Cardiovascular disease risk across psychosocial and genetic factors in severe mental disorders

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2 LIST OF STUDIES

Study I

Cardiovascular risk remains high in schizophrenia with modest improvements in bipolar disorder during past decade

Linn Rødevand L, Nils Eiel Steen, Torbjørn Elvsåshagen T, Daniel S. Quintana, Elina J. Reponen, Ragni H. Mørch, Synve H. Lunding, Trude S. J. Vedal, Ingrid Dieset, Ingrid Melle, Trine V. Lagerberg, Ole A. Andreassen

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Study II

Polygenic overlap and shared genetic loci between loneliness, severe mental disorders and cardiovascular disease risk factors suggest shared molecular mechanisms

Linn Rødevand, Shahram Bahrami, Oleksandr Frei, Aihua Lin, Osman Gani , Alexey Shadrin, Olav B. Smeland, Kevin S. O'Connell, Torbjørn Elvsåshagen, Adriano Winterton, Daniel S. Quintana, Guy F. L. Hindley, Maren C. F. Werner, Srdjan Djurovic, Anders M. Dale, Trine V. Lagerberg, Nils Eiel Steen, Ole A. Andreassen

Translational Psychiatry (2021); 11(1): 3.

Study III

Extensive bidirectional genetic overlap between bipolar disorder and cardiovascular disease phenotypes

Linn Rødevand, Shahram Bahrami, Oleksandr Frei, Yunhan Chu, Alexey Shadrin, Kevin S. O'Connell, Olav B. Smeland, Torbjørn Elvsåshagen, Guy F. L. Hindley, Srdjan Djurovic, Anders M. Dale, Trine V. Lagerberg, Nils Eiel Steen, Ole A. Andreassen

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The paper study was published before the defence in Translational Psychiatry (2021) July 23; 11(1):407.

3 ABBREVIATIONS

BD	Bipolar disorder
BMI	Body mass index
CAD	Coronary artery disease
CVD	Cardiovascular disease
CondFDR	Conditional false discovery rate
ConjFDR	Conjunctional false discovery rate
DBP	Diastolic blood pressure
DSM	Diagnostic and Statistical Manual
FPG	Fasting plasma glucose
GAF	Global Assessment of Functioning
GWAS	Genome-wide association study
HDL-C	High-density lipoprotein cholesterol
ICD	International Classification of Disease
IDS	Inventory of Depressive Symptoms
LD	Linkage disequilibrium
LDL-C	Low-density lipoprotein cholesterol
MD	Major depression
MDD	Major depressive disorder
MiXeR	Bivariate causal mixture model
PANSS	Positive and Negative Syndrome Scale
PGRS	Polygenic risk score
SBP	Systolic blood pressure
SCID-1	Structured Clinical Interview for DSM-IV Axis 1 Disorders
SMD	Severe mental disorder
SNP	Single-nucleotide polymorphism
SCZ	Schizophrenia and other psychotic disorders
TC	Total cholesterol
TGs	Triglycerides
TOP	Thematically Organized Psychosis Research
T2D	Type 2 diabetes
YMRS	Young Mania Rating Scale

4 SUMMARY

Background

Patients with severe mental disorders (SMDs), including schizophrenia, bipolar disorder and major depressive disorder, have 15-20 years shorter life expectancy than the general population, largely due to comorbid cardiovascular disease (CVD). While the CVD risk has decreased in the general population during the past decade, it is unknown whether CVD risk levels have changed in patients with SMDs. Further, lifestyle factors and adverse effects of medication are important contributors to the CVD comorbidity; still, the mechanisms underlying the high CVD risk in SMDs are poorly understood. Recently, evidence has merged indicating that loneliness and a genetic susceptibility to CVD may play a role in the comorbidity, although this remains to be further elucidated.

Aims and methods

The overall aim of the thesis was to increase the understanding of the high CVD risk in SMDs. In study I we investigated whether CVD risk levels have changed during the past decade by comparing two well-characterized patient samples from the same catchment area in Norway, including patients with schizophrenia and bipolar disorder, recruited from 2002 to 2005 (2005 sample) with patients recruited from 2006 to 2017 (2017 sample). The CVD risk levels in the 2005 sample were previously published and used for comparison with the 2017 sample. The 2017 sample was also compared with healthy controls and the general population from the same area and time period. Patients and healthy controls were part of the Thematically Organized Psychosis (TOP) study. Further, to improve the understanding of mechanisms underlying the CVD comorbidity, we examined whether the genetic architectures of loneliness, SMDs and CVD phenotypes are overlapping in study II. In addition, we investigated shared genetic architecture between bipolar disorder and CVD phenotypes in study III. In both study II and III we analysed large international genome-wide association studies (GWASs) of the phenotypes of interest using bivariate causal mixture model (MiXeR), which estimates the *overall* amount of shared genetic variants, and conditional/conjunctional false discovery rate (cond/conjFDR), which identifies overlap in *specific* loci.

Results

In study I, we found significantly higher levels of CVD risk factors in patients with schizophrenia and bipolar disorder in the 2017 sample compared to healthy controls and the general population. There was no significant difference in CVD risk levels in schizophrenia between the 2005 and 2017 samples, except from a slightly higher level of glucose in the 2017 sample. Patients with bipolar disorder in the 2017 sample demonstrated small to moderate reductions in total cholesterol, low-density lipoprotein cholesterol, blood pressure and obesity compared to the 2005 sample. In study II, we discovered that loneliness shares considerable genetic architecture with SMDs and body mass index using MiXeR. We also detected specific shared genetic loci at conjFDR<0.05, including 149 loci jointly associated with loneliness and SMDs (major depression, n=68 loci; schizophrenia, n=54 loci and bipolar disorder, n=28 loci), and 55 distinct loci jointly associated with loneliness and CVD phenotypes. The majority of the shared loci possessed consistent allelic effect directions, in line with positive genetic correlations. Functional analysis of the shared loci implicated genes involved in brain functions, metabolic mechanisms, immune system and chromatin. In study III, we discovered polygenic overlap between bipolar disorder and CVD phenotypes using MiXeR. At conjFDR<0.05, we identified 129 distinct loci shared between bipolar disorder and CVD phenotypes, mainly body mass index and blood pressure. There was a pattern of mixed effect directions among the shared loci (ca. 50% with consistent direction of allelic effect), in line with the insignificant genetic correlations. Functional analysis of the overlapping loci revealed genes associated with neurodevelopment, lipid metabolism, chromatin and intracellular mechanisms.

