0599	0.011	4.77E-08
rs12902973	15	85105982	C	G	-0.0791	0.0122	8.83E-11
rs4702	15	91426560	A	G	-0.08051	0.0115	2.62E-12
rs9922678	16	9946319	A	G	0.068397	0.0118	6.18E-09
rs8055219	16	13753384	A	G	0.076998	0.0127	1.45E-09
rs12691307	16	29939877	A	G	0.071902	0.0113	2.03E-10

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs12932476	16	63709630	C	G	0.059702	0.0109	4.62E-08
rs4523957	17	2208899	T	G	0.069703	0.0115	1.40E-09
rs11658257	17	17956459	C	G	-0.0662	0.0115	8.34E-09
rs11874716	18	52750688	T	G	0.067201	0.011	1.01E-09
rs9636107	18	53200117	A	G	-0.0796	0.0108	2.17E-13
rs9966779	18	53620456	T	C	-0.1329	0.0231	8.56E-09
rs715170	18	53795514	T	C	-0.0669	0.0122	4.65E-08
rs72986630	19	11849736	T	C	0.1459	0.0266	4.12E-08
rs2905426	19	19478022	T	G	-0.0677	0.0115	4.07E-09
rs2053079	19	30987423	A	G	-0.0718	0.0127	1.74E-08
rs2103655	20	37425958	A	G	0.0766	0.0119	1.24E-10
rs1509378	2	22754466	A	G	0.0692	0.0119	5.39E-09
rs11682175	2	57987593	T	C	-0.0735	0.0109	1.58E-11
rs6430095	2	1.46E+08	A	G	0.0798	0.0145	3.40E-08
rs76355118	2	1.49E+08	A	G	-0.1544	0.0278	2.78E-08
rs2909457	2	1.63E+08	A	G	-0.0597	0.0109	4.25E-08
rs11693094	2	1.86E+08	T	C	-0.0736	0.011	2.17E-11
rs59979824	2	1.94E+08	A	C	-0.071	0.0119	2.73E-09
rs281768	2	2.01E+08	A	T	0.104198	0.0137	2.64E-14
rs6434928	2	1.98E+08	A	G	-0.0787	0.0116	1.17E-11
rs5995756	22	40000313	T	C	0.072497	0.0109	2.91E-11
rs9607782	22	41587556	A	T	0.088697	0.0128	3.98E-12
rs28733092	22	42537115	T	C	0.070999	0.0121	4.36E-09
rs11685299	2	2.25E+08	A	C	-0.0662	0.0117	1.49E-08
rs7601312	2	2.29E+08	A	G	-0.059	0.0108	4.68E-08
rs6704768	2	2.34E+08	A	G	-0.0766	0.0109	2.06E-12
rs17194490	3	2547786	T	G	0.0966	0.0148	6.38E-11
rs75968099	3	36858583	T	C	0.080104	0.0114	2.31E-12
rs2535627	3	52845105	T	C	0.070403	0.0109	1.17E-10
rs832190	3	63842629	T	C	-0.0699	0.0113	5.73E-10
rs6439649	3	1.36E+08	T	G	0.070999	0.0111	1.37E-10
rs34796896	3	1.81E+08	A	G	-0.0822	0.0135	1.23E-09
rs215411	4	23423603	A	T	0.0692	0.0115	1.68E-09
rs35225200	4	1.03E+08	A	C	-0.14479	0.0203	9.56E-13
rs1106568	4	1.77E+08	A	G	-0.0694	0.0125	2.85E-08
rs17073903	4	1.84E+08	A	G	-0.08141	0.0148	3.92E-08
rs4391122	5	60598543	A	G	-0.078	0.0109	8.90E-13
rs16867576	5	88746331	A	G	0.095801	0.017	1.61E-08
rs3849046	5	1.38E+08	T	C	0.062496	0.0109	1.04E-08
rs111294930	5	1.52E+08	A	G	0.087699	0.0143	9.29E-10
rs76091702	5	1.52E+08	T	C	0.129299	0.0236	4.49E-08
rs11740474	5	1.54E+08	A	T	-0.06269	0.0112	2.00E-08
rs13437595	6	29763308	T	C	0.262203	0.0392	2.19E-11
rs13217619	6	28306671	T	C	0.219698	0.0195	1.44E-29

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs185053056	6	28680776	T	C	-0.2546	0.0303	4.00E-17
rs145607970	6	32624017	A	C	-0.1679	0.026	1.16E-10
rs9274538	6	32634661	A	G	0.097099	0.0133	3.43E-13
rs116334170	6	32598500	A	G	-0.0996	0.0144	4.54E-12
rs9461856	6	33395199	A	G	0.074996	0.0109	6.52E-12
rs1339227	6	73155701	T	C	-0.0633	0.0114	3.06E-08
rs3798869	6	84328660	A	G	-0.0668	0.011	1.09E-09
rs117074560	6	96459651	T	C	-0.1566	0.0277	1.66E-08
rs58120505	7	2029867	T	C	0.082197	0.0111	1.26E-13
rs12704290	7	86427626	A	G	-0.10611	0.0168	2.59E-10
rs6466055	7	1.05E+08	A	C	0.068798	0.0114	1.59E-09
rs13240464	7	1.11E+08	T	C	0.080704	0.0116	3.12E-12
rs7801375	7	1.32E+08	A	G	-0.083	0.015	2.88E-08
rs17529963	7	1.37E+08	T	C	0.0629	0.0114	3.24E-08
rs10108725	8	4191202	T	C	0.073204	0.0133	3.32E-08
rs73191547	8	10033425	A	T	-0.0669	0.0115	6.13E-09
rs17687067	8	17036201	A	C	-0.0763	0.0139	4.49E-08
rs73229090	8	27442127	A	C	-0.0995	0.0177	1.95E-08
rs13261481	8	60701801	T	G	0.062402	0.011	1.66E-08
rs7819570	8	89588626	T	G	0.076498	0.014	4.47E-08
rs36068923	8	1.11E+08	A	G	-0.0835	0.0134	4.14E-10
rs4129585	8	1.43E+08	A	C	0.079301	0.0109	3.61E-13
rs11139497	9	84739941	A	T	0.0656	0.0118	2.65E-08

Table B18. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to systemising and schizophrenia.

Systemising instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**β**	**SE**	**P**
rs7567262	chr2	54057363	T	C	0.81816	0.15915	2.74E-07
rs4146336	chr3	1.17E+08	C	A	-0.72824	0.130795	2.58E-08
rs7140695	chr14	65929132	T	C	0.680268	0.134573	4.31E-07
rs8045744	chr16	6284566	T	G	-0.64915	0.128407	4.3E-07
rs1559586	chr18	70727724	C	A	-0.69696	0.127662	4.78E-08
Schizophrenia instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs7002992	8	1.04E+08	T	C	0.0484	0.0083	4.48E-09
rs6715366	2	2327295	G	A	-0.0551	0.0094	4.23E-09
rs77463171	16	66942206	C	T	-0.1465	0.0263	2.41E-08
rs113113059	6	43160375	T	C	0.061396	0.0092	2.29E-11
rs10873538	14	1.04E+08	T	G	-0.0632	0.0082	9.59E-15
rs61920311	12	14423294	A	C	0.046101	0.0082	1.75E-08
rs2532240	17	44265839	C	T	0.052099	0.0083	2.72E-10
rs55938136	17	43798360	A	G	0.0615	0.0108	1.23E-08
rs6588168	1	66324118	C	T	-0.0489	0.0079	5.94E-10
rs12126806	1	2.01E+08	C	T	0.049904	0.009	2.89E-08
rs4915203	1	2E+08	A	G	0.050398	0.0085	3.3E-09
rs1658810	2	2.01E+08	C	T	0.080704	0.0096	3.54E-17
rs140001745	2	2.01E+08	T	C	0.106996	0.0155	5.13E-12
rs56335113	1	30427639	A	G	0.066602	0.0084	3.15E-15
rs581459	1	36375110	C	T	0.0743	0.0123	1.32E-09
rs1915019	8	89283689	A	G	0.057599	0.0092	3.43E-10
rs308697	3	1.61E+08	C	A	0.046903	0.0079	3.35E-09
rs13090130	3	1.62E+08	G	A	0.051396	0.0079	9.92E-11
rs2102949	12	1.24E+08	G	A	0.086003	0.0087	3.18E-23
rs75482067	12	1.23E+08	G	A	-0.0876	0.0148	3.06E-09
rs2649999	12	1.21E+08	T	C	0.049504	0.0082	1.28E-09
rs12311848	12	1.24E+08	A	G	-0.049	0.0087	1.65E-08
rs2686386	12	1.22E+08	C	T	0.054801	0.0096	1.26E-08
rs167924	3	1.07E+08	A	G	-0.0506	0.0089	1.33E-08
rs72943392	11	81178838	G	C	-0.0532	0.0094	1.44E-08
rs9975024	21	16439883	A	G	-0.0483	0.008	1.78E-09
rs75968099	3	36858583	C	T	-0.0582	0.0089	5.16E-11
rs1506297	3	30072307	T	C	0.051102	0.0091	1.98E-08
rs6538539	12	95195293	G	T	0.047704	0.0077	5.63E-10
rs7953300	12	92254654	G	T	-0.0449	0.0082	3.94E-08
rs7312697	12	29933069	T	C	-0.0533	0.0081	4.85E-11
rs28454198	4	80204001	G	C	0.0486	0.0081	1.88E-09
rs10086619	8	1.12E+08	A	G	-0.0691	0.0104	3.3E-11

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs4702	15	91426560	G	A	0.080298	0.0081	2.15E-23
rs11210892	1	44100084	G	A	0.0675	0.0081	1.18E-16
rs11136325	8	1.45E+08	G	A	0.053	0.009	3.3E-09
rs13262595	8	1.43E+08	A	G	0.069097	0.0079	2.21E-18
rs12301769	12	72231313	A	C	-0.08379	0.014	1.93E-09
rs2022265	6	84293271	A	G	0.048504	0.0077	3.74E-10
rs10985811	9	1.01E+08	T	C	-0.0545	0.0098	2.53E-08
rs4793888	17	55737740	G	A	-0.0609	0.0097	3.63E-10
rs2381411	9	36319928	T	C	-0.045	0.0079	1.28E-08
rs39967	5	57744788	T	C	-0.0604	0.0107	1.87E-08
rs12943566	17	2157774	A	G	-0.0525	0.0083	2.29E-10
rs3752827	17	1265325	T	A	0.052203	0.0084	6.33E-10
rs77502336	11	1.23E+08	G	C	-0.0545	0.0082	3.45E-11
rs1940171	11	1.25E+08	A	G	0.073501	0.0099	8.87E-14
rs10515678	5	1.52E+08	C	T	0.065703	0.0095	4.46E-12
rs11740474	5	1.54E+08	A	T	-0.0504	0.0086	4.46E-09
rs12652777	5	1.56E+08	T	C	0.045403	0.0079	1.06E-08
rs154433	16	58659808	G	A	0.047198	0.0084	2.38E-08
rs10957321	8	65605878	G	A	-0.0482	0.0077	4.18E-10
rs298216	8	65293195	C	G	-0.0727	0.0123	3.45E-09
rs6984242	8	60700469	G	A	0.052697	0.0078	1.5E-11
rs1454606	4	33642614	C	T	-0.0716	0.0108	2.9E-11
rs58120505	7	2029867	T	C	0.083302	0.0078	1.8E-26
rs11972718	7	8549187	C	G	-0.04949	0.0088	1.57E-08
rs17731	10	3821561	G	A	-0.0575	0.0079	3.76E-13
rs4766428	12	1.11E+08	C	T	-0.0721	0.0085	2.61E-17
rs2387414	19	51034243	G	C	-0.0515	0.0084	8.01E-10
rs2304205	19	50168927	A	C	0.070403	0.0092	2.38E-14
rs758749	19	57189718	C	T	-0.0615	0.0112	4.66E-08
rs9312586	4	1.77E+08	A	G	-0.0908	0.014	8.14E-11
rs41533650	4	1.77E+08	G	A	-0.0724	0.0097	8.69E-14
rs61405217	4	1.7E+08	C	T	0.052004	0.0079	5.39E-11
rs459391	21	22120508	T	C	0.056598	0.01	1.54E-08
rs6943762	7	86403263	T	C	0.103296	0.0124	6.3E-17
rs2252074	7	1.05E+08	T	G	-0.0603	0.0078	1.27E-14
rs1510136	4	1.44E+08	A	G	0.052602	0.0093	1.39E-08
rs61828917	1	1.74E+08	C	T	0.067603	0.011	7.95E-10
rs16851048	1	1.77E+08	T	C	-0.0676	0.0097	3.06E-12
rs12363019	11	24374545	T	A	-0.0516	0.0082	2.58E-10
rs10767734	11	28642381	C	T	0.050902	0.0082	5.62E-10
rs778371	2	2.34E+08	A	G	-0.0741	0.0089	1.1E-16
rs11647188	16	82648514	A	G	0.044495	0.0081	3.75E-08
rs11076631	16	89877975	A	G	0.052203	0.0088	2.59E-09
rs6919146	6	1.65E+08	T	G	-0.0488	0.0085	8.42E-09

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs2456020	15	78868398	C	T	0.068499	0.0088	5.35E-15
rs28521069	4	1.19E+08	C	T	-0.0457	0.0083	3.78E-08
rs10117	5	1.38E+08	G	A	0.055501	0.0082	9.54E-12
rs9687282	5	1.39E+08	T	G	-0.0486	0.0086	1.66E-08
rs28490262	3	80814042	G	C	0.053199	0.0086	6.68E-10
rs13195636	6	27509493	A	C	0.210504	0.0159	6.55E-40
rs356183	4	90626098	G	C	0.044304	0.008	3.37E-08
rs13230189	7	1.37E+08	C	T	0.071902	0.0081	1.04E-18
rs35792732	7	1.33E+08	C	T	0.060399	0.0106	1.08E-08
rs1593304	7	1.32E+08	A	G	-0.0642	0.0101	2.37E-10
rs10947452	6	33803752	T	C	-0.0448	0.0081	3.69E-08
rs9461856	6	33395199	G	A	-0.0639	0.0078	3.23E-16
rs3131295	6	32173257	G	A	0.0599	0.008	9.97E-14
rs11693094	2	1.86E+08	C	T	0.057297	0.0078	2.2E-13
rs12129573	1	73768366	C	A	-0.0681	0.0082	1.42E-16
rs1121296	1	72174197	T	C	0.047303	0.008	3.74E-09
rs11619756	13	44329004	G	A	0.047103	0.0082	7.97E-09
rs215483	4	23377121	G	A	-0.0507	0.0084	1.59E-09
rs4697446	4	24269622	G	T	-0.0446	0.0079	1.67E-08
rs7647398	3	1.81E+08	C	T	0.085003	0.01	2.21E-17
rs9882532	3	16865845	T	C	-0.05309	0.0087	8.57E-10
rs6577597	3	17871326	A	G	-0.0526	0.0085	5.52E-10
rs3739554	9	1.3E+08	A	G	-0.0576	0.0103	2.26E-08
rs5995756	22	40000313	T	C	0.056399	0.0084	2.38E-11
rs9607782	22	41587556	T	A	-0.0725	0.0097	7.1E-14
rs4822076	22	42364057	C	T	-0.0597	0.0089	1.94E-11
rs1451488	2	2E+08	A	G	-0.066	0.0079	6.72E-17
rs13032111	2	1.94E+08	T	G	0.043203	0.0077	2.15E-08
rs2914983	2	1.98E+08	A	G	0.062796	0.0081	1.1E-14
rs10190027	2	37190726	C	T	-0.04971	0.0089	2.57E-08
rs3770752	2	37576136	A	G	0.057401	0.0086	2.86E-11
rs6925079	6	64946311	T	C	-0.0448	0.0081	3.58E-08
rs6065094	20	37453194	A	G	-0.0634	0.0082	1.41E-14
rs13219424	6	1.28E+08	C	T	0.045996	0.0084	4.52E-08
rs60135207	3	71563777	G	T	0.049599	0.0087	1.27E-08
rs12991836	2	1.45E+08	A	C	-0.0584	0.008	2.72E-13
rs16825349	2	1.46E+08	A	G	-0.0704	0.0104	1.32E-11
rs10777187	12	89940502	T	C	0.050902	0.0092	2.82E-08
rs12713008	2	48503561	G	A	0.043002	0.0078	3.05E-08
rs500102	9	77358745	T	C	0.043299	0.0079	4.15E-08
rs72761691	9	1.35E+08	A	C	-0.0664	0.0116	1.07E-08
rs2078266	9	1.38E+08	A	G	0.0618	0.0113	4.86E-08
rs79668541	10	1.05E+08	C	T	0.120703	0.0121	2.11E-23
rs79780963	10	1.05E+08	C	T	0.118396	0.0122	2.53E-22

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs1856507	6	73157926	C	A	0.050398	0.008	3E-10
rs9454727	6	70003389	A	G	0.054801	0.0098	1.93E-08
rs578470	12	50463325	T	C	-0.0462	0.0083	2.33E-08
rs61937595	12	57682956	C	T	0.121996	0.0158	1.32E-14
rs73292401	17	12875908	T	A	-0.0659	0.0103	1.82E-10
rs9891739	17	19942177	C	T	-0.045	0.008	2.18E-08
rs4073003	17	19148305	A	G	0.080603	0.0116	4.2E-12
rs8055219	16	13753384	G	A	-0.0672	0.0095	1.57E-12
rs252812	5	1.07E+08	A	G	0.053	0.0093	1.3E-08
rs35164357	5	1.09E+08	C	T	-0.0605	0.0096	2.59E-10
rs10861176	12	1.05E+08	G	A	-0.0504	0.0086	5.23E-09
rs3764002	12	1.09E+08	C	T	-0.0517	0.0086	1.65E-09
rs2455415	13	38860697	C	T	-0.04759	0.0081	3.43E-09
rs1924377	13	38362106	G	C	0.046903	0.0082	8.71E-09
rs55929115	3	1.18E+08	T	A	0.072004	0.013	3.21E-08
rs10035564	5	45252500	A	G	-0.06481	0.0081	1.65E-15
rs1540840	14	99733384	G	C	0.054999	0.009	1.04E-09
rs17194490	3	2547786	G	T	-0.0781	0.0116	1.85E-11
rs61857878	10	92789488	A	T	0.0599	0.0099	1.46E-09
rs2514218	11	1.13E+08	C	T	0.069899	0.009	6.46E-15
rs17644050	2	1.56E+08	G	C	-0.0538	0.0098	4.02E-08
rs79210963	7	24717969	T	C	-0.0863	0.0129	2.58E-11
rs7811417	7	21534152	T	C	0.048304	0.0081	2.17E-09
rs12285419	11	46343189	C	A	-0.0812	0.01	3.73E-16
rs634940	6	93077500	G	T	-0.0649	0.0098	2.88E-11
rs6925964	6	96475894	A	T	0.097499	0.0176	3.19E-08
rs9304548	18	27500959	C	A	0.060003	0.0089	1.9E-11
rs2710323	3	52815905	T	C	0.074597	0.0077	5.92E-22
rs11917680	3	50471408	G	T	0.056702	0.0091	4.17E-10
rs7432375	3	1.36E+08	G	A	0.063801	0.0082	5.32E-15
rs2238304	15	89843950	A	T	0.049599	0.0078	1.73E-10
rs4779050	15	83368738	T	G	0.049304	0.0079	4.18E-10
rs11638554	15	85148231	T	G	0.064504	0.0089	3.62E-13
rs6673880	1	2373168	A	G	-0.061	0.0086	1.32E-12
rs11121172	1	8418644	C	A	0.054602	0.0089	7.15E-10
rs11122119	1	6768856	C	A	-0.0453	0.0081	2.31E-08
rs9597388	13	56928696	G	A	0.066798	0.0101	3.24E-11
rs9569820	13	58702746	G	T	-0.0676	0.0109	6.56E-10
rs7938083	11	57493622	C	A	-0.0524	0.0087	1.6E-09
rs10069930	5	1.4E+08	T	A	0.048304	0.0079	9.43E-10
rs6479487	9	96237373	T	G	-0.0587	0.0103	1.37E-08
rs7609876	3	1.77E+08	T	C	-0.0512	0.0089	9.4E-09
rs2224086	1	1.15E+08	C	A	-0.0577	0.0103	2.09E-08
rs144821294	19	2155136	C	T	-0.138	0.0242	1.22E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs72974269	2	2.25E+08	C	T	0.052099	0.0083	2.76E-10
rs35351411	15	61872197	A	C	-0.0573	0.0079	3.13E-13
rs3814883	16	29994922	C	T	0.060898	0.0079	8.82E-15
rs72723227	5	7245664	G	A	0.047999	0.0082	4.58E-09
rs1463209	12	39518293	C	T	0.047704	0.0081	3.34E-09
rs2190864	14	72416219	T	C	0.066097	0.008	1.12E-16
rs2206956	6	1.47E+08	G	A	-0.0462	0.0078	2.51E-09
rs9390083	6	1.44E+08	C	G	-0.05719	0.0103	2.95E-08
rs1858999	19	19497669	C	G	0.060502	0.0081	7.97E-14
rs72986630	19	11849736	C	T	-0.1117	0.0177	3.07E-10
rs322128	19	11402416	C	T	-0.0567	0.0095	2.08E-09
rs12431743	14	84673716	G	A	-0.0456	0.008	1.26E-08
rs9926049	16	9939960	C	A	-0.0556	0.0088	3.16E-10
rs8048039	16	4498486	A	T	0.049	0.0083	4.35E-09
rs10127983	1	1.54E+08	C	T	-0.0463	0.0084	3.11E-08
rs12138231	1	1.5E+08	T	A	-0.0671	0.0116	7.21E-09
rs7915131	10	64418656	C	T	0.042695	0.0078	4.94E-08
rs13107325	4	1.03E+08	C	T	-0.1587	0.0168	2.9E-21
rs6839635	4	1.04E+08	C	A	-0.0432	0.0079	3.87E-08
rs2153960	6	1.09E+08	G	A	0.051396	0.0084	9.22E-10
rs117799466	15	34659517	G	C	-0.0481	0.0087	3.86E-08
rs6504163	17	61545779	C	T	-0.0492	0.0082	1.87E-09
rs6732355	2	1.05E+08	C	A	-0.0587	0.0094	4.36E-10
rs2119242	10	21344773	G	A	-0.0602	0.0106	1.34E-08
rs11807834	1	2.3E+08	G	A	-0.053	0.0093	1.12E-08
rs11587347	1	2.39E+08	C	G	-0.1028	0.0139	1.5E-13
rs145071536	1	2.44E+08	T	C	-0.0817	0.0119	5.76E-12
rs10148671	14	29469373	T	C	-0.0479	0.0083	6.82E-09
rs6482437	10	18726326	A	C	-0.10471	0.0135	1.05E-14
rs115325222	5	88854539	A	G	0.090398	0.0151	1.93E-09
rs6969410	7	1.1E+08	T	G	0.055501	0.0083	1.9E-11
rs38752	7	1.11E+08	T	G	0.060003	0.0081	1.08E-13
rs1589726	7	79348201	C	T	0.077896	0.0137	1.2E-08
rs10238960	7	70773271	C	T	-0.0482	0.0084	7.65E-09
rs2944821	7	71795998	G	C	0.047799	0.008	1.9E-09
rs7701440	5	60620980	T	C	-0.0638	0.008	1.86E-15
rs73229090	8	27442127	C	A	0.102602	0.0142	4.34E-13
rs3808581	8	26250047	G	A	-0.06699	0.0097	3.82E-12
rs2717003	2	58143438	A	G	-0.07529	0.008	2.76E-21
rs12969453	18	52751708	A	G	0.054299	0.0078	3.53E-12
rs715170	18	53795514	C	T	0.064701	0.009	7.4E-13
rs4632195	18	50746748	C	T	-0.0498	0.0084	2.73E-09
rs9636107	18	53200117	A	G	-0.0609	0.0081	5.72E-14
rs17571951	14	30017039	T	C	-0.0645	0.0105	7.89E-10

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs12883788	14	33303540	C	T	-0.0543	0.0079	8.43E-12
rs8104557	19	31030189	T	C	-0.0604	0.011	3.76E-08
rs3810450	19	36530562	T	C	0.092497	0.016	8.27E-09
rs505061	9	22767164	C	A	-0.0499	0.0077	1.03E-10
rs9545047	13	79859456	A	C	0.053797	0.0081	3.05E-11
rs58950470	11	65383755	G	T	-0.0493	0.0086	1.1E-08
rs6546857	2	73837955	A	G	-0.0603	0.0101	2.8E-09
rs11897811	2	76267139	C	T	-0.0575	0.0102	1.49E-08
rs999494	2	73157395	C	T	0.057599	0.0101	1.04E-08
rs1198588	1	98552832	A	T	-0.0964	0.0103	7.88E-21
rs59519965	1	97168334	G	T	-0.0582	0.0098	3.36E-09
rs72728416	1	97834691	A	G	-0.0598	0.0087	4.99E-12
rs337718	18	69774278	T	C	0.0492	0.0084	4.39E-09
rs6588355	1	50113591	T	C	0.049504	0.009	3.65E-08
rs56205728	15	40567237	G	A	-0.0575	0.0093	5.43E-10
rs2929278	15	44250313	C	T	0.061904	0.0091	8.5E-12
rs9287971	2	1.75E+08	G	A	-0.0458	0.0083	3.82E-08
rs62184960	2	1.73E+08	C	T	0.069797	0.0122	1.08E-08
rs6430492	2	1.35E+08	G	A	0.057703	0.0094	6.72E-10
rs331395	5	91006918	C	G	-0.0549	0.009	1.27E-09
rs4672366	2	60389362	A	T	0.049799	0.0087	1.07E-08
rs10503253	8	4180844	C	A	-0.0602	0.0091	4.37E-11
rs72980087	18	77632194	G	A	-0.0644	0.0079	4.06E-16
rs7238071	18	77579812	A	G	-0.0629	0.0084	9.29E-14
rs4937935	11	1.35E+08	A	T	-0.0539	0.0081	2.3E-11
rs1440480	11	1.34E+08	A	G	0.057504	0.0086	2.52E-11
rs10894308	11	1.31E+08	G	A	0.047704	0.0079	1.36E-09
rs4936215	11	1.34E+08	A	G	0.082796	0.0104	1.86E-15
rs1939514	11	1.33E+08	T	C	0.055198	0.0077	1.06E-12
rs79445414	8	33863561	T	C	-0.1235	0.0222	2.63E-08
rs7816998	8	38257506	G	A	0.057797	0.0092	3.11E-10
rs35045093	7	1.28E+08	A	C	0.056598	0.0103	3.36E-08
rs61786047	1	29032580	G	A	0.078802	0.0135	4.91E-09
rs6010045	22	51103091	T	C	-0.0477	0.0085	1.82E-08
rs704364	3	63874734	A	G	0.050303	0.0082	8.41E-10
rs9813516	3	60293004	G	A	-0.0513	0.0084	1.25E-09
rs498591	9	14509105	A	T	-0.0679	0.0111	9.59E-10
rs2890914	9	10239181	A	G	-0.0432	0.0077	2.31E-08
rs10774034	12	2330458	C	T	-0.08329	0.0085	7.1E-23
rs12712510	2	22749726	T	C	0.051501	0.0084	9.34E-10
rs141216273	2	25599172	C	A	-0.1247	0.0228	4.49E-08
rs12474906	2	28033538	A	C	0.056796	0.0095	2.2E-09
rs2909457	2	1.63E+08	G	A	0.045805	0.0083	3.09E-08
rs35734242	4	706700	T	C	-0.0499	0.008	3.93E-10

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs11696755	20	48105317	T	C	-0.0653	0.0104	2.99E-10

Table B19. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to systemising and psychotic experiences.

Systemising instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**β**	**SE**	**P**
rs7567262	chr2	54057363	T	C	0.81816	0.15915	2.74E-07
rs4146336	chr3	1.17E+08	C	A	-0.72824	0.130795	2.58E-08
rs7140695	chr14	65929132	T	C	0.680268	0.134573	4.31E-07
rs8045744	chr16	6284566	T	G	-0.64915	0.128407	4.3E-07
rs1559586	chr18	70727724	C	A	-0.69696	0.127662	4.78E-08

Table B20. Effect sizes, standard errors and p-values of genetic instruments used for the analyses investigating causal links between genetic liability to systemising and schizophrenia (European ancestry only- Ripke et al., 2014).

Systemising instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**β**	**SE**	**P**
rs7567262	chr2	54057363	T	C	0.81816	0.15915	2.74E-07
rs4146336	chr3	1.17E+08	C	A	-0.72824	0.130795	2.58E-08
rs7140695	chr14	65929132	T	C	0.680268	0.134573	4.31E-07
rs8045744	chr16	6284566	T	G	-0.64915	0.128407	4.3E-07
rs1559586	chr18	70727724	C	A	-0.69696	0.127662	4.78E-08
Schizophrenia instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs4648845	1	2387101	T	C	0.067201	0.0119	1.74E-08
rs7893279	10	18745105	T	G	0.1124	0.0175	1.24E-10
rs301797	1	8487323	A	C	0.066097	0.0116	1.2E-08
rs11191419	10	1.05E+08	A	T	-0.1016	0.0118	6.69E-18
rs79780963	10	1.05E+08	T	C	-0.1597	0.0195	2.79E-16
rs1498232	1	30433951	T	C	0.072004	0.0118	1.21E-09
rs11210892	1	44100084	A	G	-0.0678	0.0115	3.42E-09
rs35998080	1	73278615	T	G	0.069004	0.0112	6.95E-10
rs1702294	1	98501984	T	C	-0.1184	0.0138	1.03E-17
rs11027857	11	24403620	A	G	0.063998	0.0109	3.67E-09
rs35324223	11	46402852	A	G	-0.09199	0.0145	2.04E-10
rs2514218	11	1.13E+08	T	C	-0.07221	0.0116	4.64E-10
rs55661361	11	1.25E+08	A	G	-0.07881	0.0116	1.04E-11
rs10791097	11	1.31E+08	T	G	0.0766	0.0109	2.05E-12
rs75059851	11	1.34E+08	A	G	0.091302	0.0136	2.18E-11
rs12062861	1	1.5E+08	A	G	-0.0911	0.0149	9.66E-10
rs1024582	12	2402246	A	G	0.098904	0.0115	6.27E-18
rs679087	12	29917265	A	C	-0.0642	0.0116	3.28E-08
rs12826178	12	57622371	T	G	-0.16821	0.0244	5.7E-12
rs4766428	12	1.11E+08	T	C	0.069395	0.0112	6.12E-10
rs1615350	12	1.24E+08	T	C	-0.0851	0.0123	4.26E-12
rs10803138	1	2.44E+08	A	G	-0.07221	0.0126	1.13E-08
rs1191551	14	30000405	T	G	0.071697	0.0131	4.21E-08
rs67981189	14	71472226	A	G	-0.0698	0.0118	3.75E-09
rs2332700	14	72417326	C	G	0.0771	0.0125	7.38E-10
rs2693698	14	99719219	A	G	-0.06171	0.0111	2.99E-08
rs12887734	14	1.04E+08	T	G	0.088304	0.0121	3.72E-13
rs2414718	15	61863133	A	G	0.069797	0.011	1.98E-10
rs28681284	15	78908565	T	C	-0.1016	0.0141	6.35E-13
rs783540	15	83254708	A	G	-0.0599	0.011	4.77E-08
rs12902973	15	85105982	C	G	-0.0791	0.0122	8.83E-11
rs4702	15	91426560	A	G	-0.08051	0.0115	2.62E-12
rs9922678	16	9946319	A	G	0.068397	0.0118	6.18E-09

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs8055219	16	13753384	A	G	0.076998	0.0127	1.45E-09
rs12691307	16	29939877	A	G	0.071902	0.0113	2.03E-10
rs12932476	16	63709630	C	G	0.059702	0.0109	4.62E-08
rs4523957	17	2208899	T	G	0.069703	0.0115	1.4E-09
rs11658257	17	17956459	C	G	-0.0662	0.0115	8.34E-09
rs11874716	18	52750688	T	G	0.067201	0.011	1.01E-09
rs9636107	18	53200117	A	G	-0.0796	0.0108	2.17E-13
rs9966779	18	53620456	T	C	-0.1329	0.0231	8.56E-09
rs715170	18	53795514	T	C	-0.0669	0.0122	4.65E-08
rs72986630	19	11849736	T	C	0.1459	0.0266	4.12E-08
rs2905426	19	19478022	T	G	-0.0677	0.0115	4.07E-09
rs2053079	19	30987423	A	G	-0.0718	0.0127	1.74E-08
rs2103655	20	37425958	A	G	0.0766	0.0119	1.24E-10
rs1509378	2	22754466	A	G	0.0692	0.0119	5.39E-09
rs11682175	2	57987593	T	C	-0.0735	0.0109	1.58E-11
rs6430095	2	1.46E+08	A	G	0.0798	0.0145	3.4E-08
rs76355118	2	1.49E+08	A	G	-0.1544	0.0278	2.78E-08
rs2909457	2	1.63E+08	A	G	-0.0597	0.0109	4.25E-08
rs11693094	2	1.86E+08	T	C	-0.0736	0.011	2.17E-11
rs59979824	2	1.94E+08	A	C	-0.071	0.0119	2.73E-09
rs281768	2	2.01E+08	A	T	0.104198	0.0137	2.64E-14
rs6434928	2	1.98E+08	A	G	-0.0787	0.0116	1.17E-11
rs5995756	22	40000313	T	C	0.072497	0.0109	2.91E-11
rs9607782	22	41587556	A	T	0.088697	0.0128	3.98E-12
rs28733092	22	42537115	T	C	0.070999	0.0121	4.36E-09
rs11685299	2	2.25E+08	A	C	-0.0662	0.0117	1.49E-08
rs7601312	2	2.29E+08	A	G	-0.059	0.0108	4.68E-08
rs6704768	2	2.34E+08	A	G	-0.0766	0.0109	2.06E-12
rs17194490	3	2547786	T	G	0.0966	0.0148	6.38E-11
rs75968099	3	36858583	T	C	0.080104	0.0114	2.31E-12
rs2535627	3	52845105	T	C	0.070403	0.0109	1.17E-10
rs832190	3	63842629	T	C	-0.0699	0.0113	5.73E-10
rs6439649	3	1.36E+08	T	G	0.070999	0.0111	1.37E-10
rs34796896	3	1.81E+08	A	G	-0.0822	0.0135	1.23E-09
rs215411	4	23423603	A	T	0.0692	0.0115	1.68E-09
rs35225200	4	1.03E+08	A	C	-0.14479	0.0203	9.56E-13
rs1106568	4	1.77E+08	A	G	-0.0694	0.0125	2.85E-08
rs17073903	4	1.84E+08	A	G	-0.08141	0.0148	3.92E-08
rs4391122	5	60598543	A	G	-0.078	0.0109	8.9E-13
rs16867576	5	88746331	A	G	0.095801	0.017	1.61E-08
rs3849046	5	1.38E+08	T	C	0.062496	0.0109	1.04E-08
rs111294930	5	1.52E+08	A	G	0.087699	0.0143	9.29E-10
rs76091702	5	1.52E+08	T	C	0.129299	0.0236	4.49E-08
rs11740474	5	1.54E+08	A	T	-0.06269	0.0112	2E-08

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs13437595	6	29763308	T	C	0.262203	0.0392	2.19E-11
rs13217619	6	28306671	T	C	0.219698	0.0195	1.44E-29
rs185053056	6	28680776	T	C	-0.2546	0.0303	4E-17
rs145607970	6	32624017	A	C	-0.1679	0.026	1.16E-10
rs9274538	6	32634661	A	G	0.097099	0.0133	3.43E-13
rs116334170	6	32598500	A	G	-0.0996	0.0144	4.54E-12
rs9461856	6	33395199	A	G	0.074996	0.0109	6.52E-12
rs1339227	6	73155701	T	C	-0.0633	0.0114	3.06E-08
rs3798869	6	84328660	A	G	-0.0668	0.011	1.09E-09
rs117074560	6	96459651	T	C	-0.1566	0.0277	1.66E-08
rs58120505	7	2029867	T	C	0.082197	0.0111	1.26E-13
rs12704290	7	86427626	A	G	-0.10611	0.0168	2.59E-10
rs6466055	7	1.05E+08	A	C	0.068798	0.0114	1.59E-09
rs13240464	7	1.11E+08	T	C	0.080704	0.0116	3.12E-12
rs7801375	7	1.32E+08	A	G	-0.083	0.015	2.88E-08
rs17529963	7	1.37E+08	T	C	0.0629	0.0114	3.24E-08
rs10108725	8	4191202	T	C	0.073204	0.0133	3.32E-08
rs73191547	8	10033425	A	T	-0.0669	0.0115	6.13E-09
rs17687067	8	17036201	A	C	-0.0763	0.0139	4.49E-08
rs73229090	8	27442127	A	C	-0.0995	0.0177	1.95E-08
rs13261481	8	60701801	T	G	0.062402	0.011	1.66E-08
rs7819570	8	89588626	T	G	0.076498	0.014	4.47E-08
rs36068923	8	1.11E+08	A	G	-0.0835	0.0134	4.14E-10
rs4129585	8	1.43E+08	A	C	0.079301	0.0109	3.61E-13
rs11139497	9	84739941	A	T	0.0656	0.0118	2.65E-08

Table B21. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to autism (excluding ID cases) and schizophrenia.