Interpretation and implications

The thesis provides new insights into the CVD comorbidity in SMDs. The results of study I suggests that CVD risk levels have remained high in patients with schizophrenia and bipolar disorder during the past decade, with only modest reductions in CVD risk factors in bipolar disorder. These findings indicate that most patients with schizophrenia and bipolar disorder have not benefited from advances in medicine and health promotion efforts, underscoring the need for improved prevention strategies. Study II indicates substantial genetic overlap between loneliness, SMDs and CVD phenotypes. The findings have important clinical implications indicating that a genetic susceptibility for loneliness may also confer increased risk of SMDs and CVD. The increased genetic risk of loneliness in SMDs may explain some of their increased CVD morbidity, although this requires further investigations. Moreover, the discovery of shared loci between bipolar disorder and CVD phenotypes with mixed effect directions (study

III) indicates variation in genetic susceptibility to CVD across bipolar disorder subgroups. Overall, the current findings underline the need for improving prevention strategies, including more targeted lifestyle interventions and personalized pharmacological treatment, to decrease CVD risk in SMDs. Moreover, the findings from the thesis underscore the importance of an integrated approach to individuals with SMDs focusing on the metabolic monitoring and improved social contact. Future research is needed to further elucidate the genetic and environmental factors underlying CVD comorbidity and SMDs. This can provide clinically relevant discoveries for the improvement of risk prediction tools and ultimately enable earlier interventions.

Sammendrag (norsk)

Bakgrunn

Pasienter med alvorlige psykiske lidelser, inkludert schizofreni, bipolar lidelse og alvorlig depressiv lidelse, har 15-20 år kortere forventet levetid enn den generelle befolkningen, særlig på grunn av hjerte- og karsykdom. Risikoen for hjerte- og karsykdom har avtatt i den generelle befolkningen i løpet av det siste tiåret, men det er ukjent om en tilsvarende positiv utvikling har funnet sted hos personer med alvorlige psykiske lidelser. Usunn livsstil og bivirkninger av medisiner bidrar til hjerte- og karsykdom, men forståelsen av årsakene til den høyere risikoen ved alvorlig psykisk lidelse er mangelfull. Nyere studier tyder på at også genetisk sårbarhet for hjerte- og karsykdom og ensomhet kan være av betydning, men dette gjenstår å undersøkes.

Mål og metoder

Målet med denne avhandlingen er å øke forståelsen av den høye risikoen for hjerte- og karsykdom hos personer med alvorlige psykiske lidelser. I studie I undersøkte vi om nivået på risikofaktorer for hjerte- og karsykdom har endret seg det siste tiåret ved å sammenligne to pasientgrupper fra samme geografiske område i Norge, inkludert pasienter med schizofreni og bipolar lidelse, rekruttert fra 2002 til 2005 (2005-utvalget) med pasienter rekruttert fra 2006 til 2017 (2017-utvalget). Risikofaktorer for hjerte- og karsykdom i 2005-utvalget er publisert tidligere og ble brukt for sammenligning med 2017-utvalget. Utvalget fra 2017 ble også sammenlignet med friske kontroller og den generelle befolkningen fra samme område og tidsperiode. Pasienter og friske kontroller var del av 'Thematically Organized Psychosis' (TOP)-studien. For å øke forståelsen av mekanismer som bidrar til den høye risikoen for hjerte- og karsykdom, undersøkte vi om ensomhet, alvorlige psykiske lidelser og hjerte- og karsykdom har felles genetisk grunnlag i studie II. I tillegg undersøkte vi om bipolar lidelse og hjerte- og karsykdom deler genetisk grunnlag i studie III. I både studie II og III analyserte vi helgenom-assosiasjonsstudier med 'bivariate causal mixture model' (MiXeR), som estimerer det *totale antallet* felles genvarianter og 'conditional/conjunctional false discovery rate' (cond/conjFDR), som identifiserer *spesifikke* felles genetiske loci.

Resultater

I studie I fant vi høyere nivåer av risikofaktorer for hjerte- og karsykdom hos pasienter med schizofreni og bipolar lidelse i 2017-utvalget sammenlignet med friske kontroller og

befolkningen generelt. Det var ingen forskjell i risikofaktorer for hjerte- og karsykdom hos personer med schizofreni mellom 2005 og 2017-utvalgene, bortsett fra et litt høyere nivå av glukose i 2017-utvalget. Pasienter med bipolar lidelse i 2017-utvalget viste lavere nivåer av total kolesterol, lav-densitet-lipoproteiner, blodtrykk og fedme sammenlignet med 2005-utvalget; forskjellene var små til moderate. I studie II fant vi at ensomhet i stor grad deler genetisk grunnlag med alvorlige psykiske lidelser og kroppsmasseindeks ved bruk av MiXeR. Vi fant også spesifikke felles genetiske loci ved conjFDR <0.05, inkludert 149 loci assosiert med både ensomhet og alvorlige psykiske lidelser (alvorlig depresjon, n=68 loci; schizofreni, n=54 loci og bipolar lidelse, n=28 loci), og 55 loci assosiert med både ensomhet og risikofaktorer for hjerte- og karsykdom. De fleste overlappende loci hadde samme effektretning, i samsvar med positive genetiske korrelasjoner. Funksjonsanalyser knyttet de overlappende loci til gener involvert i hjernefunksjoner, metabolske mekanismer, immunforsvar og kromatin. I studie III fant vi betydelig genetisk overlapp mellom bipolar lidelse og risikofaktorer for hjerte- og karsykdom og koronar hjertesykdom ved bruk av MiXeR. Ved conjFDR <0.05, identifiserte vi 129 genetiske loci som var assosiert med både bipolar lidelse og hjerte- og karsykdom. Effektretningen til de overlappende loci var blandet (ca. 50% med samme effektretning i bipolar lidelse og hjerte- og karsykdom), i tråd med ikke-signifikante genetisk korrelasjoner. Funksjonsanalyser koblet de overlappende loci til gener knyttet til hjerneutvikling, lipidmetabolisme, kromatin og intracellulære mekanismer.

Tolkning og implikasjoner

Funnene i denne avhandlingen gir ny kunnskap om hjerte- og karsykdom hos personer med alvorlige psykiske lidelser. Resultatene i studie I tyder på at risikoen for hjerte- og karsykdom har holdt seg stabilt høy hos pasienter med schizofreni og bipolar lidelse i løpet av det siste tiåret, selv om risikonivået var noe lavere ved bipolar lidelse i 2017-utvalget sammenlignet med 2005-utvalget. Funnene indikerer at de fleste personer med schizofreni og bipolar lidelse ikke har dratt nytte av nylige fremskritt innen medisin og helsefremmende tiltak som reduserer risikoen for hjerte- og karsykdom. Studie II tyder på betydelig genetisk overlapp mellom ensomhet, alvorlige psykiske lidelser og risikofaktorer for hjerte- og karsykdom. Resultatene indikerer at genetisk sårbarhet for ensomhet også innebærer økt genetisk risiko for alvorlige psykiske lidelser og hjerte- og karsykdom. Genetisk sårbarhet for ensomhet hos personer med alvorlige psykiske lidelser kan bidra til å forklare deler av deres høye risiko for hjerte- og karsykdom, men dette må undersøkes videre. Studie III avdekket genvarianter felles for bipolar

lidelse og hjerte- og karsykdom med blandede effektretninger, noe som indikerer variasjon i genetisk risiko for hjerte- og karsykdom på tvers av undergrupper av bipolar lidelse. Samlet sett understreker resultatene behovet for mer effektiv forebygging av hjerte- og karsykdom ved alvorlige psykiske lidelser, inkludert mer målrettede livsstilsintervensjoner og persontilpasset legemiddelbehandling. Funnene fra avhandlingen belyser også viktigheten av en integrert tilnærming til personer med alvorlige psykiske lidelser med fokus på metabolske målinger og hjelp til å oppnå god sosial kontakt. Mer forskning er nødvendig for å avdekke genetiske og miljømessige faktorer som bidrar til hjerte- og karsykdom ved alvorlige psykiske lidelser. Slik forskning kan gi kliniske relevante funn som legger til rette for bedre risikoprediksjon og tidligere intervensjon.

5 INTRODUCTION

5.1 History of defining mental illness

The distinction between the mind and body dates back to ancient Greek philosophers. Plato separated the *psyche* (soul), that he believed to be immortal, from the mortal *soma* (body) (1). Thus, he believed that the psyche could exist independently of the soma. Aristotle connected the psyche and soma closer together by asserting that the body is the soul's "instrument" and that the psyche and soma are mutually dependent (1). In the 17th century, Descartes returned to the division between the mind and body arguing that their natures are completely different and that each can exist by itself (2). This mechanistic understanding become known as the Cartesian dualism, which has influenced Western thinking and conceptions of the mind and body (2). While modern medicine and psychology reject the dualism in that the mind and body are inextricably linked and influence each other, the Cartesian dualism has had great impact on these disciplines (3). The division of human illness into mental and physical diseases can be seen as a continuation of the dichotomy. Moreover, the stigma of mental illness and separation of mental and somatic care departments reflect the traditional distinction between the mind and the body. The disintegration of mental and somatic health care has prevailed despite increasing evidence of comorbidity between mental illness and somatic disease (4). Observations of this comorbidity emerged before the introduction of modern psychotropic agents (5, 6). In 1897, Sir Henry Maudsley wrote that "Diabetes is a disease which often shows itself in families in which insanity prevails" (5). These observations raised the question of whether disturbances in glucose metabolism are intrinsic to certain mental disorders, particularly schizophrenia. Central researchers and psychiatrists in the 19th century, including Emil Kraepelin and Eugen Bleuler, discussed whether alteration in energy metabolism was part of the disease mechanisms in schizophrenia (7, 8), thereby challenging the sharp mind-body split. The aetiology of the comorbidity has remained a puzzle since, and it has proven difficult to disentangle the effects of pharmacological medication from the disease itself (9, 10).

Kraepelin and Bleuler are, however, first and foremost known for their contribution to psychiatric nosology. In the late 19th century, Kraepelin introduced a classification of mental disorders that formed the basis for current diagnostic classifications (11, 12). He distinguished between two main groups of mental disorders, including "dementia praecox" and "manic depressive disorder" (12). The term dementia praecox, meaning "early dementia", was initially used to refer to a deteriorating psychotic illness with early debut, while manic depressive

disorder referred to an affective illness with symptom-free intervals and better prognosis (12). Kraepelin's concept of manic-depressive disorder was broad and incorporated all types of affective disorder, including what is today known as bipolar disorder and major depressive disorder (13). In 1908, Bleuler introduced the term "schizophrenia" derived from the Greek words *skhizein* and *phren*, meaning *splitting* and *mind* respectively (14). He asserted that "schizophrenia" should replace the term "dementia praecox" because the latter was considered misleading as the onset and course of the illness vary, and do not necessarily end in deterioration, a perspective that received support from later research (15). Bleuer used the term schizophrenia to describe a disorder involving "splitting" or disintegration of psychological functions, which may give rise to disturbed thought associations, ambivalence, flattened affect and autism. These four symptoms are today known as Bleulers "four As" and bear resemblance to negative symptoms of schizophrenia described in current diagnostic manuals (16). Positive symptoms, including delusions and hallucinations, were considered secondary symptoms by Bleuler, yet were classified as primary or "first-rank symptoms" by others in the mid-20th century (17). In the same period, Kraepelin's broad category of manic depressive disorder were divided into unipolar depression defined by depressive episodes only, and bipolar disorder defined by altering episodes of mania or hypomania and depression (18).

This classification of schizophrenia and affective disorders as distinct disorders is maintained in today's diagnostic systems (19-22). However, increasing evidence suggests clinical, biological and genetic overlap between the disorders (23-25), bringing into question the traditional dichotomy. This evidence may suggest that the disorders should not be perceived as distinct categorical entities, but rather as disorders along a continuum (26). Thus, a dimensional approach has been proposed, where patients are characterized based on their most prominent symptoms (26). Nevertheless, Kraepelin's categorizations formed the basis for modern diagnostic criteria for schizophrenia and affective disorders, which have brought reproducibility to psychiatric research and improved reliability of diagnoses (23). However, the validity of the diagnostic categories remains under debate.

5.2 Severe mental disorders

Schizophrenia, bipolar disorder and major depressive disorder are considered severe mental disorders (SMDs) due to their chronicity/long duration, comorbidity and substantial disability (27). Thus, the term 'SMDs' is used in this thesis when referring to the three disorders. SMDs are among the most costly diseases worldwide; they are leading causes of years lived with

disability and pose a major financial burden on health care systems (28, 29). SMDs are associated with considerable suffering and reduced quality of life for those affected and their families (30, 31). Approximately 30% of individuals with SMDs experience no or limited benefit from pharmacotherapy, and discontinuation of treatment due to adverse side-effects is relatively common (32, 33). In addition, all-cause mortality is increased and the life expectancy is decreased by 15-20 years in people with SMDs compared to the general population (4, 34-37). The relative risk for suicide is increased by 12-20 times (38-40), but mortality from natural causes, particularly cardiovascular disease (CVD), is the main contributor to reduced life span in SMDs (34, 37). Comorbid CVD is associated with poorer quality of life and more severe illness course (41), highlighting the need for better prevention and management of CVD in SMDs. Increased understanding of the mechanisms underlying CVD comorbidity is crucial for the development of more effecting prevention strategies and treatments.