Autism no ID instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs529507	11	1.32E+08	A	G	-0.1354	0.0241	1.88E-08
rs574626	18	55882192	T	C	0.095101	0.0181	1.54E-07
rs1402807	1	96597055	T	C	0.092497	0.018	2.73E-07
rs8182800	20	21531772	A	G	0.124101	0.0203	9.02E-10
rs13012522	2	1.4E+08	T	G	0.096301	0.0177	5.73E-08
rs10197246	2	2.02E+08	T	C	0.100298	0.0186	6.94E-08
rs148587110	3	20641966	T	C	-0.4697	0.0907	2.21E-07
rs114489105	4	1.32E+08	T	G	0.199596	0.0384	2.05E-07
rs4916723	5	87854395	A	C	-0.09	0.0173	1.9E-07
rs6964453	7	78210447	A	T	-0.107	0.02	8.16E-08
Schizophrenia instruments							
CHR	**SNP**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
8	rs7002992	1.04E+08	T	C	0.0484	0.0083	4.48E-09
2	rs6715366	2327295	G	A	-0.0551	0.0094	4.23E-09
16	rs77463171	66942206	C	T	-0.1465	0.0263	2.41E-08
6	rs113113059	43160375	T	C	0.061396	0.0092	2.29E-11
14	rs10873538	1.04E+08	T	G	-0.0632	0.0082	9.59E-15
12	rs61920311	14423294	A	C	0.046101	0.0082	1.75E-08
17	rs2532240	44265839	C	T	0.052099	0.0083	2.72E-10
1	rs6588168	66324118	C	T	-0.0489	0.0079	5.94E-10
1	rs12126806	2.01E+08	C	T	0.049904	0.009	2.89E-08
1	rs4915203	2E+08	A	G	0.050398	0.0085	3.30E-09
2	rs1658810	2.01E+08	C	T	0.080704	0.0096	3.54E-17
2	rs140001745	2.01E+08	T	C	0.106996	0.0155	5.13E-12
1	rs56335113	30427639	A	G	0.066602	0.0084	3.15E-15
1	rs581459	36375110	C	T	0.0743	0.0123	1.32E-09
8	rs1915019	89283689	A	G	0.057599	0.0092	3.43E-10
3	rs308697	1.61E+08	C	A	0.046903	0.0079	3.35E-09
3	rs13090130	1.62E+08	G	A	0.051396	0.0079	9.92E-11
12	rs2102949	1.24E+08	G	A	0.086003	0.0087	3.18E-23
12	rs75482067	1.23E+08	G	A	-0.0876	0.0148	3.06E-09
12	rs2649999	1.21E+08	T	C	0.049504	0.0082	1.28E-09
12	rs12311848	1.24E+08	A	G	-0.049	0.0087	1.65E-08
12	rs2686386	1.22E+08	C	T	0.054801	0.0096	1.26E-08
3	rs167924	1.07E+08	A	G	-0.0506	0.0089	1.33E-08
11	rs72943392	81178838	G	C	-0.0532	0.0094	1.44E-08
21	rs9975024	16439883	A	G	-0.0483	0.008	1.78E-09
3	rs75968099	36858583	C	T	-0.0582	0.0089	5.16E-11
3	rs1506297	30072307	T	C	0.051102	0.0091	1.98E-08
12	rs6538539	95195293	G	T	0.047704	0.0077	5.63E-10

Schizophrenia instruments (continued)							
CHR	**SNP**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
12	rs7953300	92254654	G	T	-0.0449	0.0082	3.94E-08
2	rs7575796	97746526	A	G	0.0969	0.0171	1.57E-08
12	rs7312697	29933069	T	C	-0.0533	0.0081	4.85E-11
4	rs28454198	80204001	G	C	0.0486	0.0081	1.88E-09
8	rs10086619	1.12E+08	A	G	-0.0691	0.0104	3.30E-11
15	rs4702	91426560	G	A	0.080298	0.0081	2.15E-23
1	rs11210892	44100084	G	A	0.0675	0.0081	1.18E-16
8	rs11136325	1.45E+08	G	A	0.053	0.009	3.30E-09
8	rs13262595	1.43E+08	A	G	0.069097	0.0079	2.21E-18
12	rs12301769	72231313	A	C	-0.08379	0.014	1.93E-09
6	rs2022265	84293271	A	G	0.048504	0.0077	3.74E-10
9	rs10985811	1.01E+08	T	C	-0.0545	0.0098	2.53E-08
17	rs4793888	55737740	G	A	-0.0609	0.0097	3.63E-10
9	rs2381411	36319928	T	C	-0.045	0.0079	1.28E-08
5	rs39967	57744788	T	C	-0.0604	0.0107	1.87E-08
17	rs12943566	2157774	A	G	-0.0525	0.0083	2.29E-10
17	rs3752827	1265325	T	A	0.052203	0.0084	6.33E-10
11	rs77502336	1.23E+08	G	C	-0.0545	0.0082	3.45E-11
11	rs1940171	1.25E+08	A	G	0.073501	0.0099	8.87E-14
5	rs10515678	1.52E+08	C	T	0.065703	0.0095	4.46E-12
5	rs11740474	1.54E+08	A	T	-0.0504	0.0086	4.46E-09
5	rs12652777	1.56E+08	T	C	0.045403	0.0079	1.06E-08
16	rs154433	58659808	G	A	0.047198	0.0084	2.38E-08
8	rs10957321	65605878	G	A	-0.0482	0.0077	4.18E-10
8	rs298216	65293195	C	G	-0.0727	0.0123	3.45E-09
8	rs6984242	60700469	G	A	0.052697	0.0078	1.50E-11
4	rs1454606	33642614	C	T	-0.0716	0.0108	2.90E-11
7	rs58120505	2029867	T	C	0.083302	0.0078	1.80E-26
7	rs11972718	8549187	C	G	-0.04949	0.0088	1.57E-08
10	rs17731	3821561	G	A	-0.0575	0.0079	3.76E-13
12	rs4766428	1.11E+08	C	T	-0.0721	0.0085	2.61E-17
19	rs2387414	51034243	G	C	-0.0515	0.0084	8.01E-10
19	rs2304205	50168927	A	C	0.070403	0.0092	2.38E-14
19	rs758749	57189718	C	T	-0.0615	0.0112	4.66E-08
4	rs9312586	1.77E+08	A	G	-0.0908	0.014	8.14E-11
4	rs41533650	1.77E+08	G	A	-0.0724	0.0097	8.69E-14
4	rs61405217	1.7E+08	C	T	0.052004	0.0079	5.39E-11
21	rs459391	22120508	T	C	0.056598	0.01	1.54E-08
7	rs6943762	86403263	T	C	0.103296	0.0124	6.30E-17
7	rs2252074	1.05E+08	T	G	-0.0603	0.0078	1.27E-14
4	rs1510136	1.44E+08	A	G	0.052602	0.0093	1.39E-08
1	rs61828917	1.74E+08	C	T	0.067603	0.011	7.95E-10
1	rs16851048	1.77E+08	T	C	-0.0676	0.0097	3.06E-12
11	rs12363019	24374545	T	A	-0.0516	0.0082	2.58E-10

Schizophrenia instruments (continued)							
CHR	**SNP**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
11	rs10767734	28642381	C	T	0.050902	0.0082	5.62E-10
2	rs778371	2.34E+08	A	G	-0.0741	0.0089	1.10E-16
16	rs11647188	82648514	A	G	0.044495	0.0081	3.75E-08
16	rs11076631	89877975	A	G	0.052203	0.0088	2.59E-09
6	rs6919146	1.65E+08	T	G	-0.0488	0.0085	8.42E-09
15	rs2456020	78868398	C	T	0.068499	0.0088	5.35E-15
4	rs28521069	1.19E+08	C	T	-0.0457	0.0083	3.78E-08
5	rs10117	1.38E+08	G	A	0.055501	0.0082	9.54E-12
5	rs9687282	1.39E+08	T	G	-0.0486	0.0086	1.66E-08
3	rs28490262	80814042	G	C	0.053199	0.0086	6.68E-10
6	rs13195636	27509493	A	C	0.210504	0.0159	6.55E-40
4	rs356183	90626098	G	C	0.044304	0.008	3.37E-08
7	rs13230189	1.37E+08	C	T	0.071902	0.0081	1.04E-18
7	rs35792732	1.33E+08	C	T	0.060399	0.0106	1.08E-08
7	rs1593304	1.32E+08	A	G	-0.0642	0.0101	2.37E-10
6	rs10947452	33803752	T	C	-0.0448	0.0081	3.69E-08
6	rs9461856	33395199	G	A	-0.0639	0.0078	3.23E-16
6	rs3131295	32173257	G	A	0.0599	0.008	9.97E-14
2	rs11693094	1.86E+08	C	T	0.057297	0.0078	2.20E-13
1	rs12129573	73768366	C	A	-0.0681	0.0082	1.42E-16
1	rs1121296	72174197	T	C	0.047303	0.008	3.74E-09
13	rs11619756	44329004	G	A	0.047103	0.0082	7.97E-09
4	rs215483	23377121	G	A	-0.0507	0.0084	1.59E-09
4	rs4697446	24269622	G	T	-0.0446	0.0079	1.67E-08
3	rs7647398	1.81E+08	C	T	0.085003	0.01	2.21E-17
3	rs9882532	16865845	T	C	-0.05309	0.0087	8.57E-10
3	rs6577597	17871326	A	G	-0.0526	0.0085	5.52E-10
9	rs3739554	1.3E+08	A	G	-0.0576	0.0103	2.26E-08
22	rs5995756	40000313	T	C	0.056399	0.0084	2.38E-11
22	rs9607782	41587556	T	A	-0.0725	0.0097	7.10E-14
22	rs4822076	42364057	C	T	-0.0597	0.0089	1.94E-11
2	rs1451488	2E+08	A	G	-0.066	0.0079	6.72E-17
2	rs13032111	1.94E+08	T	G	0.043203	0.0077	2.15E-08
2	rs2914983	1.98E+08	A	G	0.062796	0.0081	1.10E-14
2	rs10190027	37190726	C	T	-0.04971	0.0089	2.57E-08
2	rs3770752	37576136	A	G	0.057401	0.0086	2.86E-11
6	rs6925079	64946311	T	C	-0.0448	0.0081	3.58E-08
20	rs6065094	37453194	A	G	-0.0634	0.0082	1.41E-14
6	rs13219424	1.28E+08	C	T	0.045996	0.0084	4.52E-08
3	rs60135207	71563777	G	T	0.049599	0.0087	1.27E-08
2	rs12991836	1.45E+08	A	C	-0.0584	0.008	2.72E-13
2	rs16825349	1.46E+08	A	G	-0.0704	0.0104	1.32E-11
12	rs10777187	89940502	T	C	0.050902	0.0092	2.82E-08
2	rs12713008	48503561	G	A	0.043002	0.0078	3.05E-08

Schizophrenia instruments (continued)							
CHR	**SNP**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
9	rs500102	77358745	T	C	0.043299	0.0079	4.15E-08
9	rs72761691	1.35E+08	A	C	-0.0664	0.0116	1.07E-08
10	rs79668541	1.05E+08	C	T	0.120703	0.0121	2.11E-23
6	rs1856507	73157926	C	A	0.050398	0.008	3.00E-10
6	rs9454727	70003389	A	G	0.054801	0.0098	1.93E-08
12	rs578470	50463325	T	C	-0.0462	0.0083	2.33E-08
12	rs61937595	57682956	C	T	0.121996	0.0158	1.32E-14
17	rs73292401	12875908	T	A	-0.0659	0.0103	1.82E-10
17	rs9891739	19942177	C	T	-0.045	0.008	2.18E-08
17	rs4073003	19148305	A	G	0.080603	0.0116	4.20E-12
16	rs8055219	13753384	G	A	-0.0672	0.0095	1.57E-12
5	rs252812	1.07E+08	A	G	0.053	0.0093	1.30E-08
5	rs35164357	1.09E+08	C	T	-0.0605	0.0096	2.59E-10
12	rs10861176	1.05E+08	G	A	-0.0504	0.0086	5.23E-09
12	rs3764002	1.09E+08	C	T	-0.0517	0.0086	1.65E-09
13	rs2455415	38860697	C	T	-0.04759	0.0081	3.43E-09
13	rs1924377	38362106	G	C	0.046903	0.0082	8.71E-09
3	rs55929115	1.18E+08	T	A	0.072004	0.013	3.21E-08
5	rs10035564	45252500	A	G	-0.06481	0.0081	1.65E-15
14	rs1540840	99733384	G	C	0.054999	0.009	1.04E-09
3	rs17194490	2547786	G	T	-0.0781	0.0116	1.85E-11
10	rs61857878	92789488	A	T	0.0599	0.0099	1.46E-09
11	rs2514218	1.13E+08	C	T	0.069899	0.009	6.46E-15
2	rs17644050	1.56E+08	G	C	-0.0538	0.0098	4.02E-08
7	rs79210963	24717969	T	C	-0.0863	0.0129	2.58E-11
7	rs7811417	21534152	T	C	0.048304	0.0081	2.17E-09
11	rs12285419	46343189	C	A	-0.0812	0.01	3.73E-16
6	rs634940	93077500	G	T	-0.0649	0.0098	2.88E-11
6	rs6925964	96475894	A	T	0.097499	0.0176	3.19E-08
18	rs9304548	27500959	C	A	0.060003	0.0089	1.90E-11
3	rs2710323	52815905	T	C	0.074597	0.0077	5.92E-22
3	rs11917680	50471408	G	T	0.056702	0.0091	4.17E-10
3	rs7432375	1.36E+08	G	A	0.063801	0.0082	5.32E-15
15	rs2238304	89843950	A	T	0.049599	0.0078	1.73E-10
15	rs4779050	83368738	T	G	0.049304	0.0079	4.18E-10
15	rs11638554	85148231	T	G	0.064504	0.0089	3.62E-13
1	rs6673880	2373168	A	G	-0.061	0.0086	1.32E-12
1	rs11121172	8418644	C	A	0.054602	0.0089	7.15E-10
1	rs11122119	6768856	C	A	-0.0453	0.0081	2.31E-08
13	rs9597388	56928696	G	A	0.066798	0.0101	3.24E-11
13	rs9569820	58702746	G	T	-0.0676	0.0109	6.56E-10
11	rs7938083	57493622	C	A	-0.0524	0.0087	1.60E-09
5	rs10069930	1.4E+08	T	A	0.048304	0.0079	9.43E-10
9	rs6479487	96237373	T	G	-0.0587	0.0103	1.37E-08

Schizophrenia instruments (continued)							
CHR	**SNP**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
3	rs7609876	1.77E+08	T	C	-0.0512	0.0089	9.40E-09
1	rs2224086	1.15E+08	C	A	-0.0577	0.0103	2.09E-08
19	rs144821294	2155136	C	T	-0.138	0.0242	1.22E-08
2	rs72974269	2.25E+08	C	T	0.052099	0.0083	2.76E-10
15	rs35351411	61872197	A	C	-0.0573	0.0079	3.13E-13
16	rs3814883	29994922	C	T	0.060898	0.0079	8.82E-15
5	rs72723227	7245664	G	A	0.047999	0.0082	4.58E-09
12	rs1463209	39518293	C	T	0.047704	0.0081	3.34E-09
14	rs2190864	72416219	T	C	0.066097	0.008	1.12E-16
6	rs2206956	1.47E+08	G	A	-0.0462	0.0078	2.51E-09
6	rs9390083	1.44E+08	C	G	-0.05719	0.0103	2.95E-08
19	rs1858999	19497669	C	G	0.060502	0.0081	7.97E-14
19	rs72986630	11849736	C	T	-0.1117	0.0177	3.07E-10
19	rs322128	11402416	C	T	-0.0567	0.0095	2.08E-09
14	rs12431743	84673716	G	A	-0.0456	0.008	1.26E-08
16	rs9926049	9939960	C	A	-0.0556	0.0088	3.16E-10
16	rs8048039	4498486	A	T	0.049	0.0083	4.35E-09
1	rs10127983	1.54E+08	C	T	-0.0463	0.0084	3.11E-08
1	rs12138231	1.5E+08	T	A	-0.0671	0.0116	7.21E-09
10	rs7915131	64418656	C	T	0.042695	0.0078	4.94E-08
4	rs13107325	1.03E+08	C	T	-0.1587	0.0168	2.90E-21
4	rs6839635	1.04E+08	C	A	-0.0432	0.0079	3.87E-08
6	rs2153960	1.09E+08	G	A	0.051396	0.0084	9.22E-10
15	rs117799466	34659517	G	C	-0.0481	0.0087	3.86E-08
17	rs6504163	61545779	C	T	-0.0492	0.0082	1.87E-09
2	rs6732355	1.05E+08	C	A	-0.0587	0.0094	4.36E-10
10	rs2119242	21344773	G	A	-0.0602	0.0106	1.34E-08
1	rs11807834	2.3E+08	G	A	-0.053	0.0093	1.12E-08
1	rs11587347	2.39E+08	C	G	-0.1028	0.0139	1.50E-13
1	rs61833239	2.44E+08	T	G	-0.0843	0.0122	5.22E-12
14	rs10148671	29469373	T	C	-0.0479	0.0083	6.82E-09
10	rs6482437	18726326	A	C	-0.10471	0.0135	1.05E-14
5	rs115325222	88854539	A	G	0.090398	0.0151	1.93E-09
7	rs6969410	1.1E+08	T	G	0.055501	0.0083	1.90E-11
7	rs38752	1.11E+08	T	G	0.060003	0.0081	1.08E-13
7	rs1589726	79348201	C	T	0.077896	0.0137	1.20E-08
7	rs10238960	70773271	C	T	-0.0482	0.0084	7.65E-09
7	rs2944821	71795998	G	C	0.047799	0.008	1.90E-09
5	rs7701440	60620980	T	C	-0.0638	0.008	1.86E-15
8	rs73229090	27442127	C	A	0.102602	0.0142	4.34E-13
8	rs3808581	26250047	G	A	-0.06699	0.0097	3.82E-12
2	rs2717003	58143438	A	G	-0.07529	0.008	2.76E-21
18	rs12969453	52751708	A	G	0.054299	0.0078	3.53E-12
18	rs715170	53795514	C	T	0.064701	0.009	7.40E-13

Schizophrenia instruments (continued)							
CHR	**SNP**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
18	rs4632195	50746748	C	T	-0.0498	0.0084	2.73E-09
18	rs9636107	53200117	A	G	-0.0609	0.0081	5.72E-14
14	rs17571951	30017039	T	C	-0.0645	0.0105	7.89E-10
14	rs12883788	33303540	C	T	-0.0543	0.0079	8.43E-12
19	rs8104557	31030189	T	C	-0.0604	0.011	3.76E-08
19	rs3810450	36530562	T	C	0.092497	0.016	8.27E-09
9	rs505061	22767164	C	A	-0.0499	0.0077	1.03E-10
13	rs9545047	79859456	A	C	0.053797	0.0081	3.05E-11
11	rs58950470	65383755	G	T	-0.0493	0.0086	1.10E-08
2	rs6546857	73837955	A	G	-0.0603	0.0101	2.80E-09
2	rs11897811	76267139	C	T	-0.0575	0.0102	1.49E-08
2	rs999494	73157395	C	T	0.057599	0.0101	1.04E-08
1	rs1198588	98552832	A	T	-0.0964	0.0103	7.88E-21
1	rs59519965	97168334	G	T	-0.0582	0.0098	3.36E-09
1	rs72728416	97834691	A	G	-0.0598	0.0087	4.99E-12
18	rs337718	69774278	T	C	0.0492	0.0084	4.39E-09
1	rs6588355	50113591	T	C	0.049504	0.009	3.65E-08
15	rs56205728	40567237	G	A	-0.0575	0.0093	5.43E-10
15	rs2929278	44250313	C	T	0.061904	0.0091	8.50E-12
2	rs9287971	1.75E+08	G	A	-0.0458	0.0083	3.82E-08
2	rs62184960	1.73E+08	C	T	0.069797	0.0122	1.08E-08
2	rs6430492	1.35E+08	G	A	0.057703	0.0094	6.72E-10
5	rs331395	91006918	C	G	-0.0549	0.009	1.27E-09
2	rs4672366	60389362	A	T	0.049799	0.0087	1.07E-08
8	rs10503253	4180844	C	A	-0.0602	0.0091	4.37E-11
18	rs72980087	77632194	G	A	-0.0644	0.0079	4.06E-16
18	rs7238071	77579812	A	G	-0.0629	0.0084	9.29E-14
11	rs4937935	1.35E+08	A	T	-0.0539	0.0081	2.30E-11
11	rs1440480	1.34E+08	A	G	0.057504	0.0086	2.52E-11
11	rs10894308	1.31E+08	G	A	0.047704	0.0079	1.36E-09
11	rs4936215	1.34E+08	A	G	0.082796	0.0104	1.86E-15
11	rs1939514	1.33E+08	T	C	0.055198	0.0077	1.06E-12
8	rs79445414	33863561	T	C	-0.1235	0.0222	2.63E-08
8	rs7816998	38257506	G	A	0.057797	0.0092	3.11E-10
7	rs35045093	1.28E+08	A	C	0.056598	0.0103	3.36E-08
1	rs61786047	29032580	G	A	0.078802	0.0135	4.91E-09
22	rs6010045	51103091	T	C	-0.0477	0.0085	1.82E-08
3	rs704364	63874734	A	G	0.050303	0.0082	8.41E-10
3	rs9813516	60293004	G	A	-0.0513	0.0084	1.25E-09
9	rs498591	14509105	A	T	-0.0679	0.0111	9.59E-10
9	rs2890914	10239181	A	G	-0.0432	0.0077	2.31E-08
12	rs10774034	2330458	C	T	-0.08329	0.0085	7.10E-23
2	rs12712510	22749726	T	C	0.051501	0.0084	9.34E-10
2	rs141216273	25599172	C	A	-0.1247	0.0228	4.49E-08

Schizophrenia instruments (continued)							
CHR	**SNP**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
2	rs12474906	28033538	A	C	0.056796	0.0095	2.20E-09
2	rs2909457	1.63E+08	G	A	0.045805	0.0083	3.09E-08
4	rs35734242	706700	T	C	-0.0499	0.008	3.93E-10
20	rs11696755	48105317	T	C	-0.0653	0.0104	2.99E-10

Table B22. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to autism (excluding ID cases) and psychotic experiences.

Autism no ID instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs529507	11	1.32E+08	A	G	-0.1354	0.0241	1.88E-08
rs574626	18	55882192	T	C	0.095101	0.0181	1.54E-07
rs1402807	1	96597055	T	C	0.092497	0.018	2.73E-07
rs8182800	20	21531772	A	G	0.124101	0.0203	9.02E-10
rs10195840	2	1.4E+08	A	G	0.094701	0.0175	5.87E-08
rs10197246	2	2.02E+08	T	C	0.100298	0.0186	6.94E-08
rs148587110	3	20641966	T	C	-0.4697	0.0907	2.21E-07
rs114489105	4	1.32E+08	T	G	0.199596	0.0384	2.05E-07
rs4916723	5	87854395	A	C	-0.09	0.0173	1.9E-07
rs6964453	7	78210447	A	T	-0.107	0.02	8.16E-08

Table B23. Effect sizes, standard errors and p-values of genetic instruments used for the Mendelian randomization (MR) analyses investigating causal links between genetic liability to autism (excluding ID cases) and schizophrenia (European ancestry only- Ripke et al., 2014).

Autism no ID instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs529507	11	1.32E+08	A	G	-0.1354	0.0241	1.88E-08
rs292441	18	55872558	A	G	-0.0958	0.0182	1.42E-07
rs1402807	1	96597055	T	C	0.092497	0.018	2.73E-07
rs1000177	20	21233198	T	C	0.123102	0.0197	3.85E-10
rs13012522	2	1.4E+08	T	G	0.096301	0.0177	5.73E-08
rs10197246	2	2.02E+08	T	C	0.100298	0.0186	6.94E-08
rs148587110	3	20641966	T	C	-0.4697	0.0907	2.21E-07
rs114489105	4	1.32E+08	T	G	0.199596	0.0384	2.05E-07
rs4916723	5	87854395	A	C	-0.09	0.0173	1.90E-07
rs6964453	7	78210447	A	T	-0.107	0.02	8.16E-08
Schizophrenia instruments							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs4648845	1	2387101	T	C	0.067201	0.0119	1.74E-08
rs7893279	10	18745105	T	G	0.1124	0.0175	1.24E-10
rs301797	1	8487323	A	C	0.066097	0.0116	1.20E-08
rs11191419	10	1.05E+08	A	T	-0.1016	0.0118	6.69E-18
rs1498232	1	30433951	T	C	0.072004	0.0118	1.21E-09
rs11210892	1	44100084	A	G	-0.0678	0.0115	3.42E-09
rs35998080	1	73278615	T	G	0.069004	0.0112	6.95E-10
rs1702294	1	98501984	T	C	-0.1184	0.0138	1.03E-17
rs11027857	11	24403620	A	G	0.063998	0.0109	3.67E-09
rs35324223	11	46402852	A	G	-0.09199	0.0145	2.04E-10
rs2514218	11	1.13E+08	T	C	-0.07221	0.0116	4.64E-10
rs55661361	11	1.25E+08	A	G	-0.07881	0.0116	1.04E-11
rs10791097	11	1.31E+08	T	G	0.0766	0.0109	2.05E-12
rs75059851	11	1.34E+08	A	G	0.091302	0.0136	2.18E-11
rs12062861	1	1.5E+08	A	G	-0.0911	0.0149	9.66E-10
rs1024582	12	2402246	A	G	0.098904	0.0115	6.27E-18
rs679087	12	29917265	A	C	-0.0642	0.0116	3.28E-08
rs12826178	12	57622371	T	G	-0.16821	0.0244	5.70E-12
rs4766428	12	1.11E+08	T	C	0.069395	0.0112	6.12E-10
rs1615350	12	1.24E+08	T	C	-0.0851	0.0123	4.26E-12
rs10803138	1	2.44E+08	A	G	-0.07221	0.0126	1.13E-08
rs77149735	1	2.44E+08	A	G	0.284502	0.0485	4.40E-09
rs1191551	14	30000405	T	G	0.071697	0.0131	4.21E-08
rs67981189	14	71472226	A	G	-0.0698	0.0118	3.75E-09
rs2332700	14	72417326	C	G	0.0771	0.0125	7.38E-10
rs2693698	14	99719219	A	G	-0.06171	0.0111	2.99E-08
rs12887734	14	1.04E+08	T	G	0.088304	0.0121	3.72E-13
rs2414718	15	61863133	A	G	0.069797	0.011	1.98E-10

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs28681284	15	78908565	T	C	-0.1016	0.0141	6.35E-13
rs783540	15	83254708	A	G	-0.0599	0.011	4.77E-08
rs12902973	15	85105982	C	G	-0.0791	0.0122	8.83E-11
rs4702	15	91426560	A	G	-0.08051	0.0115	2.62E-12
rs9922678	16	9946319	A	G	0.068397	0.0118	6.18E-09
rs8055219	16	13753384	A	G	0.076998	0.0127	1.45E-09
rs12691307	16	29939877	A	G	0.071902	0.0113	2.03E-10
rs12932476	16	63709630	C	G	0.059702	0.0109	4.62E-08
rs4523957	17	2208899	T	G	0.069703	0.0115	1.40E-09
rs11658257	17	17956459	C	G	-0.0662	0.0115	8.34E-09
rs11874716	18	52750688	T	G	0.067201	0.011	1.01E-09
rs9636107	18	53200117	A	G	-0.0796	0.0108	2.17E-13
rs9966779	18	53620456	T	C	-0.1329	0.0231	8.56E-09
rs715170	18	53795514	T	C	-0.0669	0.0122	4.65E-08
rs72986630	19	11849736	T	C	0.1459	0.0266	4.12E-08
rs2905426	19	19478022	T	G	-0.0677	0.0115	4.07E-09
rs2053079	19	30987423	A	G	-0.0718	0.0127	1.74E-08
rs2103655	20	37425958	A	G	0.0766	0.0119	1.24E-10
rs1509378	2	22754466	A	G	0.0692	0.0119	5.39E-09
rs11682175	2	57987593	T	C	-0.0735	0.0109	1.58E-11
rs6430095	2	1.46E+08	A	G	0.0798	0.0145	3.40E-08
rs76355118	2	1.49E+08	A	G	-0.1544	0.0278	2.78E-08
rs2909457	2	1.63E+08	A	G	-0.0597	0.0109	4.25E-08
rs11693094	2	1.86E+08	T	C	-0.0736	0.011	2.17E-11
rs59979824	2	1.94E+08	A	C	-0.071	0.0119	2.73E-09
rs281768	2	2.01E+08	A	T	0.104198	0.0137	2.64E-14
rs6434928	2	1.98E+08	A	G	-0.0787	0.0116	1.17E-11
rs5995756	22	40000313	T	C	0.072497	0.0109	2.91E-11
rs9607782	22	41587556	A	T	0.088697	0.0128	3.98E-12
rs28733092	22	42537115	T	C	0.070999	0.0121	4.36E-09
rs11685299	2	2.25E+08	A	C	-0.0662	0.0117	1.49E-08
rs7601312	2	2.29E+08	A	G	-0.059	0.0108	4.68E-08
rs6704768	2	2.34E+08	A	G	-0.0766	0.0109	2.06E-12
rs17194490	3	2547786	T	G	0.0966	0.0148	6.38E-11
rs75968099	3	36858583	T	C	0.080104	0.0114	2.31E-12
rs2535627	3	52845105	T	C	0.070403	0.0109	1.17E-10
rs832190	3	63842629	T	C	-0.0699	0.0113	5.73E-10
rs6439649	3	1.36E+08	T	G	0.070999	0.0111	1.37E-10
rs34796896	3	1.81E+08	A	G	-0.0822	0.0135	1.23E-09
rs215411	4	23423603	A	T	0.0692	0.0115	1.68E-09
rs35225200	4	1.03E+08	A	C	-0.14479	0.0203	9.56E-13
rs1106568	4	1.77E+08	A	G	-0.0694	0.0125	2.85E-08
rs17073903	4	1.84E+08	A	G	-0.08141	0.0148	3.92E-08
rs4391122	5	60598543	A	G	-0.078	0.0109	8.90E-13

Schizophrenia instruments (continued)							
SNP	**CHR**	**BP**	**A1**	**A2**	**logOR**	**SE**	**P**
rs16867576	5	88746331	A	G	0.095801	0.017	1.61E-08
rs3849046	5	1.38E+08	T	C	0.062496	0.0109	1.04E-08
rs111294930	5	1.52E+08	A	G	0.087699	0.0143	9.29E-10
rs76091702	5	1.52E+08	T	C	0.129299	0.0236	4.49E-08
rs11740474	5	1.54E+08	A	T	-0.06269	0.0112	2.00E-08
rs13437595	6	29763308	T	C	0.262203	0.0392	2.19E-11
rs13217619	6	28306671	T	C	0.219698	0.0195	1.44E-29
rs115296342	6	32503526	A	C	0.090398	0.0135	1.90E-11
rs9274390	6	32632660	T	G	0.160604	0.0183	1.54E-18
rs186545906	6	32478432	A	G	-0.11879	0.0196	1.41E-09
rs9461856	6	33395199	A	G	0.074996	0.0109	6.52E-12
rs1339227	6	73155701	T	C	-0.0633	0.0114	3.06E-08
rs3798869	6	84328660	A	G	-0.0668	0.011	1.09E-09
rs117074560	6	96459651	T	C	-0.1566	0.0277	1.66E-08
rs58120505	7	2029867	T	C	0.082197	0.0111	1.26E-13
rs12704290	7	86427626	A	G	-0.10611	0.0168	2.59E-10
rs6466055	7	1.05E+08	A	C	0.068798	0.0114	1.59E-09
rs13240464	7	1.11E+08	T	C	0.080704	0.0116	3.12E-12
rs7801375	7	1.32E+08	A	G	-0.083	0.015	2.88E-08
rs17529963	7	1.37E+08	T	C	0.0629	0.0114	3.24E-08
rs10108725	8	4191202	T	C	0.073204	0.0133	3.32E-08
rs73191547	8	10033425	A	T	-0.0669	0.0115	6.13E-09
rs17687067	8	17036201	A	C	-0.0763	0.0139	4.49E-08
rs73229090	8	27442127	A	C	-0.0995	0.0177	1.95E-08
rs13261481	8	60701801	T	G	0.062402	0.011	1.66E-08
rs7819570	8	89588626	T	G	0.076498	0.014	4.47E-08
rs36068923	8	1.11E+08	A	G	-0.0835	0.0134	4.14E-10
rs4129585	8	1.43E+08	A	C	0.079301	0.0109	3.61E-13
rs11139497	9	84739941	A	T	0.0656	0.0118	2.65E-08

Table B24. Genetic instruments for IQ used in multivariable Mendelian randomization (MVMR) analyses.