5.2.1 Diagnostic criteria

Today, mental disorders are classified using the World Health Organization's International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM). DSM is developed by the American Psychiatric Association (APA) and is widely used by clinicians in the United States, while ICD is mainly used by clinicians in the rest of the world (42). Both diagnostic systems are used for research purposes, especially DSM. ICD and DSM have been published in several updated versions with the latest version of ICD-11 in 2019 (22) and the latest version of DSM-5 in 2013 (20). There is considerable convergence between the two systems' criteria of schizophrenia, bipolar disorder and major depressive disorder, listing nearly identical symptoms and exclusion criteria (symptoms cannot be attributed to a substance or medical condition). Still, some differences exist in the way affective disorders are divided, the terms used to describe the disorders and specific criteria.

DSM-IV (19) was used for diagnostic classification in the TOP study which formed the basis of paper I. DSM-IV was also used in the genomewide association studies (GWASs) that formed the basis of paper II and III. Therefore, the diagnostic definitions in DSM-IV are outlined below. In addition, as some of the patients in the GWASs used for paper II and III were diagnosed with ICD-9/10 (21, 43), the most important differences between the diagnostic criteria of DSM and ICD are described. Since only a few patients were diagnosed with ICD-9 and there are minor changes in the diagnostic criteria of SMDs from ICD-9 to ICD-10, I focus on specifying relevant differences between ICD-10 and DSM-IV.

Schizophrenia and other psychotic disorders

Schizophrenia and other psychotic disorders (SCZ) include schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder not otherwise specified (NOS), delusional disorder and brief psychotic disorder in DSM-IV (19).

The DSM-IV criteria of a schizophrenia diagnosis are categorized in five main groups, including delusions (e.g., paranoid, grandiose), hallucinations (e.g., auditive, visual), disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behaviour, and negative symptoms (i.e., affective flattening, alogia/poverty of speech, or avolition/diminished motivation to initiate or perform purposeful actions) (19). Together, these symptoms constitute criterion A for schizophrenia. Delusions refer to false beliefs that are firmly maintained despite evidence to the contrary and despite what almost everyone else believes (19). A hallucination refers to a sensory perception without external stimulation of the relevant sensory organ (19). Negative symptoms involve the absence or reduction of normal mental functions, such as emotional expression, speech and motivation (19). Patients experiencing two or more of the symptoms in the five main groups (listed above) for at least one month, with signs of the disorder for minimum 6 months and negative impact on functioning (i.e., social, occupational or personal), meet the criteria for *schizophrenia*. The symptoms and functional loss are not due to a substance or medical condition; this exclusion criterion applies to schizophrenia and all the other diagnoses described here. When the symptoms last for less than 6 months, the diagnosis is *schizophreniform disorder*. Patients experiencing the symptoms for less than one month are diagnosed with *brief psychotic disorder*. *Delusional disorder* should be considered in the case of non-bizzare delusions (i.e., involving situations that can occur in real life, such as being followed) of at least one month's duration with little impact on functioning, and criterion A has never been met. However, tactile or olfactory hallucinations may be present in delusional disorder if they are related to the delusional theme (19).

Patients who experience a combination of the psychotic symptoms listed above and affective symptoms (classified as either major depressive episode, manic episode or mixed episode), may be given a diagnosis of *schizoaffective disorder* (19). Here, during the same period of illness, delusions or hallucinations persist at least 2 weeks in the absence of prominent affective symptoms. The affective symptoms must be present for a substantial portion of the total duration of the active and residual periods of the illness. If the disturbance includes a manic

or a mixed episode, the diagnosis is *schizoaffective disorder bipolar type* (19). Note that this diagnosis was included as a subtype of bipolar disorder in the GWAS of bipolar disorder used for study II and III. *Psychotic disorder NOS* is applied to describe psychotic syndromes that do not meet the criteria of any of the specific psychotic disorders, or to psychotic symptomology where there is inadequate or contradictory information on which to base a specific diagnosis (19).

There is general agreement between the DSM-IV and ICD-10 criteria of schizophrenia and related disorders (19, 44). However, the duration criteria differ: while DSM-IV requires continuous disturbance for at least 6 months, ICD-10 requires at least 1 month with symptoms. Another difference pertains to the DSM-IV's emphasis on functional impairment, while ICD-10 highlights the importance of first-rank symptoms (thought broadcast, thought insertion, thought withdrawal, auditory hallucinations and delusional perception). Further, the DSM-IV diagnosis of schizophreniform disorder does not appear in ICD-10, but largely corresponds to schizophrenia lasting for less than 6 months in ICD-10.

Bipolar spectrum disorders

The DSM-IV classifies bipolar disorders (BD) as a group of affective disorders which are characterized by depressive, manic or hypomanic episodes (19). These disorders include BD type I, BD type II, cyclothymic disorder and BD NOS.

BD type I is characterized by the occurrences of at least one manic or mixed episode (i.e., the co-occurrence of manic and depressive symptoms). A manic episode is defined by the presence of persistently elevated and/or irritable mood, along with three or more of the following symptoms (four if the mood is only irritable): inflated self-esteem, decreased need for sleep, increased talking, racing thoughts, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in pleasurable activities with a high risk of negative consequences. *BD type II is* characterized by at least one hypomanic episode and at least one depressive episode. A hypomanic episode includes the same symptoms as those of mania, but the duration and severity of the symptoms differ. DSM-IV sets four days as a minimum duration of the elevated and or/irritable mood as part of a hypomanic episode, while a manic episode lasts for at least one week or shorter if hospitalized and is associated with marked impairment, indicating that a manic episode is more severe. A further distinction between manic and hypomanic episode is that psychotic symptoms can be present during a manic episode (19).

A major depressive episode is mainly characterized by depressed mood and/or loss of interest and pleasure. In addition to these core symptoms, at least three (four if only depressed mood or loss of interest is present) of the following symptoms must be present; significant weight change or appetite disturbance, sleep disturbance (insomnia or hypersomnia), fatigue, psychomotor agitation or retardation, feeling of worthlessness or excessive guilt, diminished ability to concentrate/indecisiveness, and recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide. The symptoms are experienced most of the day, nearly daily, for at least two weeks. The symptoms must be severe enough to cause significant functional impairment (19). Psychotic symptoms may occur in a depressive episode (19).

Cyclothymic disorder involves several periods of hypomanic symptoms and periods of depressive symptoms that are not sufficient to meet the full criteria for a major depressive episode, over a period of at least 2 years. Disorders with bipolar features that do not meet criteria for any of the above BD subtypes are classified as *BD NOS*. This category may cover people who have symptoms of mania or hypomania that are too few in number or too short in duration to meet criteria of a manic or hypomanic episode (19).

The diagnostic criteria of BD in ICD-10 bear close resemblance to those in DSM-IV (19, 44). However, ICD-10 requires two discrete affective episodes, one of which must be manic or hypomanic, for a BD diagnosis. In DSM-IV, one manic or mixed episode suffice for a diagnosis of BD I. Further, both diagnostic systems distinguish between BD type I and BD type II, but BD type II is sorted under “other bipolar disorders” in ICD-10 (44).

Major depressive disorder

Major depressive disorder (MDD) is characterized by the presence of at least one major depressive episode with or without psychotic symptoms (delusions or hallucinations) in DSM-IV (19). The ICD-10 system does not use the term ‘MDD’, but uses the term ‘Recurrent depressive disorder’ and divides depressive episodes into mild, moderate and severe types (44). A moderate or severe depressive episode in ICD-10 corresponds mostly to a major depressive episode in DSM-IV. The symptoms of a depressive episode are virtually identical with only one symptom (loss of confidence or self-esteem) included in ICD-10 but not in DSM-IV. In addition, DSM-IV, but not ICD-10, specifies that the symptoms should not be explained by bereavement.

For paper II, we used a GWAS of "major depression" (MD), which includes participants meeting diagnostic criteria of MDD (DSM-IV, ICD-10) and participants with self-reported MDD diagnosis, symptoms or treatment for depression (45). Thus, the term MD is used in this thesis when discussing the results of paper II, the MD GWAS and other studies using this MD GWS sample.

5.2.2 Epidemiology

Below, central findings in epidemiological studies of SMDs are presented, with focus on lifetime risk, prevalence and yearly incidence. The *lifetime prevalence* refers to the proportion of a population that has had the disorder up to the age at assessment (46). The *lifetime risk* is the estimated proportion of a population that is expected to develop the disorder during the lifespan (46). The lifetime prevalence differs from lifetime risk in that the latter does not only refers to the proportion that has so far experienced the disorder at the time of the study, but also includes the proportion of the population that is *expected* to develop the disorder at some time in the future (based on projection from a model) (47). Lifetime risk further differs from lifetime prevalence as it attempts to include the entire lifetime of a birth cohort (both past and future), and includes those deceased at the time of the study (46). The *incidence* is a measure of the number of new cases of a disorder within a specific time period, with annual incidence referring to new cases by a year (46).

Schizophrenia occurs worldwide, and it has long been assumed to have a uniform distribution with a 1% lifetime risk across regional boundaries and sex (39). This assumption of uniform risk was challenged by meta-analyses from McGrath and colleagues that demonstrated variation across studies that could not be merely explained by differences in diagnostic definitions or methods, but rather indicated true variation in occurrence (48, 49). The median lifetime risk of schizophrenia is ~0.7% in the meta-analyses (48, 49). The lifetime prevalence of schizophrenia is estimated to be 0.4-1% (48, 50). When including other psychotic disorders (such as brief psychotic disorder, delusional disorder and psychotic disorder NOS), the lifetime estimates are 2-3 times higher (39). The yearly incidence is roughly 15 in men and 10 in women per 100 000 persons (48). Both the incidence and prevalence of schizophrenia vary across nations and are higher in urban areas compared to rural settings and among immigrants compared to native-born individuals (48, 51). Age of onset of schizophrenia is usually between late adolescence and early adulthood, with earlier debut in men than in women (39, 51). Later illness onset in women may indicate a protective effect of estrogen (51).

The estimated lifetime prevalence of BD is commonly reported to be ~1-2% in the world's population (38, 50). In a large international study, the lifetime prevalence of BD type I was 0.6%, BD type II 0.4%, and subthreshold BD (comparable with BD NOS) 1.4%, yielding a total lifetime prevalence estimate of 2.4% worldwide (38). However, the estimates vary across countries (38), and it is assumed that the lifetime prevalence of BD type II is greater, with estimates approaching 3-4% in prospective studies of adolescents (52). The lifetime risk for BD is somewhat higher than the lifetime prevalence (47). Further, BD type I has an annual incidence of 5-30 per 100 000 (53, 54), whereas the incidence of other BD subtypes is more uncertain (53). BD type I affects men and women equally, while BD type II is more common in women (55). Similar to SCZ, BD type I appears to be more prevalent in urban than in rural environments (53). BD typically debuts in adolescence or early adulthood (38, 53).

The lifetime prevalence of MDD also varies considerably across nations and is roughly 15-18 % (40, 47). The lifetime risk for MDD (23-30%) is higher than the lifetime prevalence, which may reflect the fact that many MDD cases debut in the middle years of life and may therefore not be captured at the time of lifetime prevalence assessment (47). The annual incidence of MDD is estimated to be 3 per 100, yet with significant variation between countries (56). MDD is more common in women than in men (40, 47). There is no consensus as to whether MDD is more frequent in urban areas, although recent findings do point to a preponderance of MDD in urban compared to rural regions (57). Age of illness onset ranges from mid adolescence to mid-40s, with an average age of onset in mid-20s (40).

In summary, the lifetime prevalence and risk of SCZ and BD are relatively low, while MDD is more prevalent. The estimates vary across nations for reasons unknown, but the findings may reflect true cross-national variation (as suggested for schizophrenia) (48) as well as differences in diagnostic tools and methods, awareness and stigma of mental illness (38-40, 46-56). Further analyses are needed to shed light on factors underlying the variation and possible differences in exposure to risk factors.

The prevalence of SMDs appears to have remained fairly stable over time (46, 48, 58, 59). For instance, a study from the US found no significant change in the prevalence of SMDs from 1990 to 2003 (59). Similarly, global epidemiological data indicates that the prevalence of SCZ was largely consistent from 1990 to 2016 (58). Nevertheless, as the population grow and age, the absolute number of people affected by such disorders will increase (58). Some studies, however, point to an increase in MDD. For instance, a Finnish study found greater prevalence of MDD in women, but not in men, over the 2000 to 2011 period (60). However, a Norwegian

study provided no evidence of change in MDD occurrence from 1990 to 2001 (61). Still, self-reported depressive symptoms increased from 1998 to 2012 in Norway in young women (16-24 years) (62). It remains unknown whether this self-reported change reflects a rise in mental illness, such as MDD. Further, some data may suggest that BD type II is increasing, although it is unclear whether this observation represents a real change in the prevalence or a higher number of individuals receiving the correct diagnosis (63). There is a shortage of well-conducted studies of prevalence estimates further back in time.

5.2.3 Comorbid diseases and shared characteristics

The boundaries between SMDs are considered partially arbitrary (23, 26) as there is considerable clinical overlap between SCZ, BD and MDD. All three disorders are characterized by psychiatric and somatic comorbidity as well as cognitive impairments and loneliness. The overlap across SMDs warrants the investigation of all three disorders and their co-occurring conditions.