SNP	A1	A2	β	SE	P
rs10917152	T	C	0.024213	0.004049	2.23E-09
rs7546297	A	G	-0.01998	0.002818	1.33E-12
rs12035012	A	C	-0.02699	0.003312	3.68E-16
rs3791134	A	G	0.016237	0.002839	1.07E-08
rs4660749	T	G	-0.02884	0.004446	8.72E-11
rs1831539	T	C	-0.0172	0.002762	4.72E-10
rs2420551	A	T	-0.0286	0.004344	4.6E-11
rs12124523	T	C	0.032567	0.004887	2.67E-11
rs3128341	T	C	-0.03173	0.003417	1.63E-20
rs6668048	T	C	-0.02146	0.002734	4.24E-15
rs9324380	C	G	0.02378	0.004267	2.5E-08
rs11804556	A	G	0.034049	0.005481	5.24E-10
rs1528204	T	C	-0.01819	0.002774	5.47E-11
rs1144593	A	G	-0.01911	0.002987	1.57E-10
rs112780312	A	G	-0.01828	0.003099	3.66E-09
rs34320898	C	G	0.022869	0.003844	2.7E-09
rs199928	T	C	0.020051	0.003624	3.15E-08
rs2678210	T	C	0.018786	0.003046	6.97E-10
rs10779271	A	G	0.016375	0.002925	2.17E-08
rs12470949	T	C	-0.01717	0.003021	1.32E-08
rs967569	T	C	-0.01798	0.002927	8.21E-10
rs2955280	T	C	-0.01491	0.002734	4.9E-08
rs62131236	T	C	-0.01825	0.003342	4.8E-08
rs7557525	T	C	0.015927	0.002902	4.04E-08
rs58593843	A	G	-0.02768	0.004652	2.67E-09
rs10189857	A	G	0.018995	0.00275	4.91E-12
rs2576835	A	G	-0.01941	0.003206	1.4E-09
rs4852252	T	C	-0.02079	0.002747	3.84E-14
rs11898362	A	G	-0.01798	0.003008	2.25E-09
rs11678106	T	C	0.016086	0.002745	4.62E-09
rs2309812	T	C	0.022835	0.002845	9.95E-16
rs60262711	T	C	0.015949	0.002825	1.65E-08
rs2558096	T	G	-0.01563	0.002774	1.74E-08
rs10189912	A	G	-0.01934	0.002853	1.22E-11
rs3106666	A	G	-0.01659	0.00278	2.42E-09
rs6436555	A	C	0.01905	0.002746	3.99E-12
rs10192369	A	G	-0.01605	0.002744	4.91E-09
rs62194171	T	G	-0.01544	0.002831	4.95E-08
rs1267042	T	C	-0.01654	0.002996	3.4E-08
rs2268894	T	C	0.020785	0.002749	3.98E-14
rs3956504	A	C	0.017902	0.003052	4.47E-09
rs13421971	A	T	0.01738	0.002893	1.88E-09
rs3749034	A	G	-0.01926	0.003322	6.74E-09

IQ instruments (continued)					
SNP	**A1**	**A2**	**β**	**SE**	**P**
rs62181012	T	C	0.021146	0.003511	1.73E-09
rs62198803	A	G	0.019065	0.003225	3.4E-09
rs7573001	C	G	-0.01625	0.00286	1.32E-08
rs1455344	A	G	-0.01618	0.002769	5.2E-09
rs35731967	T	C	0.021838	0.003658	2.38E-09
rs13024268	A	G	-0.01666	0.002879	7.15E-09
rs73139272	T	G	-0.02484	0.004057	9.24E-10
rs6550835	A	G	-0.02481	0.002929	2.44E-17
rs1589652	A	G	0.017094	0.002759	5.82E-10
rs2352974	T	C	-0.03084	0.002751	3.69E-29
rs4687625	T	C	0.019343	0.002748	1.92E-12
rs4485754	A	G	0.018878	0.00334	1.59E-08
rs11720523	A	C	0.018326	0.002773	3.89E-11
rs6770622	A	G	-0.04496	0.006864	5.76E-11
rs7652296	A	G	0.016533	0.002799	3.51E-09
rs3860537	T	C	0.018854	0.003402	2.99E-08
rs13071190	T	C	0.018095	0.002917	5.55E-10
rs59142272	A	G	0.022696	0.003685	7.32E-10
rs10804681	A	T	0.021055	0.003797	2.94E-08
rs12646225	T	C	0.025128	0.004215	2.51E-09
rs2295499	T	C	-0.0164	0.002753	2.59E-09
rs4484297	C	G	0.018267	0.00316	7.45E-09
rs11932971	T	C	0.027484	0.00381	5.46E-13
rs34811474	A	G	0.028996	0.003594	7.15E-16
rs67482514	C	G	-0.01786	0.003229	3.21E-08
rs6819372	A	G	-0.0198	0.002729	4.02E-13
rs1972860	A	G	-0.01756	0.00293	2.09E-09
rs4459994	A	C	0.018552	0.00329	1.71E-08
rs34592089	A	G	-0.05699	0.006462	1.15E-18
rs2726491	A	G	-0.02828	0.002857	4.17E-23
rs6840804	A	G	-0.01659	0.002966	2.25E-08
rs6535809	A	G	0.019647	0.002734	6.65E-13
rs17826816	A	G	0.018375	0.003257	1.68E-08
rs1840847	A	G	0.016342	0.002883	1.44E-08
rs75973558	A	G	0.025636	0.004465	9.42E-09
rs13165296	A	C	0.019636	0.00352	2.44E-08
rs36033	T	C	0.015969	0.002788	1.02E-08
rs1812587	T	G	-0.01734	0.002767	3.68E-10
rs80170948	T	G	0.045381	0.007378	7.69E-10
rs34316	A	C	0.021049	0.002767	2.82E-14
rs166820	A	G	0.024334	0.003599	1.37E-11
rs4308464	C	G	-0.01837	0.002853	1.22E-10
rs76160968	A	G	-0.04171	0.007252	8.84E-09
rs10477894	A	G	-0.01621	0.002908	2.49E-08

IQ instruments (continued)					
SNP	**A1**	**A2**	**β**	**SE**	**P**
rs1438660	A	T	0.015846	0.002874	3.52E-08
rs1145123	T	C	0.020557	0.002772	1.2E-13
rs405321	A	G	-0.01643	0.002975	3.32E-08
rs4463213	A	G	0.019065	0.002732	3E-12
rs31768	A	T	0.018177	0.003054	2.65E-09
rs6860963	T	C	0.020262	0.003476	5.57E-09
rs2450333	A	G	-0.01883	0.002799	1.73E-11
rs9503599	T	C	-0.01711	0.002785	8.05E-10
rs566237	A	G	-0.01872	0.002935	1.82E-10
rs6459098	T	C	-0.01615	0.002933	3.67E-08
rs6903716	A	G	0.017758	0.002975	2.39E-09
rs1233578	A	G	-0.0238	0.003903	1.08E-09
rs1280049	A	C	0.014993	0.002729	3.92E-08
rs12190777	A	G	0.01703	0.003092	3.63E-08
rs1906252	A	C	0.031662	0.002741	7.48E-31
rs3823036	T	C	-0.01899	0.002929	9.11E-11
rs9384679	T	C	-0.02672	0.002783	7.94E-22
rs13212044	T	G	-0.01837	0.003242	1.46E-08
rs287879	A	G	-0.01887	0.003075	8.47E-10
rs4725065	A	G	-0.01653	0.002736	1.52E-09
rs115064	T	C	0.016096	0.002814	1.07E-08
rs1580019	A	T	0.016257	0.002876	1.59E-08
rs799444	T	C	0.018415	0.002759	2.48E-11
rs13223152	A	G	0.017645	0.002784	2.34E-10
rs56150095	A	C	-0.02197	0.002747	1.28E-15
rs12535854	C	G	-0.01823	0.002953	6.73E-10
rs2402857	A	G	0.015446	0.00278	2.76E-08
rs4731392	A	G	-0.02174	0.002975	2.69E-13
rs1043595	A	G	0.018957	0.003123	1.27E-09
rs1362739	A	C	0.020945	0.002734	1.83E-14
rs13253386	T	G	-0.02013	0.002748	2.37E-13
rs1473634	A	G	-0.01809	0.002978	1.25E-09
rs10954779	T	C	-0.01638	0.002762	3.04E-09
rs13276212	T	G	0.015071	0.002755	4.48E-08
rs2920940	T	C	-0.02474	0.003252	2.76E-14
rs2111490	A	G	0.015491	0.002753	1.83E-08
rs1106761	A	G	-0.01775	0.002899	9.12E-10
rs4976976	A	G	0.017317	0.002777	4.53E-10
rs2721173	T	C	-0.01623	0.002734	2.89E-09
rs11793831	T	G	0.027834	0.002804	3.25E-23
rs702222	T	C	-0.01983	0.002872	5.02E-12
rs28620532	A	G	-0.01635	0.002889	1.51E-08
rs1057687	A	G	-0.01953	0.003481	2.02E-08
rs913264	T	C	0.019725	0.003026	7.09E-11

IQ instruments					
SNP	**A1**	**A2**	**β**	**SE**	**P**
rs2987390	C	G	-0.0178	0.003123	1.19E-08
rs7069887	A	C	0.022532	0.003898	7.44E-09
rs2393967	A	C	-0.01871	0.002963	2.7E-10
rs1891273	T	C	0.015414	0.002786	3.17E-08
rs1408579	T	C	0.016049	0.002748	5.23E-09
rs3740422	C	G	-0.0241	0.002912	1.25E-16
rs3896224	A	G	-0.01531	0.002772	3.29E-08
rs35608616	A	G	-0.01809	0.002937	7.33E-10
rs7921305	A	G	0.018192	0.00323	1.77E-08
rs11605348	A	G	-0.01661	0.002896	9.73E-09
rs7941785	A	G	0.015512	0.002841	4.75E-08
rs2373353	A	G	-0.01632	0.002887	1.56E-08
rs2508713	A	T	0.016531	0.002841	5.92E-09
rs7116046	T	C	0.015707	0.002842	3.27E-08
rs2885208	T	C	0.018939	0.003464	4.58E-08
rs17128425	A	T	0.025557	0.004544	1.87E-08
rs329672	T	C	0.01743	0.002853	1E-09
rs55754731	T	C	0.021369	0.003675	6.06E-09
rs1054442	A	C	-0.02146	0.002816	2.52E-14
rs1962047	A	G	-0.01953	0.002863	8.89E-12
rs6539284	T	C	-0.01948	0.002827	5.56E-12
rs7312919	C	G	0.018146	0.002915	4.83E-10
rs1727307	A	G	0.017817	0.003007	3.1E-09
rs9569206	A	G	-0.01541	0.002824	4.85E-08
rs3843954	C	G	-0.02076	0.003343	5.31E-10
rs9516855	A	G	0.033427	0.006096	4.19E-08
rs2478286	C	G	-0.02579	0.003127	1.64E-16
rs8006700	A	T	-0.01823	0.00293	4.96E-10
rs176217	T	C	0.026141	0.003989	5.64E-11
rs971681	T	C	-0.01675	0.002807	2.44E-09
rs2239647	A	C	-0.02054	0.002766	1.14E-13
rs11622558	T	C	-0.01751	0.002824	5.66E-10
rs35760956	A	G	0.019798	0.002823	2.35E-12
rs17106817	T	C	0.016911	0.003025	2.26E-08
rs1007934	A	G	0.016077	0.002806	1E-08
rs17698580	T	C	0.019033	0.003177	2.09E-09
rs2071407	T	C	-0.02197	0.002859	1.52E-14
rs11634187	T	G	0.022032	0.003857	1.12E-08
rs55881236	T	C	-0.01541	0.002794	3.48E-08
rs7172979	T	G	0.060634	0.009084	2.47E-11
rs72739469	T	C	-0.03436	0.005648	1.18E-09
rs8025964	A	G	0.017031	0.002749	5.78E-10
rs1369429	T	C	0.017633	0.002896	1.15E-09
rs11076962	T	C	0.016936	0.003042	2.57E-08

IQ instruments (continued)					
SNP	**A1**	**A2**	**β**	**SE**	**P**
rs11646221	T	G	0.017735	0.002772	1.57E-10
rs72774059	A	C	0.02713	0.00459	3.41E-09
rs2457192	A	C	-0.01975	0.003131	2.84E-10
rs62029752	A	G	0.019616	0.003149	4.68E-10
rs72773563	A	G	-0.02181	0.003773	7.4E-09
rs9788857	A	C	-0.02024	0.003495	7.03E-09
rs34172651	T	C	-0.0211	0.002962	1.06E-12
rs2008514	A	G	-0.02868	0.002799	1.25E-24
rs2647995	T	C	-0.01975	0.003044	8.68E-11
rs8054299	C	G	-0.02301	0.002927	3.84E-15
rs12446238	A	G	0.016054	0.002742	4.8E-09
rs9888986	A	G	-0.0235	0.004262	3.52E-08
rs7196032	T	C	0.015242	0.002786	4.47E-08
rs8051038	A	G	0.018924	0.003146	1.78E-09
rs2285640	A	G	0.017514	0.002765	2.38E-10
rs4793161	A	G	-0.01772	0.00325	4.97E-08
rs17698176	T	G	-0.02011	0.003566	1.7E-08
rs11079849	T	C	0.016548	0.00296	2.26E-08
rs16951547	T	G	-0.01925	0.0031	5.31E-10
rs66954617	A	G	-0.02088	0.002834	1.72E-13
rs71367283	A	C	0.055974	0.008746	1.55E-10
rs6508220	A	G	-0.02275	0.002737	9.56E-17
rs76608582	A	C	0.042223	0.007581	2.55E-08
rs17002025	A	G	0.025598	0.004261	1.89E-09
rs10411958	T	C	0.016409	0.002759	2.71E-09
rs2072490	T	C	0.016996	0.002745	5.93E-10
rs7248006	T	C	-0.01918	0.00282	1.05E-11
rs144026674	T	C	0.041307	0.007468	3.19E-08
rs889169	A	G	0.016071	0.002892	2.75E-08
rs73068339	C	G	0.018858	0.003046	5.96E-10
rs78084033	A	C	-0.02288	0.004049	1.62E-08
rs6019535	A	G	0.025105	0.002976	3.28E-17
rs2836921	A	G	0.020346	0.002963	6.54E-12
rs5753383	A	G	0.01591	0.002919	5E-08
rs4396807	C	G	-0.01573	0.002855	3.58E-08
rs5750830	A	C	0.022891	0.003127	2.46E-13
rs62236533	A	G	0.035363	0.004977	1.2E-12

Table B25. Causal effect estimates of common variant genetic liability to autism on risk of schizophrenia.

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	9	1.01015	0.085702	0.9062	0.853954	1.194915
MR Egger	9	0.932988	0.414738	0.871907	0.413851	2.103335
SIMEX corrected MR Egger	9	0.907723	0.582622	0.873	0.289745	2.843749
Weighted median	9	1.075862	0.070254	0.297954	0.937466	1.23469
Weighted mode	9	1.141966	0.143219	0.381087	0.862467	1.512041
MR Egger Intercept: 0.007; p= 0.85; providing limited evidence for horizontal pleiotropy influencing causal effect estimates. I2GX= 0.53; suggesting a 47% attenuation of the Egger estimate towards zero.						

Table B26. Causal effect estimates of common variant genetic liability to autism on risk of schizophrenia (European ancestry sample only).

METHOD	NSNP	OR	SE	P	95% CIs	
Inverse variance weighted	10	1.06026	0.080422	0.466865	0.905641	1.241277
MR Egger	10	0.923741	0.257233	0.765677	0.557942	1.529368
SIMEX corrected MR Egger	10	0.919486	0.31369	0.796	0.659383	1.282192
Weighted median	10	0.940746	0.071522	0.393082	0.817695	1.082313
Weighted mode	10	0.906877	0.085486	0.282354	0.766975	1.072297
MR Egger Intercept: 0.013; p= 0.59; providing limited evidence for horizontal pleiotropy influencing causal effect estimates. I2GX= 0.67; suggesting a 33% attenuation of the Egger estimate towards zero.						

Table B27. Causal effect estimates of common variant genetic liability to autism (excluding ID cases) on risk of schizophrenia.

METHOD	NSNP	OR	SE	P	95% CIs	
Inverse variance weighted	10	1.059317	0.052585	0.273152	0.955575	1.174321
MR Egger	10	0.965194	0.175409	0.844984	0.68439	1.36121
SIMEX corrected MR Egger	10	0.966388	0.22185	0.881	0.625618	1.492774
Weighted median	10	1.020162	0.046548	0.668043	0.931208	1.117613
Weighted mode	10	0.984174	0.066979	0.817081	0.863093	1.12224
MR Egger Intercept: 0.011; p= 0.59; providing limited evidence for horizontal pleiotropy influencing causal effect estimates. I2GX= 0.66; suggesting a 34% attenuation of the Egger estimate towards zero.						

Table B28. Causal effect estimates of common variant genetic liability to autism (excluding ID cases) on risk of schizophrenia (European ancestry sample only).

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	10	1.083956	0.064162	0.208945	0.955864	1.229213
MR Egger	10	1.000151	0.200136	0.999416	0.675626	1.480556
SIMEX corrected MR Egger	10	1.006681	0.242451	0.979	0.625912	1.619088
Weighted median	10	1.021988	0.057807	0.706735	0.912513	1.144596
Weighted mode	10	0.979826	0.084221	0.814216	0.830728	1.155684
MR Egger Intercept: 0.01; p= 0.68; providing limited evidence for horizontal pleiotropy influencing causal effect estimates. I2GX= 0.66; suggesting a 34% attenuation of the Egger estimate towards zero.						

Table B29. Direct effects of common variant genetic liability to autism and IQ on schizophrenia.

	NSNP	OR	SE	P	95%CIs	
Autism	7	1.238623	0.055766	0.000165	1.110302	1.381774
IQ	210	0.71177	0.07768	1.86E-05	0.611224	0.828857

Table B30. Direct effects of common variant genetic liability to autism and IQ on schizophrenia (European ancestry sample).

	NSNP	OR	SE	P	95%CIs	
Autism	7	1.293045	0.062181	5.1E-05	1.144638	1.460694
IQ	209	0.693503	0.086525	3.51E-05	0.585353	0.821634

Table B31. Causal effect estimates of common variant genetic liability to autism on IQ.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	8	-0.00262	0.0136	0.84715	-0.02928	0.024034
MR Egger	8	-0.01012	0.060983	0.87364	-0.12965	0.109406
SIMEX corrected MR Egger	8	-0.016	0.083032	0.854	-0.17874	-0.17874
Weighted median	8	0.000639	0.018696	0.972743	-0.036	0.037282
Weighted mode	8	0.009959	0.028474	0.736806	-0.04585	0.065767
MR Egger intercept: 0.0007; p= 0.9; providing limited evidence of horizontal pleiotropy influencing causal effect estimates. I2GX= 0.56; suggesting a 44% attenuation of the Egger estimate towards zero.						

Table B32. Causal effect estimates of common variant genetic liability to autism on psychotic experiences.

METHOD	NSNP	OR	SE	P	95% CIs	
Inverse variance weighted	9	1.099962	0.08509	0.262842	0.930995	1.299594
MR Egger	9	0.81754	0.350845	0.583805	0.411021	1.626128
SIMEX corrected MR Egger	9	0.762807	0.43523	0.554	0.325042	0.762807
Weighted median	9	1.183494	0.116379	0.147727	0.942111	1.486722
Weighted mode	9	1.229463	0.16494	0.245782	0.889847	1.698696
MR Egger Intercept: 0.026; p= 0.41; providing limited evidence for horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.53; suggesting a 47% attenuation of the Egger estimate towards zero.						

Table B33. Causal effect estimates of common variant genetic liability to autism (excluding ID cases) on psychotic experiences.

METHOD	NSNP	OR	SE	P	95% CIs	
Inverse variance weighted	10	0.978766	0.063731	0.736294	0.863834	1.108991
MR Egger	10	1.107003	0.191408	0.609775	0.76071	1.610936
SIMEX corrected MR Egger	10	1.128174	0.21035	0.582	0.747003	1.703843
Weighted median	10	0.975212	0.085392	0.768799	0.82492	1.152885
Weighted mode	10	0.990865	0.143064	0.950256	0.748576	1.311574
MR Egger Intercept: -0.015; p= 0.51; providing limited evidence for horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.66; suggesting a 34% attenuation of the Egger estimate towards zero.						

Table B34. Direct effects of common variant genetic liability to autism and IQ on psychotic experiences.

	NSNP	OR	SE	P	95% CIs	
Autism	7	1.061412	0.0531	0.263	0.956499	1.177833
IQ	208	1.050325	0.0743	0.509	0.907985	1.21498

Table B35. Causal effect estimates of common variant genetic liability to social communication difficulties on risk of schizophrenia.

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	3	1.198773	0.191975	0.344973	0.822857	1.746424
MR Egger	3	1.10782	0.511899	0.874317	0.406192	3.021388
SIMEX corrected MR Egger	3	1.084374	0.465969	0.89	0.435049	2.702838
Weighted median	3	1.352054	0.251013	0.229507	0.82666	2.211368
Weighted mode	3	1.414134	0.288649	0.352852	0.803134	2.489965
MR Egger Intercept: 0.003; p= 0.89; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.88; suggesting a 12% attenuation of the Egger estimate towards zero.						

Table B36. Causal effect estimates of common variant genetic liability to social communication difficulties on risk of schizophrenia (European ancestry sample).

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	3	1.259945	0.279537	0.408459	0.728458	2.179208
MR Egger	3	0.944719	0.779398	0.953632	0.205053	4.352509
SIMEX corrected MR Egger	3	0.980395	0.89078	0.986	0.171062	5.61886
Weighted median	3	1.509373	0.300477	0.170644	0.837579	2.719993
Weighted mode	3	1.652741	0.382548	0.319495	0.780861	3.49813
MR Egger Intercept: 0.012; p= 0.75; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.88; suggesting a 12% attenuation of the Egger estimate towards zero.						

Table B37. Causal effect estimates of common variant genetic liability to empathising on risk of schizophrenia.

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	2	0.989913	0.013167	0.441289	0.964693	1.015791

Table B38. Causal effect estimates of common variant genetic liability to empathising on risk of schizophrenia (European ancestry sample).

METHOD	NSNP	OR	SE	P	95% CIs	
Inverse variance weighted	3	0.992417	0.014158	0.590823	0.965256	1.020342
MR Egger	3	1.032967	0.036595	0.538316	0.961471	1.10978
SIMEX corrected MR Egger	3	1.037454	0.01955	0.201	0.998453	1.077979
Weighted median	3	0.987651	0.017586	0.479846	0.954188	1.022288
Weighted mode	3	0.980403	0.021611	0.456445	0.939743	1.022823
MR Egger Intercept: -0.024; p= 0.45; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.74; suggesting a 26% attenuation of the Egger estimate towards zero.						

Table B39. Causal effect estimates of common variant genetic liability to systemizing on risk of schizophrenia.

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	5	1.001607	0.007498	0.830448	0.986995	1.016435
MR Egger	5	0.945633	0.113132	0.655141	0.75757	1.180383
SIMEX corrected MR Egger	5	0.868142	0.195	0.521	0.592384	1.272267
Weighted median	5	0.996495	0.007285	0.629848	0.982367	1.010826
Weighted mode	5	0.992695	0.010555	0.525556	0.972369	1.013447
MR Egger Intercept: 0.041; p= 0.65; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0						

Table B40. Causal effect estimates of common variant genetic liability to systemising on risk of schizophrenia (European ancestry sample).

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	5	0.999439	0.012601	0.964495	0.975057	1.024431
MR Egger	5	0.978513	0.191351	0.916791	0.67249	1.423794
SIMEX corrected MR Egger	5	0.956447	0.3273	0.9	0.503567	1.816621
Weighted median	5	1.000826	0.011998	0.945133	0.977566	1.02464
Weighted mode	5	1.004551	0.018734	0.820394	0.968334	1.042123
MR Egger Intercept: 0.015; p= 0.92; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX=0						

Table B41. Direct effects of common variant genetic liability to social communication difficulties and IQ on risk of schizophrenia.

	NSNP	OR	SE	P	95%CIs	
SCDC	3	1.437636	0.278	0.193	0.833701	2.479061
IQ	154	0.740818	0.0894	0.000991	0.621746	0.882695

Table B42. Direct effects of common variant genetic liability to social communication difficulties and IQ on risk of schizophrenia (European ancestry sample).

	NSNP	OR	SE	P	95%CIs	
SCDC	3	1.645427	0.322	0.124	0.87536	3.092934
IQ	154	0.708929	0.105	0.00128	0.577065	0.870925

Table B43. Direct effects of common variant genetic liability to empathising and IQ on risk of schizophrenia.

	NSNP	OR	SE	P	95% CIs	
EQ	2	1.007951	0.0122	0.518	0.984135	1.032344
IQ	211	0.770281	0.0809	0.00146	0.657333	0.902636

Table B44. Direct effects of common variant genetic liability to empathising and IQ on risk of schizophrenia (European ancestry sample).

	NSNP	OR	SE	P	95%CIs	
EQ	2	1.012477	0.0141	0.38	0.98488	1.040848
IQ	210	0.76338	0.0907	0.00325	0.63905	0.911897

Table B45. Direct effects of common variant genetic liability to systemising and IQ on risk of schizophrenia.

	NSNP	OR	SE	P	95% CIs	
SQ	5	1.000289	0.00768	0.97	0.985345	1.01546
IQ	211	0.758813	0.079	0.000575	0.649963	0.885892

Table B46. Direct effects of common variant genetic liability to systemising and IQ on risk of schizophrenia (European ancestry sample).

	NSNP	OR	SE	P	95%CIs	
SQ	5	1.001241	0.00856	0.885	0.984583	1.018181
IQ	210	0.745277	0.0886	0.00107	0.626469	0.886615

Table B47. Causal effect estimates of common variant genetic liability to social communication difficulties on IQ.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	3	-0.12965	0.065386	0.047387	-0.2578	-0.00149
MR Egger	3	-0.25115	0.140007	0.323751	-0.52557	0.023259
SIMEX corrected MR Egger	3	-0.22695	0.049424	0.137	-0.32382	-0.13008
Weighted median	3	-0.12355	0.085697	0.149395	-0.29151	0.044419
Weighted mode	3	-0.11431	0.10239	0.380373	-0.31499	0.086373
MR Egger Intercept: 0.005; p= 0.51; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.88; suggesting a 12% attenuation of the Egger estimate towards zero.						

Table B48. Causal effect estimates of common variant genetic liability to higher IQ on social communication difficulties.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	154	-0.03607	0.020864	0.083849	-0.07696	0.004824
MR Egger	154	-0.08789	0.098247	0.372407	-0.28046	0.104671
SIMEX corrected MR Egger	154	-0.09308	0.133707	0.487	-0.35514	-0.35514
Weighted median	154	-0.0053	0.030777	0.863391	-0.06562	0.055027
Weighted mode	154	0.035057	0.086472	0.685743	-0.13443	0.204542
MR Egger Intercept: 0.001; p= 0.59; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.44; suggesting a 56% attenuation of the Egger estimate towards zero.						

Table B49. Causal effect estimates of common variant genetic liability to higher empathising on IQ.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	2	-0.00074	0.005711	0.896317	-0.01194	0.01045

Table B50. Causal effect estimates of common variant genetic liability to higher IQ on empathising.

METHOD	NSNP	β	SE	P	95% CIs	
Inverse variance weighted	211	-1.72577	0.402638	1.82E-05	-2.51494	-0.9366
MR Egger	211	-3.2513	1.864715	0.082701	-6.90614	0.403545
SIMEX corrected MR Egger	211	-4.91482	2.59012	0.0591	-9.99146	0.161815
Weighted median	211	-1.71828	0.490521	0.00046	-2.6797	-0.75686
Weighted mode	211	-1.28099	1.439308	0.374481	-4.10204	1.54005
MR Egger Intercept: 0.031; p= 0.4; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates I2GX= 0.5; suggesting a 50% attenuation of the Egger estimate towards zero.						

Table B51. Causal effect estimates of common variant genetic liability to systemising on IQ.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	4	0.003286	0.002428	0.176	-0.00147	0.008045
MR Egger	4	0.019812	0.035403	0.632055	-0.04958	0.089201
SIMEX corrected MR Egger	4	0.049	0.05933	0.496	-0.06729	0.165287
Weighted median	4	0.001507	0.002575	0.558361	-0.00354	0.006554
Weighted mode	4	0.000428	0.003675	0.914648	-0.00677	0.00763
MR Egger Intercept: -0.012; p= 0.68; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0						

Table B52. Causal effect estimates of common variant genetic liability to higher IQ on systemising.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	211	1.683525	0.579703	0.003683	0.547308	2.819743
MR Egger	211	-1.45942	2.681705	0.586875	-6.71556	3.796724
SIMEX corrected MR Egger	211	-2.21291	3.764	0.557	-9.59035	5.16453
Weighted median	211	2.879484	0.762903	0.00016	1.384194	4.374774
Weighted mode	211	4.272162	2.255218	0.059553	-0.14806	8.69239
MR Egger Intercept: 0.064; p= 0.231; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX=0.5; suggesing a 50% attenuation of the Egger estimate towards zero.						