Clinical overlap and psychiatric comorbidity

SCZ, BD and MDD share clinical features. Psychotic symptoms, such as hallucinations and delusions, are prominent in SCZ (64), but also in a substantial proportion of individuals with BD and MDD. About 60 % of patients with BD (65) and 16-50% of patients with MDD experience psychotic symptoms (66, 67). Moreover, affective symptoms are the defining features of BD and MDD, but they are also common in SCZ (68). Depressive symptoms are reported in up to 80% and manic symptoms are reported in 20% of patients with SCZ (68). However, distinguishing between negative and depressive symptoms in SCZ is a challenge. For instance, affect flattening and lack of motivation may represent negative symptoms, but can also suggest depressive symptoms. Thus, the prevalence of depressive symptoms in SCZ may be overestimated and underestimated in some cases, and the difficulty in distinguishing between negative symptoms and depressive symptoms may contribute to the reported variation in frequency of depression in SCZ (20-80%) (69, 70). Furthermore, patients with SMDs frequently have other comorbid psychiatric disorders, particularly anxiety and substance use disorders (mostly alcohol, cannabis and stimulant use disorder) (71-73). SMDs are also associated with elevated risk of personality disorders (74, 75) and higher levels of the personality trait neuroticism (i.e., a tendency to experience negative emotions and shifting moods) and lower

levels of extraversion (i.e., tendency to be sociable and active and experience positive emotions) (76, 77).

Somatic comorbidity

Patients with SMDs have a 2-3 fold increased mortality rate compared to the general population (35, 36, 78, 79). Suicide contributes to the increased relative risk of mortality; however, most of the excess mortality is explained by physical illness, accounting for ca. 70% of all deaths in SMDs (35, 36, 79). CVD is the most common somatic comorbidity and cause of death, followed by respiratory diseases, infectious diseases and cancer (35, 36, 79). Still, the findings regarding cancer rates in people with SMDs are somewhat inconsistent, with some studies reporting lower or similar levels of cancer in patients compared to controls (80, 81), although risk factors for cancer (e.g., smoking and obesity) tend to be higher in this patient population (82). The conflicting results may be related to various factors that can reduce the estimates of diagnosed cancer in SMDs, such as limited access to screening and dying at an earlier age from CVD before being diagnosed with cancer (4). Further information about the CVD comorbidity is presented in a separate section below (5.3).

Cognitive impairments across SMDs

Cognitive impairment is a core feature of SCZ and is present across a wider range of neurocognitive functions, including working memory, executive functioning, processing speed and verbal and visual memory (83). These cognitive deficits are important predictors of occupational and social functioning (84). In addition, social cognitive difficulties are common, including reduced ability to understand intentions and emotions of others (85), also contributing to difficulties functioning in society (86). Patients with BD and MDD appear to have substantial, albeit on average less severe neurocognitive (83) and social cognitive difficulties than SCZ (85), and related functional impairments (87). Although cognitive deficits are prominent in SCZ, they are not included in current diagnostic criteria for SCZ (19-22), largely because cognitive impairment does not seem to sufficiently distinguish SCZ from related disorders, i.e. other SMDs that are also associated with cognitive difficulties (88). Thus, despite an ongoing debate, cognitive impairment may not constitute a useful diagnostic criterion per se (86, 89). *Subjective* cognitive difficulties (i.e., perceived reduced concentration, distractibility or difficulty making decisions) are included in the diagnostic criteria of affective episodes (see separate section about diagnostic criteria above).

Loneliness and social isolation across SMDs

People with SMDs experience difficulties in preserving meaningful relationships (90), have limited social network and restricted access to social support (90-92). Given these social deficiencies, people with SMDs may be particularly vulnerable to loneliness (93), defined as the *subjective* experience of a discrepancy between the desired and achieved level of social relationships (94). Loneliness differs from objective aspects of the social environment, such as living alone, marital status, number of friends and family, and frequency of interactions (95-99). Still, loneliness correlates with these objective measures, indicating that objective and subjective social isolation are related; however, the association is modest, suggesting that quantitative and qualitative aspects of social relationships are distinct (95-99). It is important to note that loneliness in itself is not necessarily a problem. Rather, loneliness is an universal human emotion that that most people experience at some time point during a life span (100). Loneliness signals that the social need is not being met and motivates to connect or reconnect with others (100). Thus, feelings of loneliness usually motivate individuals to seek social contact, thereby diminishing loneliness (100). However, in some individuals, loneliness is a frequent and enduring feeling, which is a cause for concern (100-102). Notably, people with SMDs score higher on measures of frequency of loneliness compared to the general population and expect to continue feeling lonely in the future, but rarely receive help for these experiences (90, 103-107). Thus, patients with SMDs are at risk for experiencing loneliness over a longer time. Longitudinal research with repeated measures of loneliness in SMDs is scarce. Nevertheless, a large national Australian study indicates that the majority (80%) of individuals with SMDs report feeling lonely during the past 12 months (90, 108, 109) (Figure 1) and rank loneliness as being a major challenge anticipated over the next 12 months (104, 107). The estimated annual rate of loneliness is approximately 2.3 times higher in adults with SMDs compared to the general population (90, 108). However, loneliness estimates in SMDs and the general population vary across studies, which may be related to differences in loneliness measurements, time frame and sample composition (90, 103, 105-108, 110-113). Despite heterogeneity in methodology, studies consistently indicate that loneliness is significantly associated with SMDs (90, 103, 105-108, 110-113). Moreover, nearly 50% of people with SMDs report a need for more friends (104, 107). There is a shortage of studies comparing the level of loneliness across SMDs, but recent findings suggest that loneliness is particularly prevalent in MDD (108). Loneliness is related to poorer quality of life, functioning and recovery

in SMDs (114-116). Loneliness is also associated with higher levels of symptoms, especially depressive symptoms, but also anxiety and psychotic symptoms (93, 113, 117-119), highlighting the clinical relevance of loneliness.

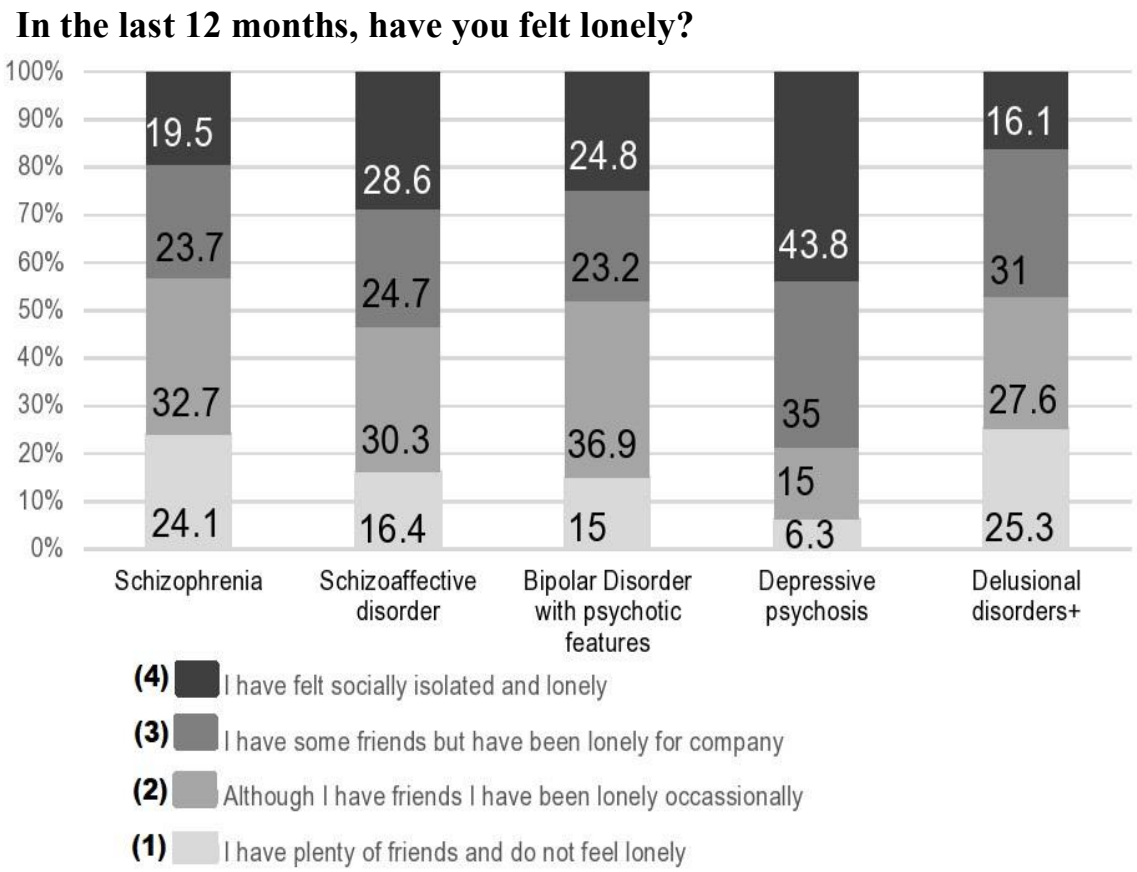

Figure 1. Distribution of responses (%) to a loneliness measure across different severe mental disorders. Individuals were classified as "lonely" if they gave a response of 2, 3 or 4 to the loneliness question, yielding a total of ca. 80% identified as feeling lonely. Original figure from Badcock et al. 2015 (108); figure adapted by Badcock & Morgan 2016 (109) (https://atlasofscience.org/loneliness-matters-for-people-with-psychotic-disorders/)

5.2.4 Etiology and disease mechanisms

Despite decades of research, the etiology of SMDs remains poorly understood. A multifactorial model is thought to best fit the current knowledge, in which a complex interplay between genetic and environmental factors interferes with brain development, especially synaptic formation and connectivity (39, 120, 121). These brain changes can lead to aberrant information processing and influence behaviour, thereby increasing the risk of SMDs (39, 120, 121). The risk factors are organized in a biopsychosocial model described below. First, a description of the human genome is provided as a basis for understanding the complex etiology of SMDs and study II and III.

Genetic risk factors

The human genome contains 3.2 billion base pairs across 23 pairs of chromosomes. The first sequencing of the human genome was published in 2001 (122), and around 21 000 protein-coding genes have been detected, each with its own position on the chromosome (i.e., locus) (123, 124). People are ca. 99.5% identical in their genetic makeup; that is what makes us human (125, 126). Thus, only ~0.5% of the genome differs across individuals, yet this variance plays an important role in making each individual unique and accounts for individual differences in human traits and disease susceptibility (127). The most common type of genetic variation (or allele) is single nucleotide polymorphism (SNP): variation in a single base pair with a frequency of >1% in a certain population (128). Most complex traits and diseases are polygenic, i.e., influenced by several SNPs, each with a small effect (129) (130). Given the relatively small number of genes and high number of human traits and diseases, some genes must influence several phenotypes, i.e., exhibit pleiotropy (130). Identifying the degree to which complex human phenotypes share a genetic basis is important to understand the etiology of phenotypic associations, which can form the basis for disease classification and progress in prevention and treatment (130, 131).

Twin and family studies have revealed that SCZ, BD and MDD are influenced by genetic factors with heritability estimates of 0.6-0.8 for SCZ and BD (132), while the heritability of MDD is approximately 0.3-0.4 (133). There is considerable genetic overlap between SCZ and BD with a genetic correlation (rg) of 0.6-0.7, and moderate genetic correlation between SCZ and MDD (rg=0.4) and BD and MDD (rg=0.5) (25). Genome-wide association studies (GWASs) have offered new insights into the aetiology of these disorders (134, 135). GWASs search the genome for genetic variations (typically SNPs) associated with

a given phenotype (e.g., SCZ) by comparing the genotype frequency in cases (patients) and controls. GWASs have revealed that the genetic architecture of SMDs is highly polygenic, influenced by numerous common genetic variants that each have a small effect (136-138). Recent large GWASs have identified several individual loci associated with SMDs (136-138), but the identified risk loci explain only a small fraction of the total heritability (136-138). Thus, a substantial proportion of the heritability remains to be discovered, referred to as the "missing heritability" (139). Further, some of the genetic variants are specific to each SMD, while a considerable proportion of the variants are shared between the disorders, especially between SCZ and BD (140-142). The identified risk loci are implicated in neurodevelopment, neuronal excitability and synaptic function (136-138), consistent with leading hypotheses of pathophysiological mechanisms (see below) (120). In addition, the risk loci have been linked to immune-related genes (136-138), providing support for the proposed link between the immune system and SMDs (see below) (143).

Environmental factors

Current models of the aetiology of SMDs propose that early life stressors and other environmental factors experienced by genetically vulnerable individuals interfere with development of the nervous system, thus increasing the risk of SMDs (39, 120, 121). In line with this hypothesis, SMDs are commonly preceded by early life events that are likely to interfere with brain development. In particular, prenatal insults (e.g., maternal stress, maternal infections and nutritional deficiency), birth complications, childhood trauma (e.g., abuse or neglect) and socioeconomic disadvantage at critical stages of development are related to increased risk of SMDs (39, 40, 120, 121). In addition, evidence points to substance use, especially of cannabis, in adolescence as a risk factor for SMDs (39, 40, 120, 121).