Table B53. Causal effect estimates of common variant genetic liability to empathising on psychotic experiences.

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	2	1.016456	0.030331	0.590493	0.957789	1.078716

Table B54. Causal effect estimates of common variant genetic liability to systemising on psychotic experiences.

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	5	1.005119	0.014917	0.732138	0.976158	1.034939
MR Egger	5	1.167097	0.213507	0.521564	0.76801	1.773567
SIMEX corrected MR Egger	5	1.470349	0.3638	0.367	0.720689	2.999807
Weighted median	5	1.00221	0.017315	0.898546	0.968768	1.036807
Weighted mode	5	0.989446	0.024566	0.688085	0.942933	1.038254
MR Egger Intercept: -0.106; p= 0.53; providing limited evidence of horizontal pleiotropy influencing causal effect estimates. I2GX= 0						

Table B55. Causal effect estimates of common variant genetic liability to social communication difficulties on psychotic experiences.

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	3	2.200316	0.421278	0.061217	0.963576	5.024396
MR Egger	3	2.152994	0.897393	0.549831	0.370823	12.50026
SIMEX corrected MR Egger	3	2.050099	0.672551	0.479	0.548641	7.660582
Weighted median	3	2.456973	0.512701	0.079547	0.899457	6.711514
Weighted mode	3	2.650613	0.59809	0.244698	0.820808	8.559545
MR Egger Intercept: 0.001; p= 0.98; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.88; suggesting a 12% attenuation of the Egger estimate towards zero.						

Table B56. Direct effects of common variant genetic liability to social communication difficulties and IQ on psychotic experiences.

	NSNP	OR	SE	P	95%CIs	
SCDC	3	1.139968	0.269	0.627	0.672845	1.93139
IQ	153	1.090679	0.0884	0.328	0.917169	1.297013

Table B57. Direct effects of common variant genetic liability to empathising and IQ on psychotic experiences.

	NSNP	OR	SE	P	95%CIs	
EQ	2	0.994565	0.0113	0.63	0.972779	1.016838
IQ	209	1.067586	0.0752	0.385	0.921279	1.237127

Table B58. Direct effects of common variant genetic liability to systemising and IQ on psychotic experiences.

	NSNP	OR	SE	P	95%CIs	
SQ	5	1.01684	0.00694	0.0166	1.003102	1.030766
IQ	209	1.049695	0.0728	0.506	0.910112	1.210687

Table B59. Causal effect estimates of common variant genetic liability to schizophrenia on autism.

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	241	1.146115	0.021223	1.31E-10	1.099419	1.194795
MR Egger	241	1.342735	0.086302	0.00075	1.133778	1.590202
SIMEX corrected MR Egger	241	1.502463	0.113908	0.000425	1.201831	1.878297
Weighted median	241	1.140014	0.027693	2.22E-06	1.079785	1.203602
Weighted mode	241	1.102208	0.078284	0.215042	0.945424	1.284993
MR Egger Interecept: -0.01; p= 0.06; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.6; suggesting a 40% attenuation of the Egger estimate towards zero.						

Table B60. Causal effect estimates of common variant genetic liability to schizophrenia (European ancestry sample) on autism.

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	97	1.135066	0.027921	5.69E-06	1.074619	1.198914
MR Egger	97	1.334834	0.102757	0.006006	1.091336	1.632662
SIMEX Corrected MR Egger	97	1.475814	0.13189	0.00399	1.139632	1.911168
Weighted median	97	1.159559	0.031475	2.56E-06	1.090185	1.233347
Weighted mode	97	1.310627	0.073164	0.000363	1.135535	1.512716
MR Egger Intercept: -0.014; p= 0.1; providing limited evidence of horizontal pleiotropy influencing the causal estimates. I2GX= 0.62; suggesting a 38% attenuation of the Egger estimate towards zero.						

Table B61. Causal effect estimates of common variant genetic liability to schizophrenia on autism excluding ID cases.

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	241	1.14658	0.02448	2.30E-08	1.092866	1.202935
MR Egger	241	1.41308	0.099155	0.000581	1.163494	1.716207
SIMEX Corrected MR Egger	241	1.629043	0.131872	0.000267	1.258001	2.109524
Weighted median	241	1.16871	0.034257	5.34E-06	1.092814	1.249876
Weighted mode	241	1.206209	0.097431	0.055506	0.996523	1.460016
MR Egger Intercept: -0.013; p= 0.03; providing evidence of horizontal pleiotropy. I2GX= 0.6; suggesting a 40% attenuation of the Egger estimate towards zero.						

Table B62. Causal effect estimates of common variant genetic liability to schizophrenia (European ancestry sample) on autism excluding ID cases.

METHOD	NSNP	OR	SE	P	95%CIs	
Inverse variance weighted	98	1.114762	0.03129	0.000516	1.048451	1.185268
MR Egger	98	1.39782	0.113749	0.00406	1.118475	1.746934
SIMEX Corrected MR Egger	98	1.576615	0.14718	0.00259	1.181526	2.103816
Weighted median	98	1.184715	0.03666	3.77E-06	1.102576	1.272974
Weighted mode	98	1.268525	0.103396	0.023566	1.035826	1.553501
MR Egger Intercept: 0.019; p= 0.04; providing evidence of horizontal pleiotropy. I2GX= 0.62; suggesting a 38% attenuation of the Egger estimate towards zero.						

Table B63. Direct effects of common variant genetic liability to schizophrenia and IQ on autism.

	NSNP	OR	SE	P	95%CIs	
SCZ	210	1.185305	0.0231	1.35E-12	1.132836	1.240204
IQ	179	1.426181	0.0731	1.74e- 6	1.235807	1.645881

Table B64. Direct effects of common variant genetic liability to schizophrenia (European ancestry sample) and IQ on autism.

	NSNP	OR	SE	P	95%CIs	
SCZ	77	1.174685	0.0286	4.89E-08	1.110648	1.242414
IQ	194	1.416232	0.0782	1.23E-05	1.21498	1.65082

Table B65. Causal effect estimates of common variant genetic liability to schizophrenia on social communication difficulties.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	209	0.018795	0.006132	0.002177	0.006776	0.030814
MR Egger	209	0.033675	0.026259	0.201138	-0.01779	0.085143
SIMEX Corrected MR Egger	209	0.047171	0.033548	0.161	-0.01858	0.112925
Weighted median	209	0.021054	0.009051	0.020014	0.003314	0.038795
Weighted mode	209	0.014006	0.022366	0.53187	-0.02983	0.057843
MR Egger Intercept: -0.0009; p=0.56; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.6; suggesting a 40% attenuation of the Egger estimate towards zero.						

Table B66. Causal effect estimates of common variant genetic liability to schizophrenia (European ancestry sample) on social communication difficulties.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	80	0.023363	0.007519	0.001888	0.008626	0.0381
MR Egger	80	-0.00811	0.032741	0.804915	-0.07229	0.056058
SIMEX Corrected MR Egger	80	-0.01152	0.03787	0.762	-0.08575	0.062704
Weighted median	80	0.024564	0.010527	0.019629	0.003931	0.045197
Weighted mode	80	0.027892	0.025086	0.269571	-0.02128	0.07706
MR Egger Intercept: 0.003; p= 0.33; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.57; suggesting a 43% attenuation of the Egger estimate towards zero.						

Table B67. Causal effect estimates of common variant genetic liability to schizophrenia on empathy.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	244	0.308064	0.121771	0.011411	0.069393	0.546734
MR Egger	244	0.216064	0.501254	0.666818	-0.76639	1.198522
SIMEX Corrected MR Egger	244	0.321361	0.658545	0.626	-0.96939	1.612109
Weighted median	244	0.261601	0.164677	0.112157	-0.06117	0.584367
Weighted mode	244	0.250624	0.47577	0.598831	-0.68189	1.183134
MR Egger Intercept: 0.006; p = 0.85; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.61; suggesting a 39% attenuation of the Egger estimate towards zero.						

Table B68. Causal effect estimates of common variant genetic liability to schizophrenia (European ancestry sample) on empathy.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	100	0.369404	0.133874	0.005792	0.107011	0.631798
MR Egger	100	0.850944	0.49309	0.087546	-0.11551	1.817401
SIMEX Corrected MR Egger	100	1.12241	0.63416	0.0799	-0.12054	2.365364
Weighted median	100	0.402149	0.1886	0.032984	0.032493	0.771806
Weighted mode	100	0.41521	0.471829	0.38099	-0.50958	1.339996
MR Egger Intercept: -0.041; p= 0.31; providing limited evidence of horizontal pleiotropy influencing the causal effect estimates. I2GX= 0.65; suggesting a 35% attenuation of the Egger estimate towards zero.						

Table B69. Causal effect estimates of common variant genetic liability to schizophrenia on systemising.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	244	0.340755	0.203726	0.094403	-0.05855	0.740058
MR Egger	244	1.275327	0.83601	0.128442	-0.36325	2.913908
SIMEX Corrected MR Egger	244	1.75136	1.08259	0.107	-0.37052	3.873236
Weighted median	244	0.182125	0.246246	0.459539	-0.30052	0.664767
Weighted mode	244	0.116867	0.686705	0.865007	-1.22907	1.462808
MR Egger Intercept: -0.058; p= 0.25; providing limited evidence of horizontal pleiotropy influencing causal effect estimates. I2GX= 0.61; suggesting a 39% attenuation of the Egger estimate towards zero.						

Table B70. Causal effect estimates of common variant genetic liability to schizophrenia (European ancestry sample) on systemising.

METHOD	NSNP	β	SE	P	95%CIs	
Inverse variance weighted	100	0.073314	0.240538	0.760524	-0.39814	0.544769
MR Egger	100	-0.11581	0.888535	0.896566	-1.85734	1.625719
SIMEX Corrected MR Egger	100	-0.12619	1.15728	0.913	-2.39446	2.142079
Weighted median	100	-0.06374	0.284685	0.822836	-0.62172	0.494242
Weighted mode	100	-0.14803	0.67132	0.825932	-1.46382	1.167758
MR Egger Intercept: 0.016; p= 0.83; providing limited evidence of horizontal pleiotropy influencing causal effect estimates . I2GX= 0.65; suggesting a 35% attenuation of the Egger estimate towards zero.						

Table B71. Direct effects of common variant genetic liability to schizophrenia and IQ on social communication difficulties.

	NSNP	β	SE	P	95%CIs	
SCZ	183	0.0166	0.00603	6.15E-03	0.004781	0.028419
IQ	134	-0.0248	0.02	0.216	-0.064	0.0144

Table B72. Direct effects of common variant genetic liability to schizophrenia (European ancestry sample) and IQ on social communication difficulties.

	NSNP	β	SE	P	95%CIs	
SCZ	62	0.0181	0.00728	1.35E-02	0.003831	0.032369
IQ	142	-0.0407	0.0202	0.0459	-0.08029	-0.00111

Table B73. Direct effects of common variant genetic liability to schizophrenia and IQ on empathy.

	NSNP	β	SE	P	95%CIs	
SCZ	212	0.169	0.125	1.77E-01	-0.076	0.414
IQ	180	-1.91	0.395	2.02E-06	-2.6842	-1.1358

Table B74. Direct effects of common variant genetic liability to schizophrenia (European ancestry sample) and IQ on empathy.

	NSNP	β	SE	P	95%CIs	
SCZ	77	0.228	0.147	1.23E-01	-0.06012	0.51612
IQ	195	-1.66	0.397	3.84E-05	-2.43812	-0.88188

Table B75. Direct effects of common variant genetic liability to schizophrenia on systemising.

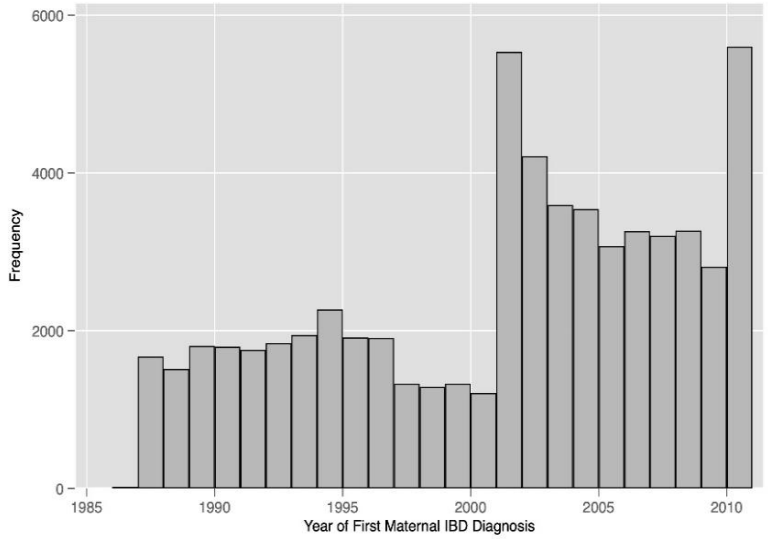
	NSNP	β	SE	P	95%CIs	
SCZ	212	0.169	0.125	1.77E-01	-0.076	0.414
IQ	180	-1.91	0.395	2.02E-06	-2.6842	-1.1358

Table B76. Direct effects of common variant genetic liability to schizophrenia (European ancestry sample) on systemising.

	NSNP	β	SE	P	95%CIs	
SCZ	77	0.228	0.147	1.23E-01	-0.06012	0.51612
IQ	195	-1.66	0.397	3.84E-05	-2.43812	-0.88188

Appendix C

Figure C1. Frequency of IBD diagnoses (for mothers and fathers of the study cohort) in National Patient Register (NPR) from 1987 to 2010. Data quality from outpatient specialist care were not originally included in the NPR and these were added starting in the late 1990s. This is reflected in the figures bellow, justifying therefore the use of parental lifetime IBD diagnosis as the primary exposure in the study investigating the associations between parental diagnoses of IBD and offspring autism.



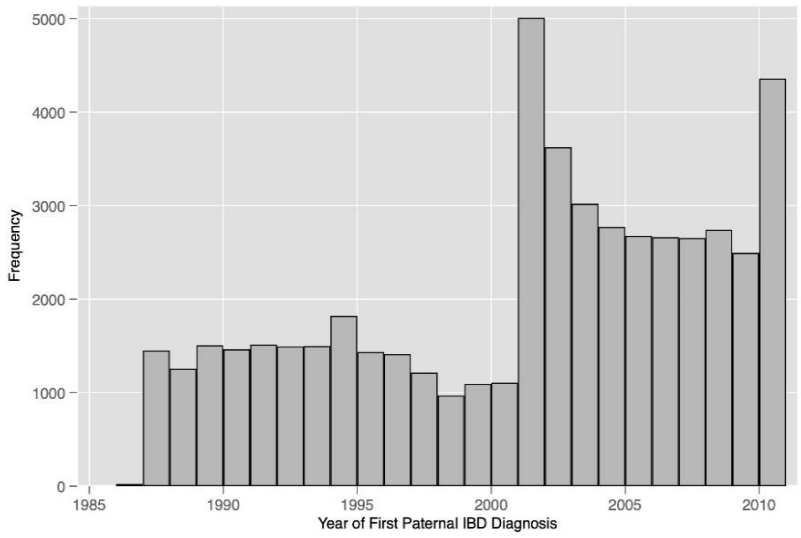


Figure C2. Genetic instrument extraction process for the MR analyses investigating the causal links between common variant genetic liability to autism without intellectual disabilities (ID) and Inflammatory bowel disease (IBD), Crohn's (CD), ulcerative colitis (UC).

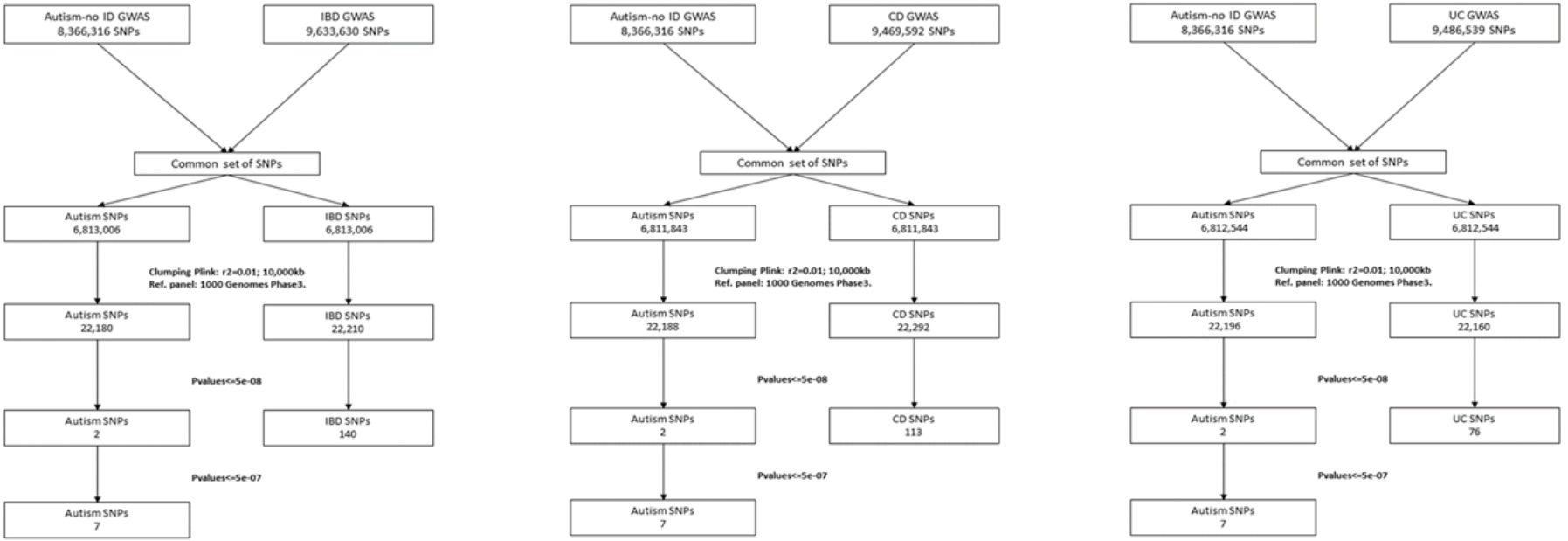
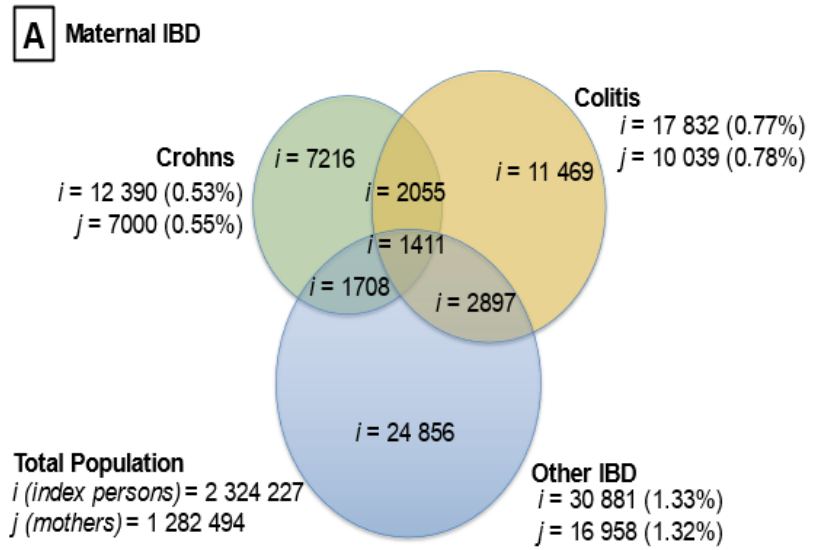
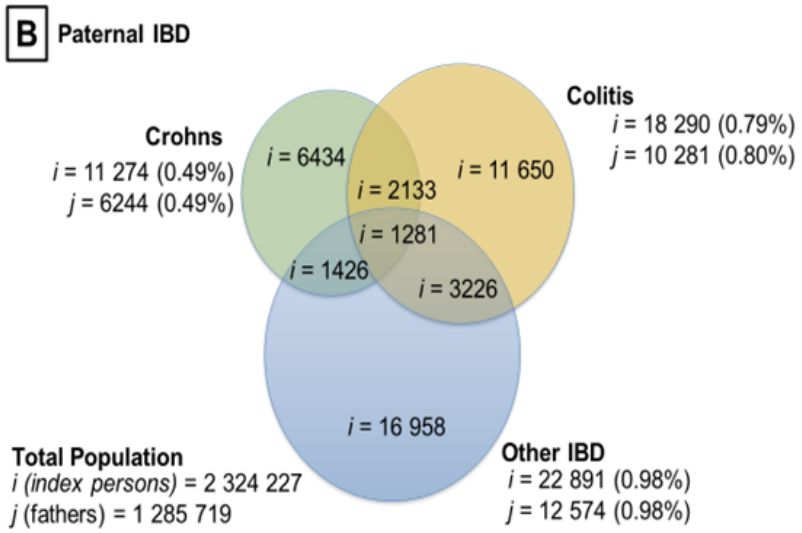


Figure C3. Overall prevalence of Crohn's disease (Crohn's), ulcerative colitis (colitis) and other inflammatory bowel disease (IBD) in the mothers and fathers of the cohort.





Note [A]: Overall prevalence of Crohn's, UC, and other IBD diagnoses are shown in terms of mothers diagnosed (j), as well as children born to those mothers and followed up for autism (i). Overlap in diagnoses is only shown for index persons (i) included in the study, to align with values presented in table 4.2 in Chapter4. The extent of overlap is virtually identical if mothers or index persons are displayed, for example of the 7,000 mothers diagnoses with Crohn's, 1,984 (28.3%) were also diagnosed with UC, with the analogous proportion in children being 28% (3,466/12,390).

Note [B]: Overall prevalence of Crohn's, UC, and other IBD diagnoses are shown in terms of fathers diagnosed (j), as well as children born to those fathers and followed up for autism (i). Overlap in diagnoses is only shown for index persons (i) included in the study, to align with values presented in table 4.2 in Chapter4. The extent of overlap is virtually identical if fathers or index persons are displayed, for example of the 6,244 fathers diagnoses with Crohn's, 1,925 (30.8%) were also diagnosed with UC, with the analogous proportion in children being 30.3% (3,414/11,274).

Table C4. Diagnostic codes and register sources for ascertainment of outcomes and exposures.

Data Sources and Coding System	**Autism Spectrum Disorders (ASD)**	**Intellectual Disability**	**Parental Psychiatric History**	**Any IBD (Crohn's UC, unspecified diagnoses combined)**	**Ulcerative Colitis**	**Crohn's Disease**	**Other IBD**
ICD-9[a]	299	317-319	290-319	555, 556, 558	556	555	558
ICD-10[a]	F84	F70-F79	F chapter	K50, K51, K52.3, K52.9	K51	K50	K52.3, K52.9

[a]The National Patient Register (NPR): including inpatient care beginning in 1973, outpatient physician visits in specialist care beginning in 1997, outpatient psychiatric diagnoses from 2006, and children and adolescent psychiatric care (2011).

Table C5. Effect sizes, standard errors and p-values of the genetic instruments used in the Mendelian randomisation (MR) analyses investigating the bidirectional causal effects of common variant genetic liability to autism with inflammatory bowel disease (IBD), Crohn's disease (Crohn's) and ulcerative colitis (UC).

Autism					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs910805	A	G	-0.0957	0.016	2.04E-09
rs2224274	T	C	0.070999	0.0138	2.86E-07
rs325485	A	G	0.072804	0.0143	3.25E-07
rs112635299	T	G	0.220997	0.0432	3.04E-07
rs10099100	C	G	0.084304	0.0147	1.07E-08
rs45595836	T	C	0.138996	0.0272	3.13E-07
rs2391769	A	G	-0.0769	0.0145	1.14E-07
rs6701243	A	C	0.073501	0.0144	3.07E-07
rs1452075	T	C	0.080704	0.0155	2.07E-07
IBD					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs6584282	G	A	-0.152	0.0124	1.19E-34
rs11195128	T	C	0.0792	0.0133	2.74E-09
rs111456533	A	G	-0.1031	0.017	1.18E-09
rs10826797	T	G	-0.099	0.0136	3.99E-13
rs2384352	G	A	0.0951	0.0131	3.12E-13
rs10761659	G	A	0.1585	0.0126	2.3E-36
rs1250573	A	G	-0.098	0.0138	1.11E-12
rs2343551	C	A	0.104	0.0156	2.99E-11
rs7918084	T	C	0.071	0.0125	1.38E-08
rs11221335	C	T	0.0827	0.0148	2.44E-08
rs11236797	A	C	0.1488	0.0125	7.19E-33
rs11066188	A	G	0.0874	0.013	1.76E-11
rs117981694	A	G	0.3452	0.0411	4.53E-17
rs12825700	A	G	0.1324	0.0127	1.28E-25
rs3897234	C	T	0.0971	0.0145	1.9E-11
rs140933577	C	T	-0.1857	0.0305	1.13E-09
rs7995004	T	C	0.0833	0.0148	1.79E-08
rs194746	T	C	0.0833	0.0124	1.84E-11
rs3850378	C	T	0.1536	0.0207	1.1E-13
rs56062135	T	C	0.1382	0.0145	1.37E-21
rs2301127	A	G	0.0783	0.0126	4.96E-10
rs7190426	C	A	-0.0872	0.0155	2.06E-08
rs28374519	A	G	-0.1105	0.0137	6.55E-16
rs9934775	T	C	-0.1116	0.0172	8.77E-11
rs749910	A	G	0.1961	0.0138	7.83E-46
rs8056255	A	T	0.2765	0.0327	2.99E-17
rs145126485	C	A	0.2464	0.0356	4.77E-12
rs11548656	G	A	-0.2374	0.0362	5.18E-11

IBD instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs1143687	T	C	-0.1382	0.0251	3.83E-08
rs16940202	C	T	0.113	0.0169	2.51E-11
rs11870407	A	C	-0.101	0.014	4.83E-13
rs12936409	T	C	0.1406	0.0124	7.73E-30
rs744166	G	A	-0.1109	0.0126	1.34E-18
rs4072601	A	G	-0.1264	0.0177	8.43E-13
rs80262450	A	G	0.1581	0.019	1.04E-16
rs1319951	G	C	-0.0851	0.0147	7.5E-09
rs12720356	C	A	0.1585	0.0214	1.44E-13
rs11669299	T	C	-0.1107	0.0157	1.84E-12
rs4807569	C	A	0.1281	0.0152	4.24E-17
rs62126610	G	A	0.1407	0.0166	2.6E-17
rs11804831	C	T	0.0908	0.0164	3.31E-08
rs1336900	A	G	-0.0848	0.0128	2.98E-11
rs78703675	A	G	0.1078	0.0187	7.62E-09
rs4845604	A	G	-0.1388	0.0185	7.09E-14
rs12411216	C	A	0.083	0.0126	3.85E-11
rs7532133	G	A	0.0789	0.0134	3.83E-09
rs10800309	G	A	-0.123	0.0133	1.94E-20
rs12136659	C	T	0.087	0.0142	1.02E-09
rs2224873	A	T	0.0989	0.0147	1.7E-11
rs2816972	G	A	0.1107	0.0202	3.9E-08
rs35730213	C	G	-0.1346	0.014	7.5E-22
rs1317209	A	G	0.1164	0.016	3.79E-13
rs3820328	G	A	-0.0926	0.0129	8.31E-13
rs6674040	T	G	-0.1129	0.0124	6.31E-20
rs3024493	A	C	0.1911	0.0165	4.04E-31
rs59043219	A	G	0.0738	0.0129	1.09E-08
rs34963268	C	G	-0.1315	0.0166	2.34E-15
rs116760029	A	G	0.1842	0.0311	3.13E-09
rs112874012	T	C	-0.1991	0.0318	3.9E-10
rs11581607	A	G	-0.6578	0.0294	4.6E-111
rs11576006	C	T	-0.0872	0.0154	1.49E-08
rs10746475	A	T	0.1308	0.0164	1.58E-15
rs6017342	C	A	0.1156	0.0135	1.07E-17
rs6063502	G	A	-0.0734	0.0134	4.55E-08
rs154873	A	G	-0.0813	0.0132	7.38E-10
rs4256018	G	T	0.0786	0.0138	1.23E-08
rs6062496	A	G	0.137	0.0129	2.83E-26
rs1297264	G	A	-0.1462	0.0126	3.98E-31
rs2284553	G	A	0.0742	0.0128	7.4E-09
rs2836881	T	G	-0.1643	0.0146	1.96E-29
rs2838517	C	T	-0.128	0.0125	1.84E-24
rs5754100	C	T	0.1293	0.016	7.14E-16

IBD instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs1978083	G	C	0.0875	0.0141	6.03E-10
rs2413583	T	C	-0.1732	0.0171	4.6E-24
rs62228374	A	G	0.2669	0.0445	2E-09
rs1558619	T	G	-0.0843	0.0123	8.9E-12
rs72852162	C	A	-0.1129	0.0202	2.3E-08
rs6740847	G	A	-0.0924	0.0125	1.22E-13
rs13422838	C	T	-0.1143	0.0205	2.56E-08
rs62180107	C	G	-0.0797	0.0132	1.55E-09
rs62183956	T	C	-0.078	0.0125	4.49E-10
rs3792111	T	C	0.1391	0.0124	5.12E-29
rs4676408	A	G	0.1011	0.013	7.63E-15
rs76527535	T	C	-0.0864	0.0156	2.87E-08
rs76286777	C	T	0.0996	0.0151	4.66E-11
rs11677002	C	T	-0.0931	0.0126	1.37E-13
rs55946629	A	C	0.1298	0.018	5.45E-13
rs7608697	C	A	0.1395	0.0126	1.67E-28
rs503734	G	A	-0.0692	0.0124	2.67E-08
rs56116661	T	C	-0.1	0.0163	9.27E-10
rs1131095	C	T	0.1635	0.0131	1.22E-35
rs2593855	T	C	-0.0832	0.014	2.54E-09
rs62324212	A	C	0.0886	0.0127	2.67E-12
rs11734570	A	G	0.0694	0.0127	4.8E-08
rs341295	T	C	0.0702	0.0124	1.45E-08
rs11739135	C	G	0.1366	0.0125	1.1E-27
rs2961704	T	C	-0.1459	0.0227	1.31E-10
rs17656349	T	C	0.0731	0.0125	5.17E-09
rs17800987	G	A	0.1843	0.0222	1.07E-16
rs10052709	G	C	-0.1236	0.0187	3.44E-11
rs1157509	G	A	0.1449	0.0172	3.35E-17
rs755374	T	C	0.1767	0.0134	1.59E-39
rs56235845	G	T	0.0877	0.0138	1.77E-10
rs395157	T	C	0.0776	0.0124	4.63E-10
rs72748445	A	C	-0.11	0.0141	5.37E-15
rs1445004	T	C	0.1689	0.0127	3.48E-40
rs10055349	A	G	0.1038	0.0148	2.17E-12
rs6873866	C	T	-0.0919	0.0128	6.15E-13
rs11152949	G	A	0.1019	0.0133	1.56E-14
rs13200059	A	G	0.2114	0.0346	9.69E-10
rs6933404	C	T	0.0863	0.0149	6.64E-09
rs1267496	C	G	0.1053	0.0159	3.39E-11
rs212402	A	G	-0.0743	0.013	1.06E-08
rs35171809	G	A	0.1088	0.0123	1.16E-18
rs4712528	C	G	0.1043	0.0152	7.14E-12
rs4710973	C	T	-0.0842	0.0132	1.67E-10

IBD instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs1265098	C	T	-0.1278	0.0157	4.25E-16
rs117292830	A	G	0.3398	0.0394	6.69E-18
rs77108272	A	C	0.457	0.0505	1.49E-19
rs143210366	G	T	0.2836	0.036	3.14E-15
rs114751021	G	A	0.39	0.0407	9.24E-22
rs62402717	A	G	-0.2081	0.0367	1.43E-08
rs138753323	C	T	0.5947	0.0351	1.47E-64
rs687308	T	C	-0.2294	0.0174	1.13E-39
rs77318243	A	T	-0.1617	0.0237	8.4E-12
rs12206377	G	A	0.2504	0.0416	1.72E-09
rs67289879	T	C	0.0898	0.0162	3.04E-08
rs62408218	T	C	-0.0818	0.0129	2.4E-10
rs62482552	A	G	-0.0737	0.0131	1.97E-08
rs4730263	A	C	-0.0746	0.0127	4.29E-09
rs10953551	G	A	-0.1033	0.0127	4.94E-16
rs243505	G	A	-0.0805	0.0128	3.04E-10
rs149169037	A	G	-0.1338	0.0242	3.26E-08
rs1456896	T	C	0.0879	0.0133	4.5E-11
rs11768365	G	A	-0.0837	0.0152	3.88E-08
rs2529269	C	T	0.1042	0.0163	1.7E-10
rs4236540	T	G	-0.081	0.0139	5.54E-09
rs4380956	A	G	0.0907	0.0127	1.12E-12
rs938650	A	G	-0.1074	0.0189	1.41E-08
rs10114470	C	T	0.1475	0.0137	4.1E-27
rs3829110	G	A	0.1574	0.0125	3.52E-36
rs1887428	C	G	-0.1643	0.0131	2.46E-36
UC					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs7911680	C	A	-0.1525	0.0159	6.71E-22
rs7911117	G	T	-0.1342	0.0239	1.84E-08
rs10761659	G	A	0.1276	0.016	1.33E-15
rs2045241	A	G	-0.1063	0.0169	2.83E-10
rs2212434	T	C	0.1252	0.0159	2.8E-15
rs12825700	A	G	0.1889	0.0161	7.33E-32
rs1359946	A	G	0.1571	0.0202	6.58E-15
rs56062135	T	C	0.1078	0.0184	4.66E-09
rs11645239	G	C	-0.1174	0.02	4.14E-09
rs7203363	A	T	0.1071	0.0189	1.41E-08
rs16940186	C	T	0.1357	0.0214	2.19E-10
rs12936409	T	C	0.1365	0.0158	5.62E-18
rs11651246	G	T	0.147	0.0219	2.01E-11
rs8073117	A	G	-0.1548	0.0225	6.4E-12
rs78064630	A	G	0.1759	0.0308	1.08E-08

UC instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs10408351	A	G	0.1548	0.0204	2.92E-14
rs1336900	A	G	-0.0887	0.0163	4.95E-08
rs79051659	A	G	0.1605	0.0264	1.3E-09
rs6658353	C	G	-0.1569	0.016	1.17E-22
rs2816980	T	G	0.1941	0.026	9.18E-14
rs7554511	A	C	-0.1448	0.0178	4.27E-16
rs2294633	T	C	-0.0985	0.0177	2.79E-08
rs1317209	A	G	0.1818	0.0203	2.9E-19
rs3820328	G	A	-0.1662	0.0164	3.66E-24
rs10737481	G	T	0.2173	0.0159	2.56E-42
rs3024493	A	C	0.21	0.0209	7.46E-24
rs34920465	G	A	-0.1708	0.0213	9.01E-16
rs7544646	G	C	-0.1168	0.016	2.53E-13
rs11209026	A	G	-0.483	0.0358	2E-41
rs7523335	A	G	-0.1389	0.021	3.42E-11
rs6017342	C	A	0.1944	0.017	3.95E-30
rs6062496	A	G	0.1359	0.0163	8.97E-17
rs1736161	A	G	-0.1227	0.0161	2.22E-14
rs2836881	T	G	-0.2217	0.0186	1.11E-32
rs2838517	C	T	-0.1177	0.016	1.78E-13
rs4993442	T	G	-0.0988	0.0179	3.54E-08
rs138788	A	G	0.0896	0.0162	2.95E-08
rs9611131	C	T	-0.1494	0.0227	5.11E-11
rs137845	G	A	0.1011	0.0158	1.5E-10
rs16830407	A	G	0.1078	0.0166	7.62E-11
rs62180181	T	C	0.1226	0.0171	8.08E-13
rs1811711	G	C	-0.1299	0.0223	6.09E-09
rs4676408	A	G	0.1433	0.0167	1.19E-17
rs7608697	C	A	0.1597	0.0161	3.03E-23
rs1131095	C	T	0.1593	0.0168	2.18E-21
rs17715902	A	G	0.0974	0.0166	4.62E-09
rs17656349	T	C	0.09	0.0159	1.54E-08
rs116724447	A	G	-0.339	0.0572	3.01E-09
rs1157509	G	A	0.1311	0.0217	1.54E-09
rs755374	T	C	0.1714	0.0171	9.73E-24
rs67111717	G	A	0.0944	0.0171	3.27E-08
rs6889364	A	G	0.1318	0.0228	7.87E-09
rs72704802	T	C	-0.1223	0.0206	2.89E-09
rs13200059	A	G	0.2944	0.0436	1.48E-11
rs6933404	C	T	0.1486	0.0188	2.69E-15
rs113986290	T	C	-0.3066	0.0531	7.59E-09
rs974334	G	C	0.1181	0.0206	9.96E-09
rs17190351	A	G	0.4301	0.0561	1.79E-14
rs9263719	T	C	-0.1692	0.0269	3.09E-10

UC instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs1265098	C	T	-0.1646	0.0203	4.71E-16
rs114849343	T	G	0.302	0.0458	4.11E-11
rs77108272	A	C	0.5479	0.062	1.02E-18
rs57256697	T	C	0.3794	0.0469	6.16E-16
rs9296004	C	A	0.3119	0.0281	1.15E-28
rs9271176	G	A	-0.3495	0.0173	4.2E-91
rs1846190	A	G	-0.2267	0.019	1.16E-32
rs3097666	C	G	-0.2154	0.0304	1.46E-12
rs872956	A	T	-0.1378	0.021	5.24E-11
rs2301989	A	G	-0.1294	0.0161	1.08E-15
rs10272963	T	C	-0.1512	0.016	4.11E-21
rs4728142	A	G	0.0995	0.0158	3.23E-10
rs798506	C	T	-0.1206	0.0179	1.47E-11
rs10817678	A	G	0.1332	0.017	4.42E-15
rs3812565	C	T	0.1335	0.016	6.5E-17
rs1887428	C	G	-0.167	0.0166	9.65E-24
rs1411262	T	C	0.101	0.0179	1.83E-08
Crohn's instruments					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs6584282	G	A	-0.1658	0.016	3.44E-25
rs10884966	A	G	0.1131	0.0171	4.13E-11
rs2002695	G	A	-0.1293	0.0189	8.31E-12
rs1148246	T	C	-0.1323	0.0167	2.09E-15
rs61839660	T	C	0.1468	0.0261	1.98E-08
rs10822050	C	T	0.1827	0.0162	2.35E-29
rs2675670	C	G	0.1074	0.0161	2.9E-11
rs1250573	A	G	-0.1522	0.0179	1.92E-17
rs1870148	A	G	0.1351	0.0206	5.44E-11
rs11236797	A	C	0.176	0.0161	8.51E-28
rs77566919	A	G	-0.1089	0.0185	4.13E-09
rs34635748	T	C	0.4794	0.0504	1.95E-21
rs28999107	T	G	0.1083	0.0178	1.06E-09
rs80244186	C	T	0.1246	0.0226	3.66E-08
rs1373904	G	A	0.141	0.0189	9.11E-14
rs194746	T	C	0.0975	0.0161	1.24E-09
rs3850378	C	T	0.199	0.0267	8.31E-14
rs72743461	A	C	0.1684	0.0187	2.26E-19
rs6416647	C	T	0.1007	0.0178	1.46E-08
rs2021511	T	C	-0.1082	0.0182	2.63E-09
rs42861	G	A	0.1243	0.0167	8.87E-14
rs55938681	T	A	0.141	0.0209	1.47E-11
rs7206852	A	T	-0.1287	0.0223	7.71E-09
rs67373269	C	G	-0.1151	0.0194	3.21E-09

Crohn's instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs4486887	T	C	-0.1686	0.0172	1.37E-22
rs2076756	G	A	0.385	0.0174	1.8E-108
rs59145923	C	G	-0.1717	0.0309	2.72E-08
rs72798422	C	T	0.5495	0.0382	6.05E-47
rs145126485	C	A	0.5236	0.0431	6.4E-34
rs7198678	T	A	-0.1398	0.0229	1.08E-09
rs59926756	A	G	0.1062	0.0176	1.74E-09
rs2948542	G	A	0.1016	0.0163	5.15E-10
rs3091315	G	A	-0.1579	0.0182	3.76E-18
rs12936409	T	C	0.1426	0.016	4.31E-19
rs744166	G	A	-0.1142	0.0162	1.8E-12
rs80262450	A	G	0.2268	0.0244	1.34E-20
rs144309607	T	C	-0.3712	0.047	2.69E-15
rs142770866	A	G	0.1753	0.0292	1.99E-09
rs4807570	A	G	0.1811	0.0193	6.03E-21
rs62126620	A	G	0.144	0.0201	8.61E-13
rs492602	G	A	0.1084	0.0162	2.33E-11
rs2476601	G	A	0.2312	0.0286	6.44E-16
rs12131079	T	C	-0.1088	0.0174	3.99E-10
rs34687326	A	G	-0.1649	0.0288	1.06E-08
rs114802258	T	C	-0.2245	0.0384	5.11E-09
rs6704109	T	C	0.1748	0.0181	5.1E-22
rs1775448	G	A	-0.122	0.017	6.78E-13
rs35730213	C	G	-0.1166	0.0181	1.17E-10
rs3122605	A	G	-0.1748	0.0227	1.24E-14
rs59805578	C	T	-0.2674	0.034	3.92E-15
rs12041056	T	C	0.1284	0.0163	3.75E-15
rs7517847	G	T	-0.3447	0.0165	5.84E-97
rs4655709	A	G	0.1224	0.0183	2.46E-11
rs3761158	A	G	-0.1098	0.0165	2.65E-11
rs6062496	A	G	0.1223	0.0167	2.62E-13
rs1297264	G	A	-0.1769	0.0163	1.59E-27
rs2284553	G	A	0.1277	0.0165	1.14E-14
rs2838517	C	T	-0.1456	0.0162	2.03E-19
rs5754100	C	T	0.1687	0.0206	3.02E-16
rs4821544	C	T	0.0966	0.0171	1.76E-08
rs2143178	C	T	-0.2087	0.0223	6.84E-21
rs62228374	A	G	0.3164	0.0557	1.36E-08
rs2110735	G	A	-0.1372	0.0185	1.2E-13
rs11683692	C	T	-0.2144	0.038	1.75E-08
rs151175749	G	C	0.2483	0.0428	6.73E-09
rs6740847	G	A	-0.104	0.0161	9.72E-11
rs1583792	T	C	-0.0882	0.016	3.26E-08
rs7563433	C	T	0.1525	0.02	2.14E-14

Crohn's instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs3816234	A	G	0.2704	0.0162	1.51E-62
rs4343432	G	A	0.1123	0.0162	3.5E-12
rs1260326	C	T	-0.1053	0.0161	6.32E-11
rs11677002	C	T	-0.1124	0.0163	4.57E-12
rs55946629	A	C	0.1755	0.0231	2.85E-14
rs7608697	C	A	0.1229	0.0163	4.03E-14
rs6808936	G	A	0.0904	0.0161	1.93E-08
rs56116661	T	C	-0.1312	0.0212	5.67E-10
rs9836291	A	G	0.1722	0.017	3.77E-24
rs2581828	G	C	-0.0941	0.0162	6.46E-09
rs13107325	T	C	0.2006	0.0284	1.67E-12
rs62324212	A	C	0.106	0.0163	8.02E-11
rs73243877	G	A	0.1164	0.0212	4.12E-08
rs2188962	T	C	0.2004	0.016	5.59E-36
rs181826	A	C	0.1162	0.0167	3.25E-12
rs9637870	A	G	0.2558	0.0275	1.33E-20
rs10052709	G	C	-0.141	0.0242	5.76E-09
rs1157509	G	A	0.1519	0.0224	1.26E-11
rs755374	T	C	0.1969	0.0174	1.38E-29
rs72748445	A	C	-0.1369	0.0181	4.31E-14
rs6451494	C	T	0.2605	0.0166	8.26E-56
rs10055349	A	G	0.1734	0.019	5.59E-20
rs137976175	A	G	-0.2564	0.0372	5.59E-12
rs6873866	C	T	-0.1314	0.0164	1.35E-15
rs73516754	C	A	0.1423	0.0169	4.04E-17
rs9482770	C	T	0.0987	0.0162	1.01E-09
rs212408	T	G	-0.1136	0.0167	9.12E-12
rs35171809	G	A	0.1566	0.0159	9.07E-23
rs1012636	T	G	0.1291	0.0198	7.01E-11
rs7753014	G	C	-0.0989	0.0163	1.39E-09
rs2240069	G	A	-0.1568	0.0252	4.73E-10
rs9264360	T	A	0.1246	0.0225	3.23E-08
rs4151651	A	G	0.3682	0.0409	2.25E-19
rs401775	C	T	0.2023	0.0203	2.17E-23
rs2073045	A	G	-0.1032	0.0188	4.28E-08
rs9501632	T	C	0.3872	0.0637	1.18E-09
rs13203429	C	G	0.1264	0.0169	6.74E-14
rs4959116	T	C	0.1362	0.0227	1.86E-09
rs11965964	T	C	0.3044	0.0529	8.83E-09
rs1321859	T	C	-0.1049	0.0172	1.18E-09
rs9656588	C	T	0.1183	0.0173	8.73E-12
rs4380956	A	G	0.132	0.0165	1.15E-15
rs938650	A	G	-0.1747	0.0247	1.65E-12
rs10114470	C	T	0.1687	0.0177	1.76E-21

Crohn's instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs4077515	T	C	0.1848	0.0162	3.15E-30
rs1887428	C	G	-0.166	0.0169	8.54E-23

Table C6. Effect sizes, standard errors and p-values of the genetic instruments used in the Mendelian randomisation (MR) analyses investigating the bidirectional causal effects of common variant genetic liability to autism without intellectual disabilities (ID) with inflammatory bowel disease (IBD), Crohn's disease (Crohn's) and ulcerative colitis (UC).

Autism without ID					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs529507	A	G	-0.1354	0.0241	1.88E-08
rs292441	A	G	-0.0958	0.0182	1.42E-07
rs1402807	T	C	0.092497	0.018	2.73E-07
rs1000177	T	C	0.123102	0.0197	3.85E-10
rs10195840	A	G	0.094701	0.0175	5.87E-08
rs10197246	T	C	0.100298	0.0186	6.94E-08
rs114489105	T	G	0.199596	0.0384	2.05E-07
IBD					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs6584282	G	A	-0.152	0.0124	1.19E-34
rs11195128	T	C	0.0792	0.0133	2.74E-09
rs111456533	A	G	-0.1031	0.017	1.18E-09
rs10826797	T	G	-0.099	0.0136	3.99E-13
rs2384352	G	A	0.0951	0.0131	3.12E-13
rs10761659	G	A	0.1585	0.0126	2.3E-36
rs1250573	A	G	-0.098	0.0138	1.11E-12
rs2343551	C	A	0.104	0.0156	2.99E-11
rs7918084	T	C	0.071	0.0125	1.38E-08
rs11221335	C	T	0.0827	0.0148	2.44E-08
rs11236797	A	C	0.1488	0.0125	7.19E-33
rs11066188	A	G	0.0874	0.013	1.76E-11
rs117981694	A	G	0.3452	0.0411	4.53E-17
rs12825700	A	G	0.1324	0.0127	1.28E-25
rs3897234	C	T	0.0971	0.0145	1.9E-11
rs140933577	C	T	-0.1857	0.0305	1.13E-09
rs7995004	T	C	0.0833	0.0148	1.79E-08
rs194746	T	C	0.0833	0.0124	1.84E-11
rs3850378	C	T	0.1536	0.0207	1.1E-13
rs56062135	T	C	0.1382	0.0145	1.37E-21
rs2301127	A	G	0.0783	0.0126	4.96E-10
rs7190426	C	A	-0.0872	0.0155	2.06E-08
rs28374519	A	G	-0.1105	0.0137	6.55E-16
rs9934775	T	C	-0.1116	0.0172	8.77E-11
rs749910	A	G	0.1961	0.0138	7.83E-46
rs8056255	A	T	0.2765	0.0327	2.99E-17
rs145126485	C	A	0.2464	0.0356	4.77E-12
rs11548656	G	A	-0.2374	0.0362	5.18E-11
rs1143687	T	C	-0.1382	0.0251	3.83E-08
rs16940202	C	T	0.113	0.0169	2.51E-11

IBD instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs11870407	A	C	-0.101	0.014	4.83E-13
rs12936409	T	C	0.1406	0.0124	7.73E-30
rs744166	G	A	-0.1109	0.0126	1.34E-18
rs4072601	A	G	-0.1264	0.0177	8.43E-13
rs80262450	A	G	0.1581	0.019	1.04E-16
rs1319951	G	C	-0.0851	0.0147	7.5E-09
rs12720356	C	A	0.1585	0.0214	1.44E-13
rs11669299	T	C	-0.1107	0.0157	1.84E-12
rs4807569	C	A	0.1281	0.0152	4.24E-17
rs62126610	G	A	0.1407	0.0166	2.6E-17
rs11804831	C	T	0.0908	0.0164	3.31E-08
rs1336900	A	G	-0.0848	0.0128	2.98E-11
rs78703675	A	G	0.1078	0.0187	7.62E-09
rs4845604	A	G	-0.1388	0.0185	7.09E-14
rs12411216	C	A	0.083	0.0126	3.85E-11
rs7532133	G	A	0.0789	0.0134	3.83E-09
rs10800309	G	A	-0.123	0.0133	1.94E-20
rs12136659	C	T	0.087	0.0142	1.02E-09
rs2224873	A	T	0.0989	0.0147	1.7E-11
rs2816972	G	A	0.1107	0.0202	3.9E-08
rs35730213	C	G	-0.1346	0.014	7.5E-22
rs1317209	A	G	0.1164	0.016	3.79E-13
rs3820328	G	A	-0.0926	0.0129	8.31E-13
rs6674040	T	G	-0.1129	0.0124	6.31E-20
rs3024493	A	C	0.1911	0.0165	4.04E-31
rs59043219	A	G	0.0738	0.0129	1.09E-08
rs34963268	C	G	-0.1315	0.0166	2.34E-15
rs116760029	A	G	0.1842	0.0311	3.13E-09
rs112874012	T	C	-0.1991	0.0318	3.9E-10
rs11581607	A	G	-0.6578	0.0294	4.6E-111
rs10746475	A	T	0.1308	0.0164	1.58E-15
rs6017342	C	A	0.1156	0.0135	1.07E-17
rs6063502	G	A	-0.0734	0.0134	4.55E-08
rs154873	A	G	-0.0813	0.0132	7.38E-10
rs4256018	G	T	0.0786	0.0138	1.23E-08
rs6062496	A	G	0.137	0.0129	2.83E-26
rs1297264	G	A	-0.1462	0.0126	3.98E-31
rs2284553	G	A	0.0742	0.0128	7.4E-09
rs2836881	T	G	-0.1643	0.0146	1.96E-29
rs2838517	C	T	-0.128	0.0125	1.84E-24
rs5754100	C	T	0.1293	0.016	7.14E-16
rs1978083	G	C	0.0875	0.0141	6.03E-10
rs2413583	T	C	-0.1732	0.0171	4.6E-24
rs62228374	A	G	0.2669	0.0445	2E-09

IBD instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs1558619	T	G	-0.0843	0.0123	8.9E-12
rs72852162	C	A	-0.1129	0.0202	2.3E-08
rs6740847	G	A	-0.0924	0.0125	1.22E-13
rs13422838	C	T	-0.1143	0.0205	2.56E-08
rs62180107	C	G	-0.0797	0.0132	1.55E-09
rs62183956	T	C	-0.078	0.0125	4.49E-10
rs3792111	T	C	0.1391	0.0124	5.12E-29
rs4676408	A	G	0.1011	0.013	7.63E-15
rs76527535	T	C	-0.0864	0.0156	2.87E-08
rs76286777	C	T	0.0996	0.0151	4.66E-11
rs11677002	C	T	-0.0931	0.0126	1.37E-13
rs55946629	A	C	0.1298	0.018	5.45E-13
rs7608697	C	A	0.1395	0.0126	1.67E-28
rs503734	G	A	-0.0692	0.0124	2.67E-08
rs56116661	T	C	-0.1	0.0163	9.27E-10
rs1131095	C	T	0.1635	0.0131	1.22E-35
rs2593855	T	C	-0.0832	0.014	2.54E-09
rs62324212	A	C	0.0886	0.0127	2.67E-12
rs11734570	A	G	0.0694	0.0127	4.8E-08
rs341295	T	C	0.0702	0.0124	1.45E-08
rs11739135	C	G	0.1366	0.0125	1.1E-27
rs2961704	T	C	-0.1459	0.0227	1.31E-10
rs17656349	T	C	0.0731	0.0125	5.17E-09
rs17800987	G	A	0.1843	0.0222	1.07E-16
rs10052709	G	C	-0.1236	0.0187	3.44E-11
rs1157509	G	A	0.1449	0.0172	3.35E-17
rs755374	T	C	0.1767	0.0134	1.59E-39
rs56235845	G	T	0.0877	0.0138	1.77E-10
rs395157	T	C	0.0776	0.0124	4.63E-10
rs72748445	A	C	-0.11	0.0141	5.37E-15
rs1445004	T	C	0.1689	0.0127	3.48E-40
rs10055349	A	G	0.1038	0.0148	2.17E-12
rs6873866	C	T	-0.0919	0.0128	6.15E-13
rs11152949	G	A	0.1019	0.0133	1.56E-14
rs13200059	A	G	0.2114	0.0346	9.69E-10
rs6933404	C	T	0.0863	0.0149	6.64E-09
rs1267496	C	G	0.1053	0.0159	3.39E-11
rs212402	A	G	-0.0743	0.013	1.06E-08
rs35171809	G	A	0.1088	0.0123	1.16E-18
rs4712528	C	G	0.1043	0.0152	7.14E-12
rs4710973	C	T	-0.0842	0.0132	1.67E-10
rs1265098	C	T	-0.1278	0.0157	4.25E-16
rs117292830	A	G	0.3398	0.0394	6.69E-18
rs77108272	A	C	0.457	0.0505	1.49E-19

IBD instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs143210366	G	T	0.2836	0.036	3.14E-15
rs114751021	G	A	0.39	0.0407	9.24E-22
rs62402717	A	G	-0.2081	0.0367	1.43E-08
rs138753323	C	T	0.5947	0.0351	1.47E-64
rs687308	T	C	-0.2294	0.0174	1.13E-39
rs77318243	A	T	-0.1617	0.0237	8.4E-12
rs12206377	G	A	0.2504	0.0416	1.72E-09
rs67289879	T	C	0.0898	0.0162	3.04E-08
rs62408218	T	C	-0.0818	0.0129	2.4E-10
rs62482552	A	G	-0.0737	0.0131	1.97E-08
rs4730263	A	C	-0.0746	0.0127	4.29E-09
rs10953551	G	A	-0.1033	0.0127	4.94E-16
rs243505	G	A	-0.0805	0.0128	3.04E-10
rs149169037	A	G	-0.1338	0.0242	3.26E-08
rs1456896	T	C	0.0879	0.0133	4.5E-11
rs11768365	G	A	-0.0837	0.0152	3.88E-08
rs4236540	T	G	-0.081	0.0139	5.54E-09
rs4380956	A	G	0.0907	0.0127	1.12E-12
rs938650	A	G	-0.1074	0.0189	1.41E-08
rs10114470	C	T	0.1475	0.0137	4.1E-27
rs3829110	G	A	0.1574	0.0125	3.52E-36
rs1887428	C	G	-0.1643	0.0131	2.46E-36
UC					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs7911680	C	A	-0.1525	0.0159	6.71E-22
rs7911117	G	T	-0.1342	0.0239	1.84E-08
rs10761659	G	A	0.1276	0.016	1.33E-15
rs2045241	A	G	-0.1063	0.0169	2.83E-10
rs2212434	T	C	0.1252	0.0159	2.8E-15
rs12825700	A	G	0.1889	0.0161	7.33E-32
rs1359946	A	G	0.1571	0.0202	6.58E-15
rs56062135	T	C	0.1078	0.0184	4.66E-09
rs11645239	G	C	-0.1174	0.02	4.14E-09
rs7203363	A	T	0.1071	0.0189	1.41E-08
rs16940186	C	T	0.1357	0.0214	2.19E-10
rs12936409	T	C	0.1365	0.0158	5.62E-18
rs11651246	G	T	0.147	0.0219	2.01E-11
rs8073117	A	G	-0.1548	0.0225	6.4E-12
rs78064630	A	G	0.1759	0.0308	1.08E-08
rs10408351	A	G	0.1548	0.0204	2.92E-14
rs1336900	A	G	-0.0887	0.0163	4.95E-08
rs79051659	A	G	0.1605	0.0264	1.3E-09
rs6658353	C	G	-0.1569	0.016	1.17E-22

UC instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs2816980	T	G	0.1941	0.026	9.18E-14
rs7554511	A	C	-0.1448	0.0178	4.27E-16
rs2294633	T	C	-0.0985	0.0177	2.79E-08
rs1317209	A	G	0.1818	0.0203	2.9E-19
rs3820328	G	A	-0.1662	0.0164	3.66E-24
rs10737481	G	T	0.2173	0.0159	2.56E-42
rs3024493	A	C	0.21	0.0209	7.46E-24
rs34920465	G	A	-0.1708	0.0213	9.01E-16
rs7544646	G	C	-0.1168	0.016	2.53E-13
rs11209026	A	G	-0.483	0.0358	2E-41
rs7523335	A	G	-0.1389	0.021	3.42E-11
rs6017342	C	A	0.1944	0.017	3.95E-30
rs6062496	A	G	0.1359	0.0163	8.97E-17
rs1736161	A	G	-0.1227	0.0161	2.22E-14
rs2836881	T	G	-0.2217	0.0186	1.11E-32
rs2838517	C	T	-0.1177	0.016	1.78E-13
rs4993442	T	G	-0.0988	0.0179	3.54E-08
rs138788	A	G	0.0896	0.0162	2.95E-08
rs9611131	C	T	-0.1494	0.0227	5.11E-11
rs137845	G	A	0.1011	0.0158	1.5E-10
rs16830407	A	G	0.1078	0.0166	7.62E-11
rs62180181	T	C	0.1226	0.0171	8.08E-13
rs1811711	G	C	-0.1299	0.0223	6.09E-09
rs4676408	A	G	0.1433	0.0167	1.19E-17
rs7608697	C	A	0.1597	0.0161	3.03E-23
rs1131095	C	T	0.1593	0.0168	2.18E-21
rs17715902	A	G	0.0974	0.0166	4.62E-09
rs17656349	T	C	0.09	0.0159	1.54E-08
rs116724447	A	G	-0.339	0.0572	3.01E-09
rs1157509	G	A	0.1311	0.0217	1.54E-09
rs755374	T	C	0.1714	0.0171	9.73E-24
rs67111717	G	A	0.0944	0.0171	3.27E-08
rs6889364	A	G	0.1318	0.0228	7.87E-09
rs72704802	T	C	-0.1223	0.0206	2.89E-09
rs13200059	A	G	0.2944	0.0436	1.48E-11
rs6933404	C	T	0.1486	0.0188	2.69E-15
rs113986290	T	C	-0.3066	0.0531	7.59E-09
rs974334	G	C	0.1181	0.0206	9.96E-09
rs17190351	A	G	0.4301	0.0561	1.79E-14
rs9263719	T	C	-0.1692	0.0269	3.09E-10
rs1265098	C	T	-0.1646	0.0203	4.71E-16
rs114849343	T	G	0.302	0.0458	4.11E-11
rs77108272	A	C	0.5479	0.062	1.02E-18
rs57256697	T	C	0.3794	0.0469	6.16E-16

UC instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs9296004	C	A	0.3119	0.0281	1.15E-28
rs9271176	G	A	-0.3495	0.0173	4.2E-91
rs1846190	A	G	-0.2267	0.019	1.16E-32
rs3097666	C	G	-0.2154	0.0304	1.46E-12
rs872956	A	T	-0.1378	0.021	5.24E-11
rs2301989	A	G	-0.1294	0.0161	1.08E-15
rs10272963	T	C	-0.1512	0.016	4.11E-21
rs4728142	A	G	0.0995	0.0158	3.23E-10
rs798506	C	T	-0.1206	0.0179	1.47E-11
rs10817678	A	G	0.1332	0.017	4.42E-15
rs3812565	C	T	0.1335	0.016	6.5E-17
rs1887428	C	G	-0.167	0.0166	9.65E-24
rs1411262	T	C	0.101	0.0179	1.83E-08
Crohn's					
SNP	**A1**	**A2**	**logOR**	**standard_error**	**p_value**
rs6584282	G	A	-0.1658	0.016	3.44E-25
rs10884966	A	G	0.1131	0.0171	4.13E-11
rs2002695	G	A	-0.1293	0.0189	8.31E-12
rs1148246	T	C	-0.1323	0.0167	2.09E-15
rs61839660	T	C	0.1468	0.0261	1.98E-08
rs10822050	C	T	0.1827	0.0162	2.35E-29
rs2675670	C	G	0.1074	0.0161	2.9E-11
rs1250573	A	G	-0.1522	0.0179	1.92E-17
rs1870148	A	G	0.1351	0.0206	5.44E-11
rs11236797	A	C	0.176	0.0161	8.51E-28
rs77566919	A	G	-0.1089	0.0185	4.13E-09
rs34635748	T	C	0.4794	0.0504	1.95E-21
rs28999107	T	G	0.1083	0.0178	1.06E-09
rs80244186	C	T	0.1246	0.0226	3.66E-08
rs1373904	G	A	0.141	0.0189	9.11E-14
rs194746	T	C	0.0975	0.0161	1.24E-09
rs3850378	C	T	0.199	0.0267	8.31E-14
rs72743461	A	C	0.1684	0.0187	2.26E-19
rs6416647	C	T	0.1007	0.0178	1.46E-08
rs2021511	T	C	-0.1082	0.0182	2.63E-09
rs42861	G	A	0.1243	0.0167	8.87E-14
rs55938681	T	A	0.141	0.0209	1.47E-11
rs7206852	A	T	-0.1287	0.0223	7.71E-09
rs67373269	C	G	-0.1151	0.0194	3.21E-09
rs4486887	T	C	-0.1686	0.0172	1.37E-22
rs2076756	G	A	0.385	0.0174	1.8E-108
rs59145923	C	G	-0.1717	0.0309	2.72E-08
rs72798422	C	T	0.5495	0.0382	6.05E-47

Crohn's instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs145126485	C	A	0.5236	0.0431	6.4E-34
rs7198678	T	A	-0.1398	0.0229	1.08E-09
rs17226979	G	A	0.4514	0.073	6.22E-10
rs59926756	A	G	0.1062	0.0176	1.74E-09
rs2948542	G	A	0.1016	0.0163	5.15E-10
rs3091315	G	A	-0.1579	0.0182	3.76E-18
rs12936409	T	C	0.1426	0.016	4.31E-19
rs744166	G	A	-0.1142	0.0162	1.8E-12
rs80262450	A	G	0.2268	0.0244	1.34E-20
rs12610298	T	C	-0.1634	0.0213	1.61E-14
rs4807570	A	G	0.1811	0.0193	6.03E-21
rs62126620	A	G	0.144	0.0201	8.61E-13
rs492602	G	A	0.1084	0.0162	2.33E-11
rs2476601	G	A	0.2312	0.0286	6.44E-16
rs12131079	T	C	-0.1088	0.0174	3.99E-10
rs34687326	A	G	-0.1649	0.0288	1.06E-08
rs114802258	T	C	-0.2245	0.0384	5.11E-09
rs6704109	T	C	0.1748	0.0181	5.1E-22
rs1775448	G	A	-0.122	0.017	6.78E-13
rs35730213	C	G	-0.1166	0.0181	1.17E-10
rs3122605	A	G	-0.1748	0.0227	1.24E-14
rs59805578	C	T	-0.2674	0.034	3.92E-15
rs12041056	T	C	0.1284	0.0163	3.75E-15
rs7517847	G	T	-0.3447	0.0165	5.84E-97
rs4655709	A	G	0.1224	0.0183	2.46E-11
rs3761158	A	G	-0.1098	0.0165	2.65E-11
rs6062496	A	G	0.1223	0.0167	2.62E-13
rs1297264	G	A	-0.1769	0.0163	1.59E-27
rs2284553	G	A	0.1277	0.0165	1.14E-14
rs2838517	C	T	-0.1456	0.0162	2.03E-19
rs5754100	C	T	0.1687	0.0206	3.02E-16
rs4821544	C	T	0.0966	0.0171	1.76E-08
rs2143178	C	T	-0.2087	0.0223	6.84E-21
rs62228374	A	G	0.3164	0.0557	1.36E-08
rs2110735	G	A	-0.1372	0.0185	1.2E-13
rs11683692	C	T	-0.2144	0.038	1.75E-08
rs151175749	G	C	0.2483	0.0428	6.73E-09
rs6740847	G	A	-0.104	0.0161	9.72E-11
rs1583792	T	C	-0.0882	0.016	3.26E-08
rs7563433	C	T	0.1525	0.02	2.14E-14
rs3816234	A	G	0.2704	0.0162	1.51E-62
rs4343432	G	A	0.1123	0.0162	3.5E-12
rs1260326	C	T	-0.1053	0.0161	6.32E-11
rs11677002	C	T	-0.1124	0.0163	4.57E-12

Crohn's instruments (continued)					
SNP	**A1**	**A2**	**logOR**	**SE**	**P**
rs55946629	A	C	0.1755	0.0231	2.85E-14
rs7608697	C	A	0.1229	0.0163	4.03E-14
rs6808936	G	A	0.0904	0.0161	1.93E-08
rs56116661	T	C	-0.1312	0.0212	5.67E-10
rs9836291	A	G	0.1722	0.017	3.77E-24
rs2581828	G	C	-0.0941	0.0162	6.46E-09
rs13107325	T	C	0.2006	0.0284	1.67E-12
rs62324212	A	C	0.106	0.0163	8.02E-11
rs73243877	G	A	0.1164	0.0212	4.12E-08
rs2188962	T	C	0.2004	0.016	5.59E-36
rs181826	A	C	0.1162	0.0167	3.25E-12
rs9637870	A	G	0.2558	0.0275	1.33E-20
rs10052709	G	C	-0.141	0.0242	5.76E-09
rs1157509	G	A	0.1519	0.0224	1.26E-11
rs755374	T	C	0.1969	0.0174	1.38E-29
rs72748445	A	C	-0.1369	0.0181	4.31E-14
rs6451494	C	T	0.2605	0.0166	8.26E-56
rs10055349	A	G	0.1734	0.019	5.59E-20
rs137976175	A	G	-0.2564	0.0372	5.59E-12
rs6873866	C	T	-0.1314	0.0164	1.35E-15
rs73516754	C	A	0.1423	0.0169	4.04E-17
rs9482770	C	T	0.0987	0.0162	1.01E-09
rs212408	T	G	-0.1136	0.0167	9.12E-12
rs35171809	G	A	0.1566	0.0159	9.07E-23
rs1012636	T	G	0.1291	0.0198	7.01E-11
rs7753014	G	C	-0.0989	0.0163	1.39E-09
rs2240069	G	A	-0.1568	0.0252	4.73E-10
rs9264360	T	A	0.1246	0.0225	3.23E-08
rs4151651	A	G	0.3682	0.0409	2.25E-19
rs401775	C	T	0.2023	0.0203	2.17E-23
rs9469119	A	C	0.1874	0.034	3.62E-08
rs13203429	C	G	0.1264	0.0169	6.74E-14
rs4959116	T	C	0.1362	0.0227	1.86E-09
rs11965964	T	C	0.3044	0.0529	8.83E-09
rs1321859	T	C	-0.1049	0.0172	1.18E-09
rs9656588	C	T	0.1183	0.0173	8.73E-12
rs4380956	A	G	0.132	0.0165	1.15E-15
rs938650	A	G	-0.1747	0.0247	1.65E-12
rs10114470	C	T	0.1687	0.0177	1.76E-21
rs4077515	T	C	0.1848	0.0162	3.15E-30
rs1887428	C	G	-0.166	0.0169	8.54E-23

Appendix Table C7. Swedish cohort characteristics by exposure to maternal IBD diagnoses during index pregnancy.

		Unexposed	**Any IBD diagnosis**	**P**	**Crohn's disease diagnosis**	**P**	**Ulcerative Colitis diagnosis**	**P**
Total		2272606	51621		12390		17832	
Any autism diagnosis		43568 (1.9%)	1361 (2.6%)	<0.001	292 (2.4%)	<0.001	422 (2.4%)	<0.001
Autism with ID		6868 (0.3%)	198 (0.4%)	<0.001	41 (0.3%)	0.54	54 (0.3%)	0.96
Autism without ID		36700 (1.6%)	1163 (2.3%)	<0.001	251 (2.0%)	<0.001	368 (2.1%)	<0.001
Any paternal IBD diagnosis , Lifetime		42047 (1.9%)	1061 (2.1%)	<0.001	261 (2.1%)	0.035	319 (1.8%)	0.55
Sex	Male	1166615 (51.3%)	26580 (51.5%)	0.48	6310 (50.9%)	0.37	9120 (51.1%)	0.61
Parity	1	971026 (42.7%)	22228 (43.1%)	0.30	5456 (44.0%)	<0.001	7740 (43.4%)	<0.001
	2	826776 (36.4%)	18639 (36.1%)		4544 (36.7%)		6630 (37.2%)	
	>=3	474804 (20.9%)	10754 (20.8%)		2390 (19.3%)		3462 (19.4%)	
Maternal Age	<25	425566 (18.7%)	10783 (20.9%)	<0.001	2477 (20.0%)	<0.001	3155 (17.7%)	0.006
	25-29	773915 (34.1%)	17541 (34.0%)		4313 (34.8%)		6069 (34.0%)	
	30-34	706661 (31.1%)	15268 (29.6%)		3720 (30.0%)		5673 (31.8%)	
	35-39	307101 (13.5%)	6710 (13.0%)		1583 (12.8%)		2455 (13.8%)	
	>=40	59363 (2.6%)	1319 (2.6%)		297 (2.4%)		480 (2.7%)	
Paternal Age	<25	200567 (8.8%)	5448 (10.6%)	<0.001	1299 (10.5%)	<0.001	1528 (8.6%)	<0.001
	25-29	604562 (26.6%)	14730 (28.5%)		3606 (29.1%)		5001 (28.0%)	
	30-34	754703 (33.2%)	16698 (32.3%)		4032 (32.5%)		6033 (33.8%)	
	35-39	456579 (20.1%)	9591 (18.6%)		2331 (18.8%)		3478 (19.5%)	
	>=40	256195 (11.3%)	5154 (10.0%)		1122 (9.1%)		1792 (10.0%)	
Maternal Birth Country Region	Nordic	1963705 (86.4%)	47168 (91.4%)	<0.001	11427 (92.2%)	<0.001	16701 (93.7%)	<0.001
	Europe	94770 (4.2%)	1225 (2.4%)		285 (2.3%)		334 (1.9%)	
	Africa	38988 (1.7%)	471 (0.9%)		66 (0.5%)		76 (0.4%)	
	Asia	146293 (6.4%)	2160 (4.2%)		500 (4.0%)		557 (3.1%)	
	Other	28850 (1.3%)	597 (1.2%)		112 (0.9%)		164 (0.9%)	

Swedish cohort characteristics by exposure to maternal IBD diagnoses during index pregnancy (continued)								
		Unexposed	**Any IBD diagnosis**	**P**	**Crohn's disease diagnosis**	**P**	**Ulcerative Colitis diagnosis**	**P**
Paternal Birth Country Region	Nordic	1946005 (85.6%)	46236 (89.6%)	<0.001	11244 (90.8%)	<0.001	16430 (92.1%)	<0.001
	Europe	102238 (4.5%)	1641 (3.2%)		387 (3.1%)		464 (2.6%)	
	Africa	47495 (2.1%)	711 (1.4%)		108 (0.9%)		138 (0.8%)	
	Asia	143341 (6.3%)	2364 (4.6%)		537 (4.3%)		617 (3.5%)	
	Other	33527 (1.5%)	669 (1.3%)		114 (0.9%)		183 (1.0%)	
educational attainment 1990-2015 (maternal)	<=9 years	201674 (8.9%)	5139 (10.0%)	<0.001	1214 (9.8%)	<0.001	1366 (7.7%)	<0.001
	>9-12 years	1035320 (45.6%)	25313 (49.0%)		6297 (50.8%)		8516 (47.8%)	
	>12 years	1035612 (45.6%)	21169 (41.0%)		4879 (39.4%)		7950 (44.6%)	
educational attainment 1990-2015 (paternal)	<=9 years	314241 (13.8%)	7445 (14.4%)	<0.001	1850 (14.9%)	<0.001	2317 (13.0%)	<0.001
	>9-12 years	1162231 (51.1%)	27819 (53.9%)		6820 (55.0%)		9418 (52.8%)	
	>12 years	796134 (35.0%)	16357 (31.7%)		3720 (30.0%)		6097 (34.2%)	
Parental income quintile at birth	1	312469 (13.7%)	5967 (11.6%)	<0.001	1293 (10.4%)	<0.001	1724 (9.7%)	<0.001
	2	465484 (20.5%)	10927 (21.2%)		2538 (20.5%)		3421 (19.2%)	
	3	489970 (21.6%)	11759 (22.8%)		2832 (22.9%)		4031 (22.6%)	
	4	501710 (22.1%)	12023 (23.3%)		2970 (24.0%)		4461 (25.0%)	
	5	502973 (22.1%)	10945 (21.2%)		2757 (22.3%)		4195 (23.5%)	
Birth place	Stockholm	207400 (9.1%)	4099 (7.9%)	<0.001	990 (8.0%)	<0.001	1426 (8.0%)	<0.001
	Stockholm Suburbs (Cities/Towns/Suburbs)	258156 (11.4%)	5634 (10.9%)		1426 (11.5%)		2005 (11.2%)	
	Gotherburg and Malmö	196307 (8.6%)	3879 (7.5%)		915 (7.4%)		1329 (7.5%)	
	Other Sweden, (densely populated areas)	323645 (14.2%)	7051 (13.7%)		1738 (14.0%)		2514 (14.1%)	

Swedish cohort characteristics by exposure to maternal IBD diagnoses during index pregnancy (continued)								
		Unexposed	**Any IBD diagnosis**	**P**	**Crohn's disease diagnosis**	**P**	**Ulcerative Colitis diagnosis**	**P**
	Other Sweden, Towns and suburbs (intermediate density)	620002 (27.3%)	14847 (28.8%)		3464 (28.0%)		5151 (28.9%)	
	Rural (thinly populated areas)	665408 (29.3%)	16084 (31.2%)		3849 (31.1%)		5402 (30.3%)	
		1688 (0.1%)	27 (0.1%)		8 (0.1%)		5 (<1%)	
Maternal Psychiatric History, Any	0	2161554 (95.1%)	47195 (91.4%)	<0.001	11505 (92.9%)	<0.001	16713 (93.7%)	<0.001
	1	111052 (4.9%)	4426 (8.6%)		885 (7.1%)		1119 (6.3%)	
Paternal Psychiatric History, Any	0	2183183 (96.1%)	49341 (95.6%)	<0.001	11847 (95.6%)	0.011	17140 (96.1%)	0.71
	1	89423 (3.9%)	2280 (4.4%)		543 (4.4%)		692 (3.9%)	
Maternal anemia in pregnancy	None	2174734 (95.7%)	48657 (94.3%)	<0.001	11531 (93.1%)	<0.001	16775 (94.1%)	<0.001
	<=30 weeks	5435 (0.2%)	312 (0.6%)		121 (1.0%)		130 (0.7%)	
	>30 weeks	92437 (4.1%)	2652 (5.1%)		738 (6.0%)		927 (5.2%)	

Appendix Table C8. Swedish cohort characteristics by exposure to paternal IBD diagnoses during index pregnancy.

		Unexposed	**Any IBD diagnosis**	**P**	**Crohn's disease diagnosis**	**P**	**Ulcerative colitis diagnosis**	**P**
Total		2281119	43108		11274		18290	
Any autism diagnosis		43989 (1.9%)	940 (2.2%)	<0.001	254 (2.3%)	0.012	346 (1.9%)	0.72
Autism with ID		6946 (0.3%)	120 (0.3%)	0.35	31 (0.3%)	0.58	33 (0.2%)	0.002
Autism without ID		37043 (1.6%)	820 (1.9%)	<0.001	223 (2.0%)	0.003	313 (1.7%)	0.37
Any maternal IBD diagnosis, Lifetime		50560 (2.2%)	1061 (2.5%)	<0.001	255 (2.3%)	0.74	392 (2.1%)	0.50
Sex	Male	1171044 (51.3%)	22151 (51.4%)	0.84	5756 (51.1%)	0.55	9405 (51.4%)	0.82
Parity	1	974756 (42.7%)	18498 (42.9%)	0.66	4792 (42.5%)	0.86	7853 (42.9%)	0.008
	2	829823 (36.4%)	15592 (36.2%)		4128 (36.6%)		6781 (37.1%)	
	>=3	476540 (20.9%)	9018 (20.9%)		2354 (20.9%)		3656 (20.0%)	
Maternal age	<25	428105 (18.8%)	8244 (19.1%)	0.007	2134 (18.9%)	0.35	3133 (17.1%)	<0.001
	25-29	776659 (34.0%)	14797 (34.3%)		3799 (33.7%)		6266 (34.3%)	
	30-34	708826 (31.1%)	13103 (30.4%)		3453 (30.6%)		5829 (31.9%)	
	35-39	308036 (13.5%)	5775 (13.4%)		1592 (14.1%)		2558 (14.0%)	
	>=40	59493 (2.6%)	1189 (2.8%)		296 (2.6%)		504 (2.8%)	
Paternal age	<25	202096 (8.9%)	3919 (9.1%)	0.002	948 (8.4%)	0.062	1377 (7.5%)	<0.001
	25-29	607841 (26.6%)	11451 (26.6%)		2982 (26.5%)		4803 (26.3%)	
	30-34	757307 (33.2%)	14094 (32.7%)		3685 (32.7%)		6219 (34.0%)	
	35-39	457592 (20.1%)	8578 (19.9%)		2325 (20.6%)		3855 (21.1%)	
	>=40	256283 (11.2%)	5066 (11.8%)		1334 (11.8%)		2036 (11.1%)	
Maternal Birth Country Region	Nordic	1972730 (86.5%)	38143 (88.5%)	<0.001	9966 (88.4%)	<0.001	16568 (90.6%)	<0.001
	Europe	94576 (4.1%)	1419 (3.3%)		382 (3.4%)		554 (3.0%)	
	Africa	38886 (1.7%)	573 (1.3%)		133 (1.2%)		148 (0.8%)	
	Asia	145948 (6.4%)	2505 (5.8%)		699 (6.2%)		857 (4.7%)	
	Other	28979 (1.3%)	468 (1.1%)		94 (0.8%)		163 (0.9%)	

Swedish cohort characteristics by exposure to paternal IBD diagnoses during index pregnancy (continued)								
		Unexposed	**Any IBD diagnosis**	**P**	**Crohn's disease diagnosis**	**P**	**Ulcerative colitis diagnosis**	**P**
Paternal Birth Country Region	Nordic	1953770 (85.6%)	38471 (89.2%)	<0.001	10032 (89.0%)	<0.001	16723 (91.4%)	<0.001
	Europe	102608 (4.5%)	1271 (2.9%)		379 (3.4%)		468 (2.6%)	
	Africa	47632 (2.1%)	574 (1.3%)		134 (1.2%)		128 (0.7%)	
	Asia	143363 (6.3%)	2342 (5.4%)		646 (5.7%)		798 (4.4%)	
	Other	33746 (1.5%)	450 (1.0%)		83 (0.7%)		173 (0.9%)	
educational attainment 1990-2015 (maternal)	<=9 years	202954 (8.9%)	3859 (9.0%)	<0.001	989 (8.8%)	0.054	1365 (7.5%)	<0.001
	>9-12 years	1040094 (45.6%)	20539 (47.6%)		5268 (46.7%)		8550 (46.7%)	
	>12 years	1038071 (45.5%)	18710 (43.4%)		5017 (44.5%)		8375 (45.8%)	
educational attainment 1990-2015 (paternal)	<=9 years	315392 (13.8%)	6294 (14.6%)	<0.001	1586 (14.1%)	0.009	2492 (13.6%)	<0.001
	>9-12 years	1167083 (51.2%)	22967 (53.3%)		5896 (52.3%)		9635 (52.7%)	
	>12 years	798644 (35.0%)	13847 (32.1%)		3792 (33.6%)		6163 (33.7%)	
Parental income quintile at birth	1	312926 (13.7%)	5510 (12.8%)	<0.001	1375 (12.2%)	<0.001	2055 (11.2%)	<0.001
	2	467284 (20.5%)	9127 (21.2%)		2368 (21.0%)		3664 (20.0%)	
	3	492194 (21.6%)	9535 (22.1%)		2438 (21.6%)		4156 (22.7%)	
	4	503931 (22.1%)	9802 (22.7%)		2582 (22.9%)		4304 (23.5%)	
	5	504784 (22.1%)	9134 (21.2%)		2511 (22.3%)		4111 (22.5%)	
Birth place	Stockholm	207953 (9.1%)	3546 (8.2%)	<0.001	1045 (9.3%)	<0.001	1512 (8.3%)	<0.001
	Stockholm Suburbs (Cities/Towns/Suburbs)	259166 (11.4%)	4624 (10.7%)		1448 (12.8%)		1868 (10.2%)	
	Gotherburg and Malmö	196870 (8.6%)	3316 (7.7%)		920 (8.2%)		1377 (7.5%)	
	Other Sweden, (densely populated areas)	324790 (14.2%)	5906 (13.7%)		1492 (13.2%)		2577 (14.1%)	

Swedish cohort characteristics by exposure to paternal IBD diagnoses during index pregnancy (continued)								
		Unexposed	**Any IBD diagnosis**	**P**	**Crohn's disease diagnosis**	**P**	**Ulcerative colitis diagnosis**	**P**
	Other Sweden, Towns and suburbs (intermediate density)	622221 (27.3%)	12628 (29.3%)		3152 (28.0%)		5429 (29.7%)	
	Rural (thinly populated areas)	668429 (29.3%)	13063 (30.3%)		3209 (28.5%)		5515 (30.2%)	
		1690 (0.1%)	25 (0.1%)		8 (0.1%)		12 (0.1%)	
Maternal Psychiatric History, Any	0	2167998 (95.0%)	40751 (94.5%)	<0.001	10715 (95.0%)	1.00	17406 (95.2%)	0.44
	1	113121 (5.0%)	2357 (5.5%)		559 (5.0%)		884 (4.8%)	
Paternal Psychiatric History, Any	0	2192030 (96.1%)	40494 (93.9%)	<0.001	10619 (94.2%)	<0.001	17446 (95.4%)	<0.001
	1	89089 (3.9%)	2614 (6.1%)		655 (5.8%)		844 (4.6%)	

Table C9. Associations between maternal and paternal diagnoses of IBD prior to index person's birth and offspring autism.

		OR	95%CIs		P
Maternal Any IBD	MODEL1	1.165216	1.059561	1.281407	0.001617
	MODEL2	1.189408	1.081458	1.308132	0.000353
	MODEL3	1.196725	1.088162	1.316119	0.000215
Paternal Any IBD	MODEL1	0.983371	0.878314	1.100995	0.771136
	MODEL2	1.029532	0.919513	1.152715	0.613742
	MODEL3	1.015465	0.906744	1.137221	0.790539

MODEL1: crude model
MODEL2: adjusted for parental age at delivery, migrant status, education level, family income quintile at birth, parents' history of psychiatric diagnosis prior to the birth of the child and offspring sex, birth year and birth order.
MODEL3: in addition to covariates, mutually adjusted for maternal and paternal IBD diagnoses.

Table C10. Associations between lifetime maternal and paternal diagnoses of IBD and offspring autism with and without intellectual disabilities (ID).

		ASD with ID					ASD without ID			
		OR	95% CIs		P		OR	95% CIs		P
Maternal Any IBD	MODEL1	1.281253	1.109024	1.48023	0.000766		1.408721	1.323981	1.498886	2.59E-27
	MODEL2	1.241848	1.07534	1.434138	0.003189		1.338664	1.258024	1.424473	3.54E-20
	MODEL3	1.263476	1.094032	1.459164	0.001457		1.334084	1.253768	1.419547	9.15E-20
Paternal Any IBD	MODEL1	0.914722	0.760663	1.099983	0.343513		1.178559	1.095603	1.267797	1.03E-05
	MODEL2	0.906211	0.754124	1.088971	0.293416		1.142663	1.062167	1.22926	0.000346
	MODEL3	0.898629	0.748056	1.079509	0.253322		1.128407	1.048925	1.213912	0.001188

MODEL1: crude model
MODEL2: adjusted for parental age at delivery, migrant status, education level, family income quintile at birth, parents' history of psychiatric diagnosis prior to the birth of the child and offspring sex, birth year and birth order.
MODEL3: in addition to covariates, mutually adjusted for maternal and paternal IBD diagnoses.

Table C11. LD-score regression correlation coefficients, standard errors, p-values, heritability estimates, chi-square and intercepts for the genetic correlation analyses between autism, inflammatory bowel disease (IBD), Crohn's disease (Crohn's) and ulcerative colitis (UC).

Phenotype	Total Observed Scale H2	H2 Zscore	Mean Chi2	Intercept	Genetic Correlation	SE	P	Rg Zscore
IBD	0.3198	10.12	1.5309	1.122				
Autism	0.1939	11.75	1.1995	1.008				
					-0.0615	0.04	0.2	-1.4119
Phenotype	**Total Observed Scale H2**	**H2 Zscore**	**Mean Chi2**	**Intercept**	**Genetic Correlation**	**SE**	**P**	**Rg Zscore**
UC	0.2388	8.34	1.3292	1.0978				
Autism	0.1946	11.65	1.1998	1.008				
					-0.0656	0.05	0.2	-1.2636
Phenotype	**Total Observed Scale H2**	**H2 Zscore**	**Mean Chi2**	**Intercept**	**Genetic Correlation**	**SE**	**P**	**Rg Zscore**
Crohn's	0.4571	8.85	1.4829	1.0891				
Autism	0.1944	11.71	1.1997	1.0081				
					-0.0403	0.04	0.4	-0.9247

Table C12. Associations between maternal polygenic risk for inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (Crohn's) at 13 p-value thresholds and offspring autism factor mean score in the ALSPAC cohort.

	p.threshold	β	SE	P	95%CIs		R
Exposure: maternal polygenic risk for IBD	0.5	0.021323	0.011049	0.05367	-0.00034	0.042983	0.057632
	0.4	0.020441	0.011051	0.064392	-0.00122	0.042103	0.057593
	0.3	0.020351	0.011039	0.065284	-0.00129	0.04199	0.05759
	0.2	0.020222	0.011031	0.066818	-0.0014	0.041846	0.057585
	0.1	0.020447	0.011024	0.063674	-0.00116	0.042057	0.057595
	0.05	0.01799	0.011016	0.102488	-0.0036	0.039584	0.057496
	0.01	0.022413	0.010992	0.041479	0.000866	0.04396	0.057687
	0.001	0.021447	0.010977	0.050765	-7.1E-05	0.042965	0.057644
	0.0001	0.0206	0.010994	0.060995	-0.00095	0.042151	0.057604
	0.00001	0.016674	0.010985	0.129095	-0.00486	0.038209	0.057449
	0.000001	0.013526	0.010992	0.218544	-0.00802	0.035074	0.057348
	0.0000001	0.013466	0.011001	0.22096	-0.0081	0.035032	0.057346
	0.00000005	0.014301	0.010993	0.19331	-0.00725	0.03585	0.057371
	p.threshold	**β**	**SE**	**P**	**95%CIs**		**R**
Exposure: maternal polygenic risk for UC	0.5	0.023051	0.011033	0.036726	0.001422	0.04468	0.057714
	0.4	0.022661	0.011028	0.039932	0.001043	0.04428	0.057696
	0.3	0.022592	0.011026	0.040494	0.000979	0.044206	0.057693
	0.2	0.027196	0.011018	0.013598	0.005597	0.048795	0.057936
	0.1	0.025956	0.011012	0.018446	0.004369	0.047544	0.057867
	0.05	0.024608	0.011005	0.025375	0.003035	0.046181	0.057796
	0.01	0.017899	0.010996	0.103619	-0.00366	0.039455	0.057494
	0.001	0.012679	0.01098	0.248211	-0.00884	0.034203	0.057325
	0.0001	0.014432	0.010996	0.189422	-0.00712	0.035987	0.057375
	0.00001	0.014549	0.010986	0.185441	-0.00699	0.036085	0.057379
	0.000001	0.008006	0.010983	0.466051	-0.01352	0.029536	0.057222
	0.0000001	0.013325	0.010963	0.224203	-0.00816	0.034815	0.057343
	0.00000005	0.010703	0.010965	0.329038	-0.01079	0.032199	0.057276
	p.threshold	**β**	**SE**	**P**	**95%CIs**		**R**
Exposure: maternal polygenic risk for Crohn's	0.5	0.021401	0.011044	0.052687	-0.00025	0.043051	0.057636
	0.4	0.022011	0.011043	0.046268	0.000364	0.043658	0.057664
	0.3	0.021943	0.011045	0.046997	0.000291	0.043595	0.05766
	0.2	0.025082	0.01104	0.023117	0.003441	0.046722	0.057816
	0.1	0.033654	0.011035	0.002298	0.012023	0.055285	0.058347
	0.05	0.031748	0.01106	0.004108	0.010068	0.053428	0.058211
	0.01	0.031137	0.011016	0.004717	0.009543	0.05273	0.058179
	0.001	0.021468	0.011025	0.051551	-0.00014	0.043081	0.05764
	0.0001	0.015134	0.011044	0.17061	-0.00651	0.036782	0.057395
	0.00001	0.017353	0.011031	0.115719	-0.00427	0.038977	0.057471
	0.000001	0.014726	0.011023	0.181619	-0.00688	0.036334	0.057383
	0.0000001	0.015933	0.011034	0.148796	-0.0057	0.037562	0.057421
	0.00000005	0.015544	0.011042	0.159275	-0.0061	0.037189	0.057408

Table C13. Associations between polygenic risk for inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (Crohn's) at 13 p-value thresholds and autism factor mean score in the children of the ALSPAC cohort.

	p.threshold	β	SE	P	95%CIs		R
Exposure: polygenic risk for IBD	0.5	0.010364	0.010678	0.331772	-0.01057	0.031295	0.051926
	0.4	0.009283	0.010678	0.384711	-0.01165	0.030215	0.051902
	0.3	0.008087	0.010678	0.448881	-0.01285	0.029019	0.051879
	0.2	0.008476	0.010676	0.427248	-0.01245	0.029404	0.051886
	0.1	0.006291	0.010679	0.555808	-0.01464	0.027224	0.051851
	0.05	0.002807	0.010676	0.792598	-0.01812	0.023735	0.051815
	0.01	-0.00464	0.010656	0.662968	-0.02553	0.016245	0.051831
	0.001	-0.0097	0.010686	0.36401	-0.03065	0.011246	0.051911
	0.0001	-0.00798	0.010691	0.455572	-0.02894	0.01298	0.051877
	0.00001	-0.00699	0.010712	0.513811	-0.02799	0.014004	0.051861
	0.000001	-0.00605	0.010709	0.572377	-0.02704	0.014946	0.051847
	0.0000001	-0.00422	0.010711	0.693787	-0.02521	0.01678	0.051826
	0.00000005	-0.00259	0.010707	0.80905	-0.02358	0.018401	0.051814
	p.threshold	**β**	**SE**	**P**	**95%CIs**		**R**
Exposure: polygenic risk for UC	0.5	0.010208	0.010678	0.339121	-0.01072	0.031139	0.051922
	0.4	0.008241	0.010677	0.440246	-0.01269	0.029171	0.051882
	0.3	0.006029	0.010675	0.572275	-0.0149	0.026955	0.051847
	0.2	0.009784	0.010684	0.359836	-0.01116	0.030728	0.051913
	0.1	0.007065	0.010685	0.508514	-0.01388	0.02801	0.051862
	0.05	0.001474	0.010681	0.890262	-0.01946	0.022411	0.051809
	0.01	-0.00485	0.01069	0.649892	-0.02581	0.016103	0.051833
	0.001	-0.00619	0.010708	0.562924	-0.02719	0.014796	0.051849
	0.0001	-0.0141	0.01072	0.188299	-0.03512	0.006909	0.052026
	0.00001	-0.01702	0.010737	0.113069	-0.03806	0.004032	0.052124
	0.000001	-0.0181	0.010743	0.092138	-0.03915	0.002963	0.052166
	0.0000001	-0.01437	0.010734	0.18055	-0.03542	0.006667	0.052034
	0.00000005	-0.00927	0.010739	0.388117	-0.03032	0.011782	0.051901
	p.threshold	**β**	**SE**	**P**	**95%CIs**		**R**
Exposure: polygenic risk for Crohn's	0.5	0.010169	0.010687	0.341357	-0.01078	0.031119	0.051921
	0.4	0.009018	0.010686	0.398779	-0.01193	0.029966	0.051897
	0.3	0.007903	0.010689	0.459719	-0.01305	0.028856	0.051876
	0.2	0.007752	0.01069	0.468353	-0.0132	0.028708	0.051873
	0.1	0.007849	0.010688	0.462748	-0.0131	0.028801	0.051875
	0.05	0.00737	0.010703	0.491117	-0.01361	0.02835	0.051867
	0.01	-0.00069	0.0107	0.948589	-0.02166	0.020285	0.051807
	0.001	-0.00453	0.010699	0.67178	-0.02551	0.01644	0.051829
	0.0001	-0.00572	0.010715	0.593328	-0.02673	0.015283	0.051843
	0.00001	0.001867	0.010711	0.861597	-0.01913	0.022865	0.05181
	0.000001	-0.00031	0.010717	0.97699	-0.02132	0.0207	0.051807
	0.0000001	0.001982	0.010729	0.853444	-0.01905	0.023015	0.051811
	0.00000005	0.002123	0.010729	0.843177	-0.01891	0.023155	0.051812

Table C14. Two-sample Mendelian randomization (MR) causal effect estimates, standard errors, 95% confidence intervals, and p-values for the analyses investigating the effects of common variant genetic liability to inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease (Crohn's) on autism.

Exposure: common variant genetic liability to IBD						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95% CIs**	
Inverse variance weighted	128	1.021793	0.012921	0.0952	0.996242	1.048
MR Egger	128	1.056921	0.032187	0.087895	0.992304	1.125747
SIMEX corrected MR Egger	128	1.074197	0.035157	0.0437	1.002669	1.150827
Weighted median	128	1.028398	0.019603	0.153158	0.989634	1.06868
Weighted mode	128	1.050034	0.03337	0.145927	0.983553	1.121008
I2GX= 0.9; suggesting a 10% attenuation of the MR Egger estimate towards zero.						
MR Egger Intercept= -0.005; p-value= 0.25						
Exposure: common variant genetic liability to UC						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95%CIs**	
Inverse variance weighted	67	1.039546	0.014054	0.005785	1.011302	1.068579
MR Egger	67	1.095591	0.037923	0.018917	1.01711	1.180129
SIMEX corrected MR Egger	67	1.09008	0.041253	0.04	1.00541	1.181881
Weighted median	67	1.048284	0.019926	0.01796	1.008132	1.090035
Weighted mode	67	1.031864	0.029383	0.289633	0.974116	1.093035
I2GX= 0.88; suggesting a 12% attenuation of the MR Egger estimate towards zero.						
MR Egger Intercept= -0.009; p-value= 0.14						
Exposure: common variant genetic liability to Crohn's						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95%CIs**	
Inverse variance weighted	100	1.014962	0.01095	0.17502	0.993411	1.036981
MR Egger	100	0.997784	0.029743	0.940694	0.94128	1.05768
SIMEX Corrected MR Egger	100	0.988901	0.031849	0.727	0.929057	1.0526
Weighted median	100	1.014415	0.01632	0.380508	0.98248	1.047387
Weighted mode	100	0.992853	0.038945	0.85426	0.919887	1.071607
I2GX= 0.9; suggesting a 10% attenuation of the MR Egger estimate towards zero.						
MR Egger intercept= 0.003; 0.54						

Table C15. Two-sample Mendelian randomization (MR) causal effect estimates, standard errors, 95% confidence intervals, and p-values for the analyses investigating the effects of common variant genetic liability to inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease (Crohn's) on autism without intellectual disabilities (ID).

Exposure: common variant genetic liability to IBD						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95%CIs**	
Inverse variance weighted	126	1.046672	0.015862	0.004031	1.014632	1.079725
MR Egger	126	1.082502	0.039777	0.04846	1.001313	1.170274
SIMEX corrected MR Egger	126	1.106167	0.044693	0.0255	1.013392	1.207436
Weighted median	126	1.036236	0.023755	0.134022	0.989095	1.085623
Weighted mode	126	1.02914	0.039976	0.473781	0.951581	1.113021
I2GX= 0.9; suggesting a 10% attenuation of the MR Egger estimate towards zero.						
MR Egger Intercept= -0.004; p-value= 0.36						
Exposure: common variant genetic liability to UC						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95%CIs**	
Inverse variance weighted	67	1.075161	0.017022	2.07E-05	1.039882	1.111637
MR Egger	67	1.134762	0.046297	0.008126	1.036325	1.242549
SIMEX corrected MR Egger	67	1.131822	0.051004	0.0176	1.024148	1.250817
Weighted median	67	1.05997	0.023766	0.014261	1.011728	1.110512
Weighted mode	67	1.06105	0.037576	0.11956	0.985714	1.142144
I2GX= 0.88; suggesting a 12% attenuation of the MR Egger estimate towards zero.						
MR Egger Intercept= -0.009; p-value= 0.21						
Exposure: common variant genetic liability to Crohn's						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95%CIs**	
Inverse variance weighted	99	1.014389	0.013965	0.306304	0.987	1.042537
MR Egger	99	1.019405	0.038566	0.619372	0.945189	1.099449
SIMEX corrected MR Egger	99	1.006489	0.042215	0.879	0.926563	1.09331
Weighted median	99	1.009856	0.020174	0.626869	0.970704	1.050586
Weighted mode	99	0.987501	0.051873	0.808917	0.892036	1.093182
I2GX= 0.9; suggesting a 10% attenuation of the MR Egger estimate towards zero.						
MR Egger Intercept= -0.001; p-value= 0.89						

Table C16. Two-sample Mendelian randomization (MR) causal effect estimates, standard errors, 95% confidence intervals, and p-values for the analyses investigating the effects of common variant genetic liability to autism on inflammatory bowel disease (IBD), ulcerative colitis (UC), and Crohn's disease (Crohn's).

Outcome: IBD						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95%CIs**	
Inverse variance weighted	8	0.899	0.10821	0.32489	0.72716	1.11133
MR Egger	8	1.7405	0.37085	0.18572	0.84137	3.6004
SIMEX corrected MR Egger	8	2.2237	0.47037	0.1331	0.8845	5.59076
Weighted median	8	0.83	0.08993	0.03825	0.69584	0.98996
Weighted mode	8	0.8458	0.1294	0.23658	0.65632	1.08994
I2GX= 0.53; suggesting a 47% attenuation of the MR Egger estimate towards zero.						
MR Egger Intercept= 0.06; p-value= 0.12						
Outcome: UC						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95%CIs**	
Inverse variance weighted	8	0.9514	0.1081	0.64512	0.76978	1.17596
MR Egger	8	2.0143	0.34093	0.08577	1.03255	3.92941
SIMEX corrected MR Egger	8	2.9263	0.50045	0.0691	1.09728	7.80373
Weighted median	8	0.9251	0.10355	0.45198	0.75514	1.13324
Weighted mode	8	0.9042	0.1423	0.50206	0.68415	1.19508
I2GX= 0.53; suggesting a 47% attenuation of the MR Egger estimate towards zero.						
MR Egger Intercept= -0.07; p-value= 0.06						
Outcome: Crohn's						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95%CIs**	
Inverse variance weighted	8	0.8493	0.1543	0.2897	0.62764	1.14919
MR Egger	8	1.5917	0.60407	0.47073	0.48721	5.20116
SIMEX corrected MR Egger	8	1.9741	0.7485	0.394	0.45524	8.56077
Weighted median	8	0.9374	0.13468	0.63146	0.71994	1.22064
Weighted mode	8	0.9247	0.217135	0.728998	0.604173	1.415206
I2GX= 0.53; suggesting a 47% attenuation of the MR Egger estimate towards zero.						
MR Egger Intercept= -0.05; p-value= 0.32						

Table C17. Two-sample Mendelian randomization (MR) causal effect estimates, standard errors, 95% confidence intervals, and p-values for the analyses investigating the effects of common variant genetic liability to autism without intellectual disabilities (ID) on inflammatory bowel disease (IBD), ulcerative colitis (UC), and Crohn's disease (Crohn's).

Outcome: IBD						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95%CIs**	
Inverse variance weighted	7	0.942213	0.051555	0.248268	0.851657	1.042398
MR Egger	7	1.07521	0.244751	0.778924	0.665514	1.73712
SIMEX corrected MR Egger	7	1.104707	0.22539	0.677	0.710217	1.718315
Weighted median	7	0.959121	0.067025	0.533462	0.841048	1.093769
Weighted mode	7	1.00791	0.09822	0.938676	0.83141	1.221879
I2GX= 0.37; suggesting a 63% attenuation of the MR Egger estimate towards zero.						
MR Egger Intercept= -0.01; p-value= 0.6						
Outcome: UC						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95%CIs**	
Inverse variance weighted	7	0.946301	0.065894	0.40224	0.831648	1.076761
MR Egger	7	0.904261	0.313971	0.761528	0.488693	1.673211
SIMEX corrected MR Egger	7	0.850935	0.31603	0.631	0.458022	1.580907
Weighted median	7	0.924646	0.088291	0.374898	0.777715	1.099336
Weighted mode	7	0.888475	0.118178	0.355653	0.704774	1.120058
I2GX= 0.37; suggesting a 63% attenuation of the MR Egger estimate towards zero.						
MR Egger Intercept= 0.005; p-value= 0.89						
Outcome: Crohn's						
METHOD	**NSNP**	**OR**	**SE**	**P**	**95%CIs**	
Inverse variance weighted	7	0.97043	0.082921	0.717361	0.82486	1.141689
MR Egger	7	1.359954	0.399214	0.476009	0.62188	2.974008
SIMEX corrected MR Egger	7	1.592189	0.56498	0.448	0.526107	4.818539
Weighted median	7	0.940425	0.094064	0.51376	0.782088	1.130819
Weighted mode	7	0.892806	0.172435	0.535219	0.636762	1.251805
I2GX= 0.37; suggesting a 63% attenuation of the MR Egger estimate towards zero.						
MR Egger Intercept= -0.04; p-value= 0.43						

Appendix D

Table D1. Genetic instruments used in the Mendelian randomization (MR) analyses investigating the causal effects of common variant genetic liability to schizophrenia on levels of plasma cytokines.

SNP	A1	A2	EAF	SE	P	logOR
rs7002992	T	C	0.669	0.0083	4.48E-09	0.0484
rs6715366	G	A	0.766	0.0094	4.23E-09	-0.0551
rs77463171	C	T	0.975	0.0263	2.41E-08	-0.1465
rs113113059	T	C	0.761	0.0092	2.29E-11	0.061396
rs10873538	T	G	0.657	0.0082	9.59E-15	-0.0632
rs61920311	A	C	0.596	0.0082	1.75E-08	0.046101
rs2532240	C	T	0.598	0.0083	2.72E-10	0.052099
rs55938136	A	G	0.799	0.0108	1.23E-08	0.0615
rs6588168	C	T	0.475	0.0079	5.94E-10	-0.0489
rs12126806	C	T	0.757	0.009	2.89E-08	0.049904
rs4915203	A	G	0.329	0.0085	3.30E-09	0.050398
rs1658810	C	T	0.211	0.0096	3.54E-17	0.080704
rs140001745	T	C	0.934	0.0155	5.13E-12	0.106996
rs56335113	A	G	0.313	0.0084	3.15E-15	0.066602
rs581459	C	T	0.808	0.0123	1.32E-09	0.0743
rs1915019	A	G	0.238	0.0092	3.43E-10	0.057599
rs308697	C	A	0.606	0.0079	3.35E-09	0.046903
rs13090130	G	A	0.609	0.0079	9.92E-11	0.051396
rs2102949	G	A	0.278	0.0087	3.18E-23	0.086003
rs75482067	G	A	0.908	0.0148	3.06E-09	-0.0876
rs2649999	T	C	0.386	0.0082	1.28E-09	0.049504
rs12311848	A	G	0.702	0.0087	1.65E-08	-0.049
rs2686386	C	T	0.214	0.0096	1.26E-08	0.054801
rs167924	A	G	0.303	0.0089	1.33E-08	-0.0506
rs72943392	G	C	0.759	0.0094	1.44E-08	-0.0532
rs9975024	A	G	0.529	0.008	1.78E-09	-0.0483
rs75968099	C	T	0.705	0.0089	5.16E-11	-0.0582
rs1506297	T	C	0.744	0.0091	1.98E-08	0.051102
rs6538539	G	T	0.48	0.0077	5.63E-10	0.047704
rs7953300	G	T	0.344	0.0082	3.94E-08	-0.0449
rs7575796	A	G	0.925	0.0171	1.57E-08	0.0969
rs7312697	T	C	0.347	0.0081	4.85E-11	-0.0533
rs28454198	G	C	0.569	0.0081	1.88E-09	0.0486
rs10086619	A	G	0.834	0.0104	3.30E-11	-0.0691
rs4702	G	A	0.465	0.0081	2.15E-23	0.080298
rs11210892	G	A	0.339	0.0081	1.18E-16	0.0675
rs11136325	G	A	0.531	0.009	3.30E-09	0.053
rs13262595	A	G	0.421	0.0079	2.21E-18	0.069097
rs12301769	A	C	0.911	0.014	1.93E-09	-0.08379

Schizophrenia instruments (continued)						
SNP	**A1**	**A2**	**EAF**	**SE**	**P**	**logOR**
rs2022265	A	G	0.534	0.0077	3.74E-10	0.048504
rs10985811	T	C	0.789	0.0098	2.53E-08	-0.0545
rs4793888	G	A	0.783	0.0097	3.63E-10	-0.0609
rs2381411	T	C	0.565	0.0079	1.28E-08	-0.045
rs39967	T	C	0.15	0.0107	1.87E-08	-0.0604
rs12943566	A	G	0.314	0.0083	2.29E-10	-0.0525
rs3752827	T	A	0.669	0.0084	6.33E-10	0.052203
rs77502336	G	C	0.651	0.0082	3.45E-11	-0.0545
rs1940171	A	G	0.813	0.0099	8.87E-14	0.073501
rs10515678	C	T	0.775	0.0095	4.46E-12	0.065703
rs11740474	A	T	0.65	0.0086	4.46E-09	-0.0504
rs12652777	T	C	0.436	0.0079	1.06E-08	0.045403
rs154433	G	A	0.643	0.0084	2.38E-08	0.047198
rs10957321	G	A	0.491	0.0077	4.18E-10	-0.0482
rs298216	C	G	0.113	0.0123	3.45E-09	-0.0727
rs6984242	G	A	0.41	0.0078	1.50E-11	0.052697
rs1454606	C	T	0.822	0.0108	2.90E-11	-0.0716
rs58120505	T	C	0.569	0.0078	1.80E-26	0.083302
rs11972718	C	G	0.724	0.0088	1.57E-08	-0.04949
rs17731	G	A	0.592	0.0079	3.76E-13	-0.0575
rs4766428	C	T	0.456	0.0085	2.61E-17	-0.0721
rs2387414	G	C	0.438	0.0084	8.01E-10	-0.0515
rs2304205	A	C	0.764	0.0092	2.38E-14	0.070403
rs758749	C	T	0.853	0.0112	4.66E-08	-0.0615
rs9312586	A	G	0.914	0.014	8.14E-11	-0.0908
rs41533650	G	A	0.798	0.0097	8.69E-14	-0.0724
rs61405217	C	T	0.431	0.0079	5.39E-11	0.052004
rs459391	T	C	0.187	0.01	1.54E-08	0.056598
rs6943762	T	C	0.894	0.0124	6.30E-17	0.103296
rs2252074	T	G	0.577	0.0078	1.27E-14	-0.0603
rs1510136	A	G	0.779	0.0093	1.39E-08	0.052602
rs61828917	C	T	0.853	0.011	7.95E-10	0.067603
rs16851048	T	C	0.798	0.0097	3.06E-12	-0.0676
rs12363019	T	A	0.558	0.0082	2.58E-10	-0.0516
rs10767734	C	T	0.567	0.0082	5.62E-10	0.050902
rs778371	A	G	0.738	0.0089	1.10E-16	-0.0741
rs11647188	A	G	0.538	0.0081	3.75E-08	0.044495
rs11076631	A	G	0.504	0.0088	2.59E-09	0.052203
rs6919146	T	G	0.306	0.0085	8.42E-09	-0.0488
rs2456020	C	T	0.711	0.0088	5.35E-15	0.068499
rs28521069	C	T	0.684	0.0083	3.78E-08	-0.0457
rs10117	G	A	0.534	0.0082	9.54E-12	0.055501
rs9687282	T	G	0.697	0.0086	1.66E-08	-0.0486
rs28490262	G	C	0.721	0.0086	6.68E-10	0.053199

Schizophrenia instruments (continued)						
SNP	**A1**	**A2**	**EAF**	**SE**	**P**	**logOR**
rs13195636	A	C	0.926	0.0159	6.55E-40	0.210504
rs356183	G	C	0.487	0.008	3.37E-08	0.044304
rs13230189	C	T	0.669	0.0081	1.04E-18	0.071902
rs35792732	C	T	0.829	0.0106	1.08E-08	0.060399
rs1593304	A	G	0.183	0.0101	2.37E-10	-0.0642
rs10947452	T	C	0.398	0.0081	3.69E-08	-0.0448
rs9461856	G	A	0.506	0.0078	3.23E-16	-0.0639
rs3131295	G	A	0.538	0.008	9.97E-14	0.0599
rs11693094	C	T	0.543	0.0078	2.20E-13	0.057297
rs12129573	C	A	0.653	0.0082	1.42E-16	-0.0681
rs1121296	T	C	0.588	0.008	3.74E-09	0.047303
rs11619756	G	A	0.531	0.0082	7.97E-09	0.047103
rs215483	G	A	0.685	0.0084	1.59E-09	-0.0507
rs4697446	G	T	0.549	0.0079	1.67E-08	-0.0446
rs7647398	C	T	0.824	0.01	2.21E-17	0.085003
rs9882532	T	C	0.69	0.0087	8.57E-10	-0.05309
rs6577597	A	G	0.412	0.0085	5.52E-10	-0.0526
rs3739554	A	G	0.825	0.0103	2.26E-08	-0.0576
rs5995756	T	C	0.553	0.0084	2.38E-11	0.056399
rs9607782	T	A	0.781	0.0097	7.10E-14	-0.0725
rs4822076	C	T	0.255	0.0089	1.94E-11	-0.0597
rs1451488	A	G	0.483	0.0079	6.72E-17	-0.066
rs13032111	T	G	0.476	0.0077	2.15E-08	0.043203
rs2914983	A	G	0.361	0.0081	1.10E-14	0.062796
rs10190027	C	T	0.684	0.0089	2.57E-08	-0.04971
rs3770752	A	G	0.698	0.0086	2.86E-11	0.057401
rs6925079	T	C	0.63	0.0081	3.58E-08	-0.0448
rs6065094	A	G	0.311	0.0082	1.41E-14	-0.0634
rs13219424	C	T	0.678	0.0084	4.52E-08	0.045996
rs60135207	G	T	0.607	0.0087	1.27E-08	0.049599
rs12991836	A	C	0.594	0.008	2.72E-13	-0.0584
rs16825349	A	G	0.83	0.0104	1.32E-11	-0.0704
rs10777187	T	C	0.248	0.0092	2.82E-08	0.050902
rs12713008	G	A	0.557	0.0078	3.05E-08	0.043002
rs500102	T	C	0.438	0.0079	4.15E-08	0.043299
rs72761691	A	C	0.858	0.0116	1.07E-08	-0.0664
rs2078266	A	G	0.175	0.0113	4.86E-08	0.0618
rs79668541	C	T	0.885	0.0121	2.11E-23	0.120703
rs79780963	C	T	0.884	0.0122	2.53E-22	0.118396
rs1856507	C	A	0.627	0.008	3.00E-10	0.050398
rs9454727	A	G	0.781	0.0098	1.93E-08	0.054801
rs578470	T	C	0.621	0.0083	2.33E-08	-0.0462
rs61937595	C	T	0.922	0.0158	1.32E-14	0.121996
rs73292401	T	A	0.823	0.0103	1.82E-10	-0.0659

Schizophrenia instruments (continued)						
SNP	**A1**	**A2**	**EAF**	**SE**	**P**	**logOR**
rs9891739	C	T	0.539	0.008	2.18E-08	-0.045
rs4073003	A	G	0.73	0.0116	4.20E-12	0.080603
rs8055219	G	A	0.785	0.0095	1.57E-12	-0.0672
rs252812	A	G	0.25	0.0093	1.30E-08	0.053
rs35164357	C	T	0.725	0.0096	2.59E-10	-0.0605
rs10861176	G	A	0.271	0.0086	5.23E-09	-0.0504
rs3764002	C	T	0.668	0.0086	1.65E-09	-0.0517
rs2455415	C	T	0.614	0.0081	3.43E-09	-0.04759
rs1924377	G	C	0.492	0.0082	8.71E-09	0.046903
rs55929115	T	A	0.904	0.013	3.21E-08	0.072004
rs10035564	A	G	0.616	0.0081	1.65E-15	-0.06481
rs1540840	G	C	0.614	0.009	1.04E-09	0.054999
rs17194490	G	T	0.832	0.0116	1.85E-11	-0.0781
rs61857878	A	T	0.796	0.0099	1.46E-09	0.0599
rs2514218	C	T	0.727	0.009	6.46E-15	0.069899
rs17644050	G	C	0.8	0.0098	4.02E-08	-0.0538
rs79210963	T	C	0.897	0.0129	2.58E-11	-0.0863
rs7811417	T	C	0.361	0.0081	2.17E-09	0.048304
rs12285419	C	A	0.809	0.01	3.73E-16	-0.0812
rs634940	G	T	0.786	0.0098	2.88E-11	-0.0649
rs6925964	A	T	0.939	0.0176	3.19E-08	0.097499
rs9304548	C	A	0.265	0.0089	1.90E-11	0.060003
rs2710323	T	C	0.545	0.0077	5.92E-22	0.074597
rs11917680	G	T	0.751	0.0091	4.17E-10	0.056702
rs7432375	G	A	0.521	0.0082	5.32E-15	0.063801
rs2238304	A	T	0.546	0.0078	1.73E-10	0.049599
rs4779050	T	G	0.401	0.0079	4.18E-10	0.049304
rs11638554	T	G	0.745	0.0089	3.62E-13	0.064504
rs6673880	A	G	0.427	0.0086	1.32E-12	-0.061
rs11121172	C	A	0.289	0.0089	7.15E-10	0.054602
rs11122119	C	A	0.641	0.0081	2.31E-08	-0.0453
rs9597388	G	A	0.823	0.0101	3.24E-11	0.066798
rs9569820	G	T	0.831	0.0109	6.56E-10	-0.0676
rs7938083	C	A	0.71	0.0087	1.60E-09	-0.0524
rs10069930	T	A	0.506	0.0079	9.43E-10	0.048304
rs6479487	T	G	0.832	0.0103	1.37E-08	-0.0587
rs7609876	T	C	0.716	0.0089	9.40E-09	-0.0512
rs2224086	C	A	0.19	0.0103	2.09E-08	-0.0577
rs144821294	C	T	0.961	0.0242	1.22E-08	-0.138
rs72974269	C	T	0.687	0.0083	2.76E-10	0.052099
rs35351411	A	C	0.491	0.0079	3.13E-13	-0.0573
rs3814883	C	T	0.551	0.0079	8.82E-15	0.060898
rs72723227	G	A	0.66	0.0082	4.58E-09	0.047999
rs1463209	C	T	0.518	0.0081	3.34E-09	0.047704

Schizophrenia instruments (continued)						
SNP	**A1**	**A2**	**EAF**	**SE**	**P**	**logOR**
rs2190864	T	C	0.392	0.008	1.12E-16	0.066097
rs2206956	G	A	0.457	0.0078	2.51E-09	-0.0462
rs9390083	C	G	0.825	0.0103	2.95E-08	-0.05719
rs1858999	C	G	0.356	0.0081	7.97E-14	0.060502
rs72986630	C	T	0.935	0.0177	3.07E-10	-0.1117
rs322128	C	T	0.779	0.0095	2.08E-09	-0.0567
rs12431743	G	A	0.364	0.008	1.26E-08	-0.0456
rs9926049	C	A	0.729	0.0088	3.16E-10	-0.0556
rs8048039	A	T	0.347	0.0083	4.35E-09	0.049
rs10127983	C	T	0.69	0.0084	3.11E-08	-0.0463
rs12138231	T	A	0.157	0.0116	7.21E-09	-0.0671
rs7915131	C	T	0.425	0.0078	4.94E-08	0.042695
rs13107325	C	T	0.919	0.0168	2.90E-21	-0.1587
rs6839635	C	A	0.49	0.0079	3.87E-08	-0.0432
rs2153960	G	A	0.305	0.0084	9.22E-10	0.051396
rs117799466	G	C	0.663	0.0087	3.86E-08	-0.0481
rs6504163	C	T	0.364	0.0082	1.87E-09	-0.0492
rs6732355	C	A	0.771	0.0094	4.36E-10	-0.0587
rs2119242	G	A	0.829	0.0106	1.34E-08	-0.0602
rs11807834	G	A	0.758	0.0093	1.12E-08	-0.053
rs11587347	C	G	0.905	0.0139	1.50E-13	-0.1028
rs61833239	T	G	0.829	0.0122	5.22E-12	-0.0843
rs10148671	T	C	0.419	0.0083	6.82E-09	-0.0479
rs6482437	A	C	0.0869	0.0135	1.05E-14	-0.10471
rs115325222	A	G	0.911	0.0151	1.93E-09	0.090398
rs6969410	T	G	0.673	0.0083	1.90E-11	0.055501
rs38752	T	G	0.608	0.0081	1.08E-13	0.060003
rs1589726	C	T	0.0915	0.0137	1.20E-08	0.077896
rs10238960	C	T	0.312	0.0084	7.65E-09	-0.0482
rs2944821	G	C	0.612	0.008	1.90E-09	0.047799
rs7701440	T	C	0.557	0.008	1.86E-15	-0.0638
rs73229090	C	A	0.897	0.0142	4.34E-13	0.102602
rs3808581	G	A	0.778	0.0097	3.82E-12	-0.06699
rs2717003	A	G	0.367	0.008	2.76E-21	-0.07529
rs12969453	A	G	0.564	0.0078	3.53E-12	0.054299
rs715170	C	T	0.758	0.009	7.40E-13	0.064701
rs4632195	C	T	0.566	0.0084	2.73E-09	-0.0498
rs9636107	A	G	0.433	0.0081	5.72E-14	-0.0609
rs17571951	T	C	0.782	0.0105	7.89E-10	-0.0645
rs12883788	C	T	0.563	0.0079	8.43E-12	-0.0543
rs8104557	T	C	0.814	0.011	3.76E-08	-0.0604
rs3810450	T	C	0.932	0.016	8.27E-09	0.092497
rs505061	C	A	0.505	0.0077	1.03E-10	-0.0499
rs9545047	A	C	0.642	0.0081	3.05E-11	0.053797

Schizophrenia instruments (continued)						
SNP	**A1**	**A2**	**EAF**	**SE**	**P**	**logOR**
rs58950470	G	T	0.703	0.0086	1.10E-08	-0.0493
rs6546857	A	G	0.778	0.0101	2.80E-09	-0.0603
rs11897811	C	T	0.814	0.0102	1.49E-08	-0.0575
rs999494	C	T	0.824	0.0101	1.04E-08	0.057599
rs1198588	A	T	0.167	0.0103	7.88E-21	-0.0964
rs59519965	G	T	0.808	0.0098	3.36E-09	-0.0582
rs72728416	A	G	0.717	0.0087	4.99E-12	-0.0598
rs337718	T	C	0.305	0.0084	4.39E-09	0.0492
rs6588355	T	C	0.265	0.009	3.65E-08	0.049504
rs56205728	G	A	0.739	0.0093	5.43E-10	-0.0575
rs2929278	C	T	0.748	0.0091	8.50E-12	0.061904
rs9287971	G	A	0.587	0.0083	3.82E-08	-0.0458
rs62184960	C	T	0.882	0.0122	1.08E-08	0.069797
rs6430492	G	A	0.772	0.0094	6.72E-10	0.057703
rs331395	C	G	0.747	0.009	1.27E-09	-0.0549
rs4672366	A	T	0.686	0.0087	1.07E-08	0.049799
rs10503253	C	A	0.761	0.0091	4.37E-11	-0.0602
rs72980087	G	A	0.607	0.0079	4.06E-16	-0.0644
rs7238071	A	G	0.684	0.0084	9.29E-14	-0.0629
rs4937935	A	T	0.497	0.0081	2.30E-11	-0.0539
rs1440480	A	G	0.337	0.0086	2.52E-11	0.057504
rs10894308	G	A	0.549	0.0079	1.36E-09	0.047704
rs4936215	A	G	0.821	0.0104	1.86E-15	0.082796
rs1939514	T	C	0.526	0.0077	1.06E-12	0.055198
rs79445414	T	C	0.956	0.0222	2.63E-08	-0.1235
rs7816998	G	A	0.775	0.0092	3.11E-10	0.057797
rs35045093	A	C	0.827	0.0103	3.36E-08	0.056598
rs61786047	G	A	0.892	0.0135	4.91E-09	0.078802
rs6010045	T	C	0.321	0.0085	1.82E-08	-0.0477
rs704364	A	G	0.357	0.0082	8.41E-10	0.050303
rs9813516	G	A	0.556	0.0084	1.25E-09	-0.0513
rs498591	A	T	0.856	0.0111	9.59E-10	-0.0679
rs2890914	A	G	0.474	0.0077	2.31E-08	-0.0432
rs10774034	C	T	0.656	0.0085	7.10E-23	-0.08329
rs12712510	T	C	0.572	0.0084	9.34E-10	0.051501
rs141216273	C	A	0.959	0.0228	4.49E-08	-0.1247
rs12474906	A	C	0.725	0.0095	2.20E-09	0.056796
rs2909457	G	A	0.382	0.0083	3.09E-08	0.045805
rs35734242	T	C	0.558	0.008	3.93E-10	-0.0499
rs11696755	T	C	0.827	0.0104	2.99E-10	-0.0653

Table D2. Genetic instruments used for the Mendelian randomization analyses (MR) investigating the causal effects of genetic liability to autism on levels of plasma cytokines.

SNP	CHR	BP	A1	A2	logOR	SE	P	EAF
rs10099100	8	10576775	C	G	0.084304	0.0147	1.07E-08	0.348
rs111931861	7	1.05E+08	G	A	0.216901	0.0409	1.12E-07	0.96
rs112635299	14	94838142	T	G	0.220997	0.0432	3.04E-07	0.03
rs1452075	3	62481063	T	C	0.080704	0.0155	2.07E-07	0.738
rs2224274	20	14760747	T	C	0.070999	0.0138	2.86E-07	0.508
rs2391769	1	96978961	G	A	0.076903	0.0145	1.14E-07	0.348
rs325485	5	1.04E+08	G	A	-0.0728	0.0143	3.25E-07	0.396
rs45595836	10	16691399	T	C	0.138996	0.0272	3.13E-07	0.0783
rs6701243	1	99092784	C	A	-0.0735	0.0144	3.07E-07	0.626
rs910805	20	21248116	A	G	-0.0957	0.016	2.04E-09	0.745

Table D3. Results of the two-sample Mendelian randomization (MR) analyses investigating the causal effects of genetically proxied plasma cytokines on autism.

EXPOSURE	METHOD	NSNP	OR	SE	P	95%CIs		snp_r2.exposure	snp_r2.outcome	F	Steiger p-value	Steiger direction of effects
IFNGR1	Wald ratio	1	1.15	0.06	0.02	1.03	1.29	0.0307184115135297	0.000134716836686725	103	4.20899326738702e-20	Correct
IL10RB	Wald ratio	1	0.99	0.1	0.9	0.81	1.2	0.00985139146673176	3.64398633172044e-07	32.65	3.97172665633152e-08	Correct
IL12B	Wald ratio	1	0.98	0.07	0.77	0.85	1.13	0.0180762550712615	1.91273056977207e-06	60.02	1.09470484005069e-13	Correct
IL12RB1	Wald ratio	1	1.03	0.02	0.12	0.99	1.07	0.0891185345148932	5.31278135213319e-05	361.43	1.82034086821381e-62	Correct
IL12RB2	Wald ratio	1	0.98	0.06	0.66	0.87	1.09	0.027720562653705	4.12586249342527e-06	92.51	3.18433974672743e-20	Correct
IL13RA1	Wald ratio	1	1.16	0.07	0.04	1	1.34	0.0183891838995712	9.44616142544894e-05	61.17	2.03796081556582e-12	Correct
IL17F	Wald ratio	1	0.98	0.09	0.86	0.83	1.17	0.0093963939160747	6.69250671784797e-07	31.25	8.78232419315142e-08	Correct
IL17RA	Wald ratio	1	0.99	0.02	0.55	0.96	1.02	0.241954663085938	7.82995112134881e-06	2190.72	3.36881417169215e-194	Correct
IL21	Wald ratio	1	0.98	0.05	0.67	0.88	1.09	0.0310441548191304	3.90062144736067e-06	103.79	1.51276304788253e-22	Correct
IL22RA1	Wald ratio	1	1.03	0.07	0.64	0.9	1.19	0.0173130875580133	4.81328061952764e-06	57.58	5.12672942023646e-13	Correct
IL23R	Wald ratio	1	1.1	0.07	0.18	0.96	1.27	0.0219333584828941	4.00794110815485e-05	73.17	2.2394856401165e-15	Correct
IL2	Wald ratio	1	1.14	0.07	0.07	0.99	1.32	0.0181953322609824	7.56062270312749e-05	60.36	1.81277099024687e-12	Correct
IL4RA	Wald ratio	1	0.81	0.11	0.04	0.65	0.99	0.00971893505319867	9.99958374255671e-05	32.31	8.0894664934599e-07	Correct
IL5RA	Wald ratio	1	0.91	0.05	0.05	0.83	1	0.0581608917497482	8.73559175394038e-05	198.17	2.15791295345857e-39	Correct
IL5	Wald ratio	1	1.01	0.05	0.91	0.92	1.1	0.0423339988082879	2.78160253849368e-07	142.32	7.14329893555498e-31	Correct
IL6R	Wald ratio	1	1.02	0.02	0.34	0.98	1.05	0.307652392578125	1.93927393733216e-05	1211.43	6.19237496937966e-260	Correct
TGFB1	Wald ratio	1	0.96	0.06	0.5	0.86	1.07	0.0332506413362943	9.94918515294017e-06	116.46	8.51323233121806e-24	Correct

Table D4. Results summary of the two-sample Mendelian randomization (MR) analyses investigating the causal effects of genetically proxied plasma cytokines on autism without intellectual disabilities.

EXPOSURE	METHOD	NSNP	OR	SE	P	95%CIs		snp_r2.exposure	snp_r2.outcome	F	Steiger p-value	Steiger direction of effects
IFNGR1	Wald ratio	1	1.18	0.07	0.02	1.03	1.35	0.0307184115135297	0.000178453609162513	103	2.8379833670459e-19	Correct
IL10RB	Wald ratio	1	0.94	0.12	0.59	0.74	1.19	0.00985139146673176	8.58748234669395e-06	32.65	1.17236204485619e-07	Correct
IL12B	Wald ratio	1	1.01	0.09	0.89	0.85	1.21	0.0180762550712615	6.24068284931241e-07	60.02	1.69260922658346e-13	Correct
IL12RB1	Wald ratio	1	1.06	0.02	0.02	1.01	1.11	0.0891185345148932	0.000151066151207387	361.43	4.78191500989267e-59	Correct
IL12RB2	Wald ratio	1	1	0.07	0.97	0.87	1.14	0.027720562653705	4.13437497720941e-08	92.51	3.55689621936439e-20	Correct
IL13RA1	Wald ratio	1	1.13	0.09	0.17	0.95	1.34	0.0183891838995712	5.68395032481694e-05	61.17	1.59676029607448e-12	Correct
IL17F	Wald ratio	1	0.9	0.11	0.32	0.72	1.11	0.0093963939160747	3.0281729931363e-05	31.25	4.94610766998902e-07	Correct
IL17RA	Wald ratio	1	1.01	0.02	0.53	0.97	1.05	0.241954663085938	1.17235103040758e-05	2190.72	4.08420470845155e-189	Correct
IL21	Wald ratio	1	0.95	0.07	0.48	0.84	1.09	0.0310441548191304	1.49001420890465e-05	103.79	1.32307265659978e-21	Correct
IL22RA1	Wald ratio	1	1.04	0.09	0.66	0.88	1.23	0.0173130875580133	5.78721241445153e-06	57.58	1.06037005841878e-12	Correct
IL23R	Wald ratio	1	1.03	0.09	0.7	0.87	1.23	0.0219333584828941	4.37075371764115e-06	73.17	7.42670190950311e-16	Correct
IL2	Wald ratio	1	1.12	0.09	0.21	0.94	1.33	0.0181953322609824	4.7420140714003e-05	60.36	1.6460287296019e-12	Correct
IL4RA	Wald ratio	1	0.77	0.13	0.04	0.6	0.99	0.00971893505319867	0.000146028589432799	32.31	1.94636225633233e-06	Correct
IL5	Wald ratio	1	1.01	0.06	0.91	0.9	1.13	0.0423339988082879	4.14860816911602e-07	142.32	3.90776011185192e-30	Correct
IL6R	Wald ratio	1	1	0.02	0.91	0.96	1.04	0.307652392578125	3.9217591073621e-07	1211.43	9.0076328979132e-257	Correct
TGFB1	Wald ratio	1	1	0.07	0.96	0.87	1.14	0.0332506413362943	7.26648755856318e-08	116.46	5.91672948080351e-24	Correct

Table D5. Results summary of the two-sample Mendelian randomization (MR) analyses investigating the causal effects of genetically proxied plasma cytokines on schizophrenia.

EXPOSURE	METHOD	NSNP	OR	SE	P	95%CIs		snp_r2.exposure	snp_r2.outcome	F	Steiger p-value	Steiger direction of effects
IFNGR1	Wald ratio	1	0.99	0.04	0.79	0.92	1.06	0.0307184115135297	2.37679065217743e-07	103	6.24002273587232e-24	Correct
IL10RB	Wald ratio	1	1.05	0.05	0.33	0.95	1.17	0.00985139146673176	3.12534118209722e-06	32.65	2.30671904855814e-08	Correct
IL12B (cis)	Wald ratio	1	0.99	0.03	0.61	0.93	1.04	0.0423094555815861	8.36491159126027e-07	142.08	1.75205010506481e-32	Correct
IL12B (trans)	Wald ratio	1	1.07	0.04	0.12	0.98	1.16	0.0180762550712615	8.18989315443197e-06	60.02	3.93436481574988e-14	Correct
IL12RB1	Wald ratio	1	1.01	0.01	0.64	0.98	1.03	0.0891185345148932	6.96168735095266e-07	361.43	7.08261743972008e-69	Correct
IL12RB2	Wald ratio	1	1.06	0.03	0.08	0.99	1.13	0.027720562653705	1.03380066754519e-05	92.51	4.68140961973256e-21	Correct
IL13RA1	Wald ratio	1	0.99	0.04	0.73	0.91	1.07	0.0183891838995712	4.0594211818135e-07	61.17	8.65238664558757e-15	Correct
IL17RA	Wald ratio	1	1.01	0.01	0.15	1	1.03	0.241954663085938	6.91711051844729e-06	2190.72	8.38296128395377e-206	Correct
IL21	Wald ratio	1	0.99	0.03	0.86	0.94	1.06	0.0310441548191304	9.61594625152047e-08	103.79	3.21964165250939e-24	Correct
IL23R	Wald ratio	1	1.02	0.04	0.72	0.93	1.1	0.0219333584828941	4.17710507676201e-07	73.17	2.1504476166169e-17	Correct
IL4RA	Wald ratio	1	1.01	0.06	0.87	0.9	1.14	0.00971893505319867	9.23489986054058e-08	32.31	1.77854172356326e-08	Correct
IL5RA	Wald ratio	1	1.04	0.02	0.09	0.99	1.09	0.0581608917497482	9.5577398350554e-06	198.17	8.86971016447402e-44	Correct
IL5	Wald ratio	1	1.01	0.03	0.63	0.96	1.07	0.0423339988082879	7.65903727570493e-07	142.32	1.63448726871984e-32	Correct
IL6R	Wald ratio	1	1.03	0.01	0.01	1.01	1.05	0.307652392578125	2.19378240072056e-05	1211.43	4.35503734608149e-275	Correct
TGFB1	Wald ratio	1	1.01	0.03	0.73	0.95	1.07	0.0332506413362943	3.79707256725313e-07	116.46	8.77408952940624e-26	Correct

Table D6. Results summary of the two-sample Mendelian randomization (MR) analyses investigating the causal effects of brain-expressed cytokine genes on autism.

EXPOSURE	METHOD	NSNP	OR	SE	P	95%CIs		snp_r2.exposure	snp_r2.outcome	F	Steiger p-value	Steiger direction of effects
IFNGR1	Wald ratio	1	1.22	0.08	0.01	1.05	1.42	0.00791979536560138	0.000174404323439125	52.47	7.57854987144792e-09	Correct
IFNGR2	Wald ratio	1	0.85	0.12	0.19	0.67	1.08	0.00332398354893073	3.95984163953393e-05	21.97	9.29736083134548e-05	Correct
IL10RB	Wald ratio	1	1	0.02	0.9	0.96	1.05	0.105644876098633	3.64398633172044e-07	736.74	2.21358919702339e-144	Correct
IL12A	Wald ratio	1	1.06	0.06	0.4	0.93	1.2	0.0104892530515436	1.54326332500579e-05	69.58	5.80692917344147e-14	Correct
IL12B	Wald ratio	1	1.24	0.12	0.08	0.97	1.57	0.00290369360559042	7.78263514962334e-05	19.19	0.000606376552846105	Correct
IL12RB1	Wald ratio	1	1.1	0.06	0.11	0.98	1.23	0.0133044578830802	5.64386097721105e-05	88.38	1.80658626699463e-16	Correct
IL12RB2	Wald ratio	1	0.98	0.07	0.74	0.85	1.12	0.00934400811940007	2.31024539290677e-06	61.95	4.05124660317811e-13	Correct
IL13	Wald ratio	1	1.04	0.09	0.67	0.87	1.25	0.00471432664114052	3.91574127362146e-06	31.18	3.85546754852289e-07	Correct
IL17RA	Wald ratio	1	0.99	0.03	0.75	0.94	1.05	0.0547319820658846	2.18339971800338e-06	371.41	1.84915829159208e-72	Correct
IL21	Wald ratio	1	0.96	0.03	0.17	0.9	1.02	0.0486811984362172	4.11442426525068e-05	329.31	1.33375577304472e-61	Correct
IL23A	Wald ratio	1	0.88	0.06	0.04	0.77	1	0.0110924642151617	9.30362845012834e-05	73.6	2.85770739281018e-13	Correct
IL2RA	Wald ratio	1	0.96	0.07	0.56	0.84	1.1	0.0107540601892469	7.22537573045284e-06	71.35	1.30514699743724e-14	Correct
IL4R	Wald ratio	1	1.09	0.08	0.28	0.93	1.28	0.00608724971643971	2.59582344874258e-05	40.29	2.78686692678534e-08	Correct
IL4	Wald ratio	1	0.95	0.05	0.33	0.86	1.05	0.0179393215228082	2.01623901057362e-05	119.45	4.19058335713833e-23	Correct
IL5	Wald ratio	1	1.02	0.05	0.71	0.92	1.13	0.015688010250886	2.87682792042016e-06	104.34	3.7176560863505e-21	Correct
IL6	Wald ratio	1	1.07	0.12	0.58	0.85	1.34	0.00301487724144323	6.7939045249712e-06	19.92	6.9199103275421e-05	Correct
IL9	Wald ratio	1	1.07	0.08	0.4	0.92	1.24	0.00681915514543759	1.56365365480526e-05	45.15	2.10343213852538e-09	Correct
TGFB1	Wald ratio	1	0.89	0.14	0.41	0.67	1.18	0.00292172599094145	1.54130224601197e-05	19.31	0.000136966911449788	Correct

Table D7. Results summary of the two-sample Mendelian randomization (MR) analyses investigating the causal effects of brain-expressed cytokine genes on autism without intellectual disabilities.

EXPOSURE	METHOD	NSNP	OR	SE	P	95%CIs		snp_r2.exposure	snp_r2.outcome	F	Steiger p-value	Steiger direction of effects
IFNGR1	Wald ratio	1	1.04	0.09	0.62	0.88	1.23	0.00791979536560138	7.16774689853082e-06	52.47	1.2756005463587e-10	Correct
IFNGR2	Wald ratio	1	0.83	0.15	0.2	0.62	1.11	0.00332398354893073	5.20018628492837e-05	21.97	0.000175290249912308	Correct
IL10RB	Wald ratio	1	1.01	0.03	0.59	0.96	1.07	0.105644876098633	8.58748234669395e-06	736.74	3.49730482590905e-136	Correct
IL12A	Wald ratio	1	1.01	0.08	0.87	0.87	1.18	0.0104892530515436	7.44990336624014e-07	69.58	3.69412170999088e-14	Correct
IL12B	Wald ratio	1	1.36	0.15	0.04	1.01	1.83	0.00290369360559042	0.000157084900906989	19.19	0.00209822479154023	Correct
IL12RB1	Wald ratio	1	1.16	0.07	0.04	1.01	1.34	0.0133044578830802	0.00013554266207408	88.38	9.75081427151705e-15	Correct
IL12RB2	Wald ratio	1	0.99	0.09	0.92	0.83	1.18	0.00934400811940007	3.07886610642968e-07	61.95	7.91697088947703e-13	Correct
IL13	Wald ratio	1	1.08	0.12	0.51	0.86	1.35	0.00471432664114052	1.29565846275056e-05	31.18	1.2884442481768e-06	Correct
IL17RA	Wald ratio	1	0.96	0.03	0.21	0.89	1.02	0.0547319820658846	4.67774532434143e-05	371.41	2.64918398089192e-66	Correct
IL21	Wald ratio	1	0.98	0.04	0.66	0.91	1.06	0.0486811984362172	5.80169863058786e-06	329.31	4.58288728405345e-61	Correct
IL23A	Wald ratio	1	0.95	0.07	0.45	0.82	1.09	0.0110924642151617	1.68233827335859e-05	73.6	4.39243581833603e-14	Correct
IL2RA	Wald ratio	1	0.96	0.09	0.67	0.82	1.14	0.0107540601892469	5.30743200782619e-06	71.35	4.00678397477379e-14	Correct
IL4R	Wald ratio	1	1.09	0.1	0.38	0.9	1.32	0.00608724971643971	2.32275778073283e-05	40.29	5.03655454669623e-08	Correct
IL4	Wald ratio	1	0.93	0.06	0.25	0.83	1.05	0.0179393215228082	3.97862613226678e-05	119.45	1.40189583911848e-21	Correct
IL5	Wald ratio	1	1.02	0.06	0.8	0.9	1.15	0.015688010250886	1.91118536377766e-06	104.34	2.21317740873355e-20	Correct
IL6	Wald ratio	1	1.15	0.15	0.35	0.86	1.53	0.00301487724144323	2.66047635207761e-05	19.92	0.00021552824622655	Correct
IL9	Wald ratio	1	1.1	0.1	0.32	0.91	1.32	0.00681915514543759	2.95767167554883e-05	45.15	9.20296411355408e-09	Correct
TGFB1	Wald ratio	1	0.96	0.18	0.83	0.68	1.36	0.00292172599094145	1.40505666749897e-06	19.31	8.44113265094053e-05	Correct

Table D8. Results summary of the two-sample Mendelian randomization (MR) analyses investigating the causal effects of brain-expressed cytokine genes on schizophrenia.

EXPOSURE	METHOD	NSNP	OR	SE	P	95%CIs		snp_r2.exposure	snp_r2.outcome	F	Steiger p-value	Steiger direction of effects
IFNGR1	Wald ratio	1	0.98	0.04	0.54	0.91	1.05	0.00791979536560138	1.25899327570612e-06	52.47	1.43271192665777e-12	Correct
IFNGR2	Wald ratio	1	1.04	0.07	0.54	0.92	1.18	0.00332398354893073	1.26084354724949e-06	21.97	5.40705793376935e-06	Correct
IL10RB	Wald ratio	1	0.99	0.01	0.32	0.97	1.01	0.105644876098633	3.12534118209722e-06	736.74	4.08231466730266e-160	Correct
IL12A	Wald ratio	1	1	0.04	0.99	0.93	1.07	0.0104892530515436	2.44396857542706e-10	69.58	1.47412135434938e-16	Correct
IL12B	Wald ratio	1	0.99	0.07	0.93	0.87	1.14	0.00290369360559042	2.7280792767963e-08	19.19	1.54946067240829e-05	Correct
IL12RB1	Wald ratio	1	0.99	0.03	0.77	0.93	1.05	0.0133044578830802	2.72397498058078e-07	88.38	1.87297638884038e-20	Correct
IL12RB2	Wald ratio	1	0.96	0.04	0.3	0.88	1.04	0.00934400811940007	3.5074307848821e-06	61.95	2.13240588157958e-14	Correct
IL13	Wald ratio	1	1.07	0.06	0.25	0.96	1.19	0.00471432664114052	4.52699634690615e-06	31.18	8.52125440467961e-08	Correct
IL21	Wald ratio	1	0.97	0.02	0.16	0.94	1.01	0.0486811984362172	6.38105936808324e-06	329.31	4.49656622080333e-71	Correct
IL23A	Wald ratio	1	0.95	0.04	0.16	0.88	1.02	0.0110924642151617	6.45770065927806e-06	73.6	1.11812282358731e-16	Correct
IL2RA	Wald ratio	1	1.08	0.04	0.07	0.99	1.17	0.0107540601892469	1.10211256096467e-05	71.35	5.61485130906492e-16	Correct
IL4R	Wald ratio	1	0.99	0.04	0.85	0.91	1.08	0.00608724971643971	1.25392006912032e-07	40.29	3.98650050255397e-10	Correct
IL4	Wald ratio	1	0.94	0.03	0.04	0.89	1	0.0179393215228082	1.4037581617751e-05	119.45	6.4156212337664e-26	Correct
IL5	Wald ratio	1	1.01	0.03	0.71	0.95	1.07	0.015688010250886	4.45695293285037e-07	104.34	7.84814042605439e-24	Correct
IL6	Wald ratio	1	0.87	0.07	0.06	0.76	1	0.00301487724144323	1.45421733308495e-05	19.92	3.94436642122116e-05	Correct
IL9	Wald ratio	1	1.15	0.05	0.01	1.04	1.28	0.00681915514543759	2.89548173145669e-05	45.15	4.9970960016703e-10	Correct
TGFB1	Wald ratio	1	1.04	0.08	0.59	0.89	1.22	0.00292172599094145	9.78709914216256e-07	19.31	1.96553723154246e-05	Correct

Table D9. Detailed results of the colocalisation analyses for each exposure with MR evidence of causal effects on autism and schizophrenia.

								Colocalization Analyses						LD Check[a]	
EXPOSURE	TISSUE	ENSEMBL_ID	LEAD_VARIANT	CHR	BP[b]	Exposure Data	Outcome data	NSNPs	H0[c]	H1	H2	H3	H4[d]	Top Autism SNP	LD R2
IL12RB1	Blood	ENSG00000096996	rs376008	19	18189568	Suhre et al[e]	Autism	No region data available						rs273506	0.55
IFNGR1	Blood	ENSG00000027697	rs7080536	10	115348046	Sun et al.	Autism	2494	0%	60%	0%	18%	22%	rs2302373	0.22
IL4RA	Blood	ENSG00000077238	rs10418046	19	54327869	Sun et al.	Autism	3653	1%	83%	0%	9%	7%	rs11671984	0.77
IL5RA	Blood	ENSG00000091181	rs77400868	3	3150964	Sun et al.	Autism	4007	0%	89%	0%	10%	1%	rs4498029	0.06
IL13RA1	Blood	ENSG00000131724	rs4241818	4	187153786	Sun et al.	Autism	3409	0%	84%	0%	11%	5%	rs1039243	0.06
IL12B	Cortex	ENSG00000113302.4	rs75259819	5	158401932	Klein et al.	Autism	2204	46%	38%	5%	4%	6%	rs62378719	0.002
IL12RB1	Cortex	ENSG00000096996.16	rs2644777	19	18178616	Klein et al.	Autism	2394	0%	86%	0%	6%	8%	rs112461998	0.43
IFNGR1	Cortex	ENSG00000027697.14	rs4896249	6	137594069	Klein et al.	Autism	2645	0%	59%	0%	4%	37%	rs56061112	1
IL23A	Cortex	ENSG00000110944.9	rs59917308	12	56658708	Klein et al.	Autism	960	0%	88%	0%	2%	10%	rs75754909	1
IL6R	Blood	ENSG00000160712	rs4129267	1	154426264	Folkersen et al	Schizophrenia	1548	0%	5%	0%	94%	1%		
IL9	Cortex	ENSG00000145839.2	rs4487482	5	135201771	Klein et al.	Schizophrenia	2849	0%	27%	0%	61%	12%		
IL4	Cortex	ENSG00000113520.11	rs6879672	5	132025947	Klein et al.	Schizophrenia	1889	0%	93%	0%	4%	4%		
IL6	Cortex	ENSG00000136244.12	rs2905346	7	22618248	Klein et al.	Schizophrenia	3116	22%	56%	6%	15%	1%		

a: LDcheck analyses were performed only for colocalisation analyses using autism GWAS data.
b: Coordinates in GRCh37
c: Probability that there is no causal variant in neither exposure nor outcome datasets.
d: Probability that the independent signals in the exposure and outcome regions are consistent with a shared causal variant.
e**:** No region data were available and therefore colocalisation analyses could not be performed.
ENSEMBL_ID: gene id in Ensembl; CHR: chromosome; BP: position; LD: linkage disequilibrium.

Table D10. Causal effect estimates, standard errors and 95% confidence intervals of the Mendelian randomization (MR) analyses investigating the causal effects of common variant genetic liability to autism on levels of plasma cytokines.

Outcome: Inteleukin-2.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.29709	0.34443	0.413488	-0.97217	0.377992
Weighted median	10	-0.15911	0.138118	0.249323	-0.42982	0.1116
Inverse variance weighted	10	-0.11494	0.106481	0.280401	-0.32364	0.093765
Weighted mode	10	-0.19633	0.228223	0.411984	-0.64364	0.25099
Outcome: Inteleukin-12.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	0.059853	0.492475	0.906264	-0.9054	1.025103
Weighted median	10	0.074189	0.157589	0.637801	-0.23468	0.383063
Inverse variance weighted	10	0.019073	0.143609	0.894345	-0.2624	0.300547
Weighted mode	10	0.126872	0.270323	0.649991	-0.40296	0.656705
Outcome: Inteleukin-12 receptor subunit beta-1.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.1854	0.462703	0.699143	-1.09229	0.721502
Weighted median	10	0.003797	0.14691	0.979382	-0.28415	0.29174
Inverse variance weighted	10	-0.08806	0.135357	0.515317	-0.35336	0.177239
Weighted mode	10	0.025661	0.253575	0.921613	-0.47135	0.522669
Outcome: Inteleukin-12 receptor subunit beta-2.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	0.476211	0.34443	0.204153	-0.19887	1.151294
Weighted median	10	-0.04471	0.139286	0.748239	-0.31771	0.228296
Inverse variance weighted	10	-0.05028	0.106481	0.636771	-0.25898	0.15842
Weighted mode	10	-0.02204	0.224264	0.923869	-0.4616	0.417519
Outcome: Interferon gamma.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	0.338561	0.34431	0.354257	-0.33629	1.013408
Weighted median	10	-0.1055	0.13485	0.434029	-0.3698	0.158811
Inverse variance weighted	10	-0.05389	0.106507	0.612872	-0.26264	0.154864
Weighted mode	10	-0.09724	0.173779	0.58944	-0.43784	0.243369
Outcome: Interferon gamma receptor-1.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	0.237022	0.34443	0.510812	-0.43806	0.912105
Weighted median	10	-0.05732	0.139015	0.680089	-0.32979	0.215148
Inverse variance weighted	10	-0.1035	0.106481	0.331041	-0.3122	0.105201
Weighted mode	10	-0.06988	0.213386	0.75079	-0.48812	0.348356
Outcome: Interferon gamma receptor-2.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.22113	0.400266	0.595727	-1.00565	0.563391
Weighted median	10	0.084868	0.13764	0.537502	-0.18491	0.354641
Inverse variance weighted	10	-0.01946	0.11865	0.869715	-0.25202	0.213093
Weighted mode	10	0.120615	0.223098	0.601877	-0.31666	0.557887

Outcome: Interleukin-4 receptor subunit alpha.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.15147	0.34443	0.671739	-0.82655	0.523612
Weighted median	10	0.058953	0.12958	0.64914	-0.19502	0.31293
Inverse variance weighted	10	0.031789	0.106481	0.765288	-0.17691	0.240491
Weighted mode	10	0.017623	0.196037	0.930338	-0.36661	0.401856
Outcome: Interleukin-5.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	0.010797	0.567211	0.985279	-1.10094	1.122531
Weighted median	10	0.178406	0.156262	0.253573	-0.12787	0.484679
Inverse variance weighted	10	0.216114	0.166879	0.195308	-0.11097	0.543197
Weighted mode	10	0.109196	0.255116	0.678694	-0.39083	0.609223
Outcome: Interleukin-5 receptor subunit alpha.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	1.010261	0.35692	0.022133	0.310697	1.709825
Weighted median	10	-0.0292	0.152727	0.84839	-0.32854	0.270147
Inverse variance weighted	10	0.070928	0.145542	0.626021	-0.21433	0.356191
Weighted mode	10	-0.0444	0.218247	0.843311	-0.47217	0.383362
Outcome: Interleukin-13.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.55286	0.344305	0.147002	-1.2277	0.121979
Weighted median	10	0.062461	0.142727	0.661657	-0.21728	0.342205
Inverse variance weighted	10	0.048839	0.106471	0.646441	-0.15984	0.257522
Weighted mode	10	0.144297	0.242574	0.566591	-0.33115	0.619742
Outcome: Interleukin-13 receptor subunit alpha.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.1549	0.433432	0.730055	-1.00442	0.694628
Weighted median	10	0.040946	0.153094	0.789118	-0.25912	0.34101
Inverse variance weighted	10	-0.03081	0.127087	0.808476	-0.2799	0.218286
Weighted mode	10	0.103669	0.28297	0.722561	-0.45095	0.65829
Outcome: Interleukin-21.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	0.449219	0.431818	0.328619	-0.39715	1.295583
Weighted median	10	-0.15424	0.161243	0.338776	-0.47028	0.161793
Inverse variance weighted	10	-0.03282	0.136315	0.80972	-0.3	0.234355
Weighted mode	10	-0.29829	0.263239	0.286428	-0.81424	0.217656
Outcome: Interleukin-6 receptor subunit alpha.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.55233	0.344305	0.147338	-1.22717	0.122504
Weighted median	10	-0.16093	0.134104	0.230132	-0.42377	0.101917
Inverse variance weighted	10	-0.08293	0.106471	0.436035	-0.29161	0.125752
Weighted mode	10	-0.19691	0.215695	0.385099	-0.61967	0.225855
Outcome: Interleukin-23.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	0.364374	0.344305	0.32083	-0.31046	1.039212
Weighted median	10	-0.16911	0.140642	0.229203	-0.44477	0.106548

Outcome: Interleukin-23 (continued)						
Inverse variance weighted	10	-0.12056	0.106471	0.257507	-0.32924	0.088125
Weighted mode	10	-0.1094	0.210726	0.616163	-0.52243	0.30362
Outcome: Interleukin-23 receptor.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.35875	0.34443	0.328063	-1.03383	0.316336
Weighted median	10	-0.09628	0.138405	0.486649	-0.36756	0.174993
Inverse variance weighted	10	-0.08054	0.106481	0.449425	-0.28924	0.128163
Weighted mode	10	-0.10085	0.224408	0.663761	-0.54069	0.338988
Outcome: Interleukin-17 A.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.45239	0.394178	0.28426	-1.22498	0.320198
Weighted median	10	-0.25139	0.145445	0.083909	-0.53647	0.033679
Inverse variance weighted	10	-0.20658	0.117894	0.079734	-0.43765	0.024495
Weighted mode	10	-0.32574	0.224896	0.181433	-0.76654	0.115059
Outcome: Interleukin-17 A receptor.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.39092	0.34443	0.289248	-1.066	0.284167
Weighted median	10	0.054294	0.136259	0.690287	-0.21277	0.321362
Inverse variance weighted	10	-0.01382	0.106481	0.896713	-0.22252	0.194879
Weighted mode	10	0.156132	0.219553	0.495016	-0.27419	0.586457
Outcome: Interleukin-17 F.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.00101	0.34443	0.997729	-0.67609	0.674072
Weighted median	10	0.09998	0.125761	0.426614	-0.14651	0.34647
Inverse variance weighted	10	0.031133	0.106481	0.769992	-0.17757	0.239835
Weighted mode	10	0.136361	0.201872	0.516346	-0.25931	0.53203
Outcome: Interleukin-22.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	0.078492	0.344305	0.825387	-0.59635	0.75333
Weighted median	10	-0.05715	0.142948	0.689298	-0.33733	0.223026
Inverse variance weighted	10	0.009277	0.106471	0.930568	-0.19941	0.217959
Weighted mode	10	-0.11772	0.240443	0.636135	-0.58899	0.35355
Outcome: Interleukin-22 receptor subunit alpha-1.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	-0.11235	0.344435	0.752643	-0.78745	0.562737
Weighted median	10	-0.07446	0.12803	0.560851	-0.3254	0.17648
Inverse variance weighted	10	-0.04692	0.106517	0.659568	-0.25569	0.161851
Weighted mode	10	-0.09251	0.18334	0.625978	-0.45186	0.266838
Outcome: Interleukin-22 receptor subunit alpha-2.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	0.106119	0.344435	0.765878	-0.56897	0.781211
Weighted median	10	-0.04815	0.131193	0.71359	-0.30529	0.208986
Inverse variance weighted	10	-0.0649	0.106517	0.542315	-0.27368	0.143871
Weighted mode	10	-0.01882	0.217631	0.932985	-0.44538	0.407739

Outcome: Interleukin-10.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	0.146076	0.428017	0.74168	-0.69284	0.984988
Weighted median	10	-0.10869	0.14752	0.461238	-0.39783	0.180445
Inverse variance weighted	10	-0.13662	0.128459	0.28753	-0.3884	0.115157
Weighted mode	10	-0.13971	0.260902	0.605288	-0.65108	0.371657
Outcome: Interleukin-10 receptor subunit beta.						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	10	0.0395	0.344435	0.911525	-0.63559	0.714591
Weighted median	10	0.011946	0.133676	0.928793	-0.25006	0.27395
Inverse variance weighted	10	-0.01705	0.106517	0.872826	-0.22582	0.191723
Weighted mode	10	0.012417	0.190229	0.949385	-0.36043	0.385265

Table D11. Causal effect estimates, standard errors and 95% confidence intervals of the Mendelian randomization (MR) analyses investigating the causal effects of common variant genetic liability to schizophrenia on levels of plasma cytokines.

Outcome: Interferon gamma						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.3	0.13	0.03	0.04	0.56
Weighted median	242	0.06	0.04	0.16	-0.02	0.14
Inverse variance weighted	242	0.04	0.03	0.27	-0.03	0.1
Weighted mode	242	0.12	0.12	0.31	-0.11	0.35
Outcome: Interferon gamma receptor						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.09	0.12	0.45	-0.14	0.33
Weighted median	242	0.02	0.05	0.67	-0.07	0.11
Inverse variance weighted	242	-0.02	0.03	0.55	-0.08	0.04
Weighted mode	242	0.04	0.12	0.74	-0.2	0.28
Outcome: Interferon gamma receptor 2						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.18	0.12	0.16	-0.07	0.42
Weighted median	242	0.06	0.05	0.25	-0.04	0.15
Inverse variance weighted	242	0.05	0.03	0.13	-0.01	0.11
Weighted mode	242	0.02	0.13	0.85	-0.22	0.27
Outcome: Interleukin 10						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.08	0.13	0.55	-0.17	0.32
Weighted median	242	0.02	0.05	0.61	-0.07	0.11
Inverse variance weighted	242	0	0.03	0.95	-0.06	0.06
Weighted mode	242	0.06	0.12	0.64	-0.19	0.3
Outcome: Interleukin 10 receptor subunit beta						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.11	0.12	0.35	-0.12	0.35
Weighted median	242	0.01	0.05	0.78	-0.08	0.1

Outcome: Interleukin 10 receptor subunit beta (continued)						
Inverse variance weighted	242	0.01	0.03	0.83	-0.05	0.07
Weighted mode	242	0	0.12	1	-0.23	0.23
Outcome: Interleukin 12						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.09	0.12	0.45	-0.14	0.33
Weighted median	242	-0.03	0.04	0.55	-0.11	0.06
Inverse variance weighted	242	-0.02	0.03	0.46	-0.08	0.04
Weighted mode	242	-0.01	0.13	0.95	-0.27	0.25
Outcome: Interleukin 23						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	-0.03	0.13	0.83	-0.27	0.22
Weighted median	242	-0.03	0.04	0.45	-0.12	0.05
Inverse variance weighted	242	-0.01	0.03	0.74	-0.07	0.05
Weighted mode	242	-0.15	0.14	0.31	-0.43	0.14
Outcome: Interleukin 12 receptor subunit beta 1						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.04	0.12	0.75	-0.2	0.28
Weighted median	242	-0.03	0.04	0.57	-0.11	0.06
Inverse variance weighted	242	0.01	0.03	0.64	-0.05	0.08
Weighted mode	242	-0.06	0.11	0.57	-0.29	0.16
Outcome: Interleukin 12 receptor subunit beta 2						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	-0.13	0.12	0.27	-0.37	0.1
Weighted median	242	-0.04	0.05	0.36	-0.13	0.05
Inverse variance weighted	242	-0.02	0.03	0.56	-0.08	0.04
Weighted mode	242	-0.21	0.13	0.12	-0.47	0.05
Outcome: Interleukin 13						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.09	0.13	0.48	-0.16	0.34
Weighted median	242	0.06	0.05	0.17	-0.03	0.15
Inverse variance weighted	242	0.01	0.03	0.75	-0.05	0.07
Weighted mode	242	0.16	0.13	0.21	-0.09	0.41
Outcome: Interleukin 13 receptor subunit alpha						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	-0.08	0.12	0.54	-0.32	0.17
Weighted median	242	0.04	0.05	0.37	-0.05	0.13
Inverse variance weighted	242	0.05	0.03	0.14	-0.01	0.11
Weighted mode	242	0.04	0.12	0.75	-0.19	0.26
Outcome: Interleukin 17A						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	-0.01	0.12	0.91	-0.25	0.22
Weighted median	242	0	0.04	0.92	-0.08	0.09
Inverse variance weighted	242	0	0.03	0.94	-0.06	0.06
Weighted mode	242	-0.03	0.14	0.8	-0.3	0.23
Outcome: Interleukin 17F						

method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	-0.05	0.12	0.65	-0.29	0.18
Weighted median	242	-0.01	0.05	0.87	-0.1	0.08
Inverse variance weighted	242	0.02	0.03	0.46	-0.04	0.08
Weighted mode	242	-0.05	0.11	0.68	-0.26	0.17
Outcome: Interleukin 17 receptor A						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.13	0.12	0.31	-0.12	0.37
Weighted median	242	0.05	0.05	0.26	-0.04	0.14
Inverse variance weighted	242	0.01	0.03	0.86	-0.06	0.07
Weighted mode	242	0.15	0.14	0.27	-0.12	0.42
Outcome: Interleukin 21						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.21	0.13	0.11	-0.05	0.48
Weighted median	242	0.04	0.05	0.41	-0.05	0.13
Inverse variance weighted	242	0.08	0.03	0.01	0.02	0.15
Weighted mode	242	-0.05	0.15	0.76	-0.34	0.25
Outcome: Interleukin 22						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.17	0.12	0.16	-0.07	0.4
Weighted median	242	0.02	0.04	0.63	-0.06	0.11
Inverse variance weighted	242	0.02	0.03	0.58	-0.04	0.08
Weighted mode	242	0.06	0.11	0.56	-0.15	0.28
Outcome: Interleukin 22 receptor subunit alpha						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	-0.16	0.13	0.2	-0.41	0.08
Weighted median	242	-0.07	0.05	0.15	-0.15	0.02
Inverse variance weighted	242	-0.01	0.03	0.82	-0.07	0.05
Weighted mode	242	-0.14	0.12	0.25	-0.37	0.09
Outcome: Interleukin 22 receptor subunit alpha 2						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	-0.02	0.13	0.85	-0.27	0.23
Weighted median	242	-0.05	0.05	0.28	-0.14	0.04
Inverse variance weighted	242	0.02	0.03	0.55	-0.04	0.08
Weighted mode	242	-0.15	0.13	0.26	-0.41	0.11
Outcome: Interleukin 2						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.17	0.12	0.17	-0.07	0.4
Weighted median	242	0.01	0.05	0.81	-0.08	0.1
Inverse variance weighted	242	0.03	0.03	0.29	-0.03	0.09
Weighted mode	242	0	0.13	0.98	-0.27	0.26
Outcome: Interleukin 23 receptor						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	-0.16	0.13	0.22	-0.42	0.1
Weighted median	242	-0.02	0.05	0.65	-0.11	0.07
Inverse variance weighted	242	-0.02	0.03	0.52	-0.09	0.04

Outcome: Interleukin 23 receptor (continued)						
Weighted mode	242	0.01	0.14	0.93	-0.26	0.28
Outcome: Interleukin 4 receptor						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.01	0.13	0.94	-0.25	0.27
Weighted median	242	0.03	0.05	0.55	-0.06	0.12
Inverse variance weighted	242	0.02	0.03	0.55	-0.05	0.08
Weighted mode	242	0.01	0.13	0.94	-0.25	0.27
Outcome: Interleukin 5						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.04	0.12	0.72	-0.19	0.28
Weighted median	242	0.02	0.04	0.65	-0.07	0.11
Inverse variance weighted	242	-0.03	0.03	0.4	-0.08	0.03
Weighted mode	242	0.16	0.15	0.28	-0.13	0.45
Outcome: Interleukin 5 receptor subunit alpha						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.28	0.12	0.02	0.04	0.51
Weighted median	242	0.07	0.04	0.12	-0.02	0.15
Inverse variance weighted	242	0.01	0.03	0.72	-0.05	0.07
Weighted mode	242	0.19	0.14	0.18	-0.09	0.46
Outcome: Interleukin 6 receptor subunit alpha						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.1	0.12	0.39	-0.13	0.34
Weighted median	242	0.04	0.04	0.38	-0.05	0.13
Inverse variance weighted	242	0.03	0.03	0.29	-0.03	0.09
Weighted mode	242	0.03	0.15	0.83	-0.27	0.34
Outcome: Interleukin 9						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0.13	0.12	0.29	-0.11	0.37
Weighted median	242	0.04	0.04	0.36	-0.05	0.13
Inverse variance weighted	242	0.05	0.03	0.1	-0.01	0.11
Weighted mode	242	-0.08	0.13	0.57	-0.34	0.19
Outcome: Transforming growth factor beta-1						
method	NSNP	B	SE	P	LCI	UCI
MR Egger	242	0	0.12	0.98	-0.24	0.24
Weighted median	242	-0.02	0.04	0.68	-0.1	0.07
Inverse variance weighted	242	0	0.03	0.95	-0.06	0.06
Weighted mode	242	-0.05	0.12	0.64	-0.28	0.17

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