Further, while loneliness may be a consequence of living with a SMD, recent evidence suggests that loneliness also can occur prior to illness onset and raise the likelihood of SMDs (105, 118, 144, 145). For instance, loneliness predicts depressive symptoms and an increased tendency to experience paranoid beliefs (100, 144, 145). In addition, loneliness is found to be prevalent in the prodromal period preceding psychosis, among individuals with high risk of psychosis (146, 147) and in the first episode of psychosis (148). Limited social support, which is an important source of loneliness (149), is also associated with first episode of psychosis (91, 148, 150). To explain the mechanisms whereby loneliness can contribute to adverse health effects, Hawkley and Cacioppo (100) proposed a model where loneliness increases the

motivation to connect with others, but also elicits a hypervigilance for social threats (e.g., rejection), which can harm social interactions. This hypervigilance may introduce negative cognitive biases, including a tendency to except negative social events, interpret the social environment more negatively and remember more unpleasant social interactions (100) (151). These cognitive biases can create self-fulfilling prophecies in which lonely individuals engage in behaviours that cause more negative interactions, thereby confirming their initial beliefs and providing a sense of little personal control (100, 151). This viscous cycle can exacerbate the feeling of loneliness and, thus, put individuals at risk for continuing feeling lonely (100, 151). Hawkley and Cacioppo propose that this self-reinforcing loneliness loop is accompanied by feelings of stress, pessimism and reduced self-esteem and associated with neurobiological changes (e.g., elevated cortisol) and behaviour (e.g.. social withdrawal) that contribute to the development of mental disorders (151). Accumulating research suggests associations between loneliness and negative cognitive biases, behavioural (e.g., withdrawal) and emotional characteristics (e.g., stress, lower self-esteem), cortisol dysregulation as well as symptoms of mental disorders (e.g., depressive symptoms, anxiety and paranoia) (100, 118, 144, 145, 151). However, the causality and the etiology of these associations remain largely unknown. It is uncertain whether loneliness in itself causes these behavioural, psychological and physiological changes or vice versa. Longitudinal studies indicate that loneliness predicts depressive symptoms and paranoia (100, 152, 153) and onset of MDD after adjustment for sociodemographic factors (105, 154). Nevertheless, the relationship between loneliness and SMDs can be bidirectional (152) and influenced by common antecedents.

The co-occurrence of SMDs and loneliness may be due to environmental factors, such as limited social network and support, childhood trauma, socioeconomic challenges (e.g., unemployment) and stigma (93, 104, 106, 107, 155). In addition, the high prevalence of loneliness in SMDs may be related to genetic influence. The estimated heritability of loneliness is 40-50% (156), and recent work indicates that some of the same genetic factors influencing loneliness may also affect the risk for SMDs, particularly MDD (157, 158). A large GWAS (n=452 302) identified a positive genetic correlation between loneliness and MDD (rg=0.61) (157), similar to another study (158). This GWAS also observed significant genetic correlation between loneliness and SCZ (rg=0.17), but not with BD (157). However, the absent genetic association with BD does not necessarily imply lack of genetic overlap since a significant genetic correlation relies on consistent effect direction of the shared genetic variants (159). The lack of genetic correlation may reflect mixed effect directions of the overlapping variants (159),

which requires further investigation with appropriate methods (see section 5.4). Further studies are needed to elucidate the role of loneliness in the development of SMDs and the mechanisms underlying this relationship.

Pathophysiological mechanisms

The pathophysiology of SMDs remains unclear and several theories has been proposed to explain possible underlying mechanisms (39, 120, 121). Together, the theories point to a complex multifactorial origin involving disruption of different neurobiological systems and mechanisms (39, 120, 121). In particular, early life adversity can lead to enduring effects on brain and stress regulatory systems, including the hypothalamic pituitary adrenal (HPA) axis, that render the individual more vulnerable to stress experienced later in life (160). The HPA axis is a neuroendocrine system responsible for a cascade of hormonal events that begins in the brain and ends with release of glucocorticoids, such as cortisol, in response to stress. Increased cortisol mobilizes glucose for energy and decreases inflammation, thereby preparing for effective management of stress (161). The stress-induced cortisol secretion is adaptive in the short-term, while excessive or prolonged cortisol secretion can lead to HPA axis dysregulation and adverse health effects (161). Dysregulation of the HPA axis are reported in SMDs and assumed to play a key role in the etiology of these disorders (160, 162, 163). Moreover, elevated baseline levels of cortisol are observed in individuals with SMDs (160, 162) and predict transition to psychosis in people at high clinical risk of psychosis in some studies (160, 164). In addition to effects on the neuroendocrine system, early life stress can contribute to other pathophysiological processes associated with SMDs (165, 166). In particular, SMDs are associated with alternations in several neurotransmitter pathways that influence the balance between inhibitory and excitatory states in multiple neural systems (120, 135). Evidence suggests dysregulation of the neurotransmitters dopamine, glutamate and GABA in the striatum, midbrain, hippocampus and prefrontal cortex, which may contribute to psychotic symptoms (120, 135). Dysregulation of multiple neurotransmitters (dopamine, serotonin, noradrenaline, GABA, glutamate) and brain networks (e.g., prefrontal-limbic networks) are also implicated in the pathophysiology of affective symptoms (167, 168). Moreover, neuroimaging studies demonstrate that SMDs are associated with structural brain changes, including ventricular enlargement, reduced cortical thickness, decreased grey matter volume in several brain regions (e.g., frontotemporal regions) and white matter integrity deficits (135, 167-170). Altered brain function and structure are assumed to reflect aberrant

neurodevelopment and progress after exposure to antipsychotics and other illness-related factors (135, 167-170). Furthermore, inflammation has been implicated in the pathogenesis of SMDs (171). Studies have found abnormal levels of inflammatory markers in SMD patients (171), and epidemiological studies suggest that infections and auto-immune disease increase the risk of SMDs (172, 173).

5.2.5 Treatment

The limited understanding of the etiology and pathophysiology of SMDs has impeded development of effective treatment programs. Thus, treatment of SMDs remains a major challenge and full recovery is restricted to a subset of patients (174, 175). However, many patients benefit to some degree from interventions that are aimed at reducing symptoms and improving functioning and quality of life. Evidence-based guidelines recommend a combination of medication and psychological treatment (176-179). The primary pharmacological treatment of SCZ involves antipsychotics which target psychotic symptoms like delusions and hallucinations (180), and can prevent relapses and hospitalizations (181). However, antipsychotics have limited effect on negative symptoms (182) and cognitive impairments (183), which are strongly related to functioning (184). Antipsychotics are often used in conjunction with mood stabilizers or antidepressants, given the frequent co-occurrence of affective symptoms in SCZ (185). Mood stabilizers and antipsychotics are commonly used in the treatment of BD (186). Antidepressants may be used as adjunctive treatment for depressive episodes in BD, although their effects are supported by limited evidence (186). Further, the primary medication for MDD is antidepressants, which is sometimes combined with antipsychotics or mood stabilizers (178). While the combination of different psychotropic drugs may be important for adequate symptom control and improved functioning, the polypharmacy has raised concern owing to its adverse effects on physical illness development, particularly CVD (187).

Medication should be supplemented with psychological interventions in the treatment of SMDs. In particular, psychotherapy in the form of cognitive behavioural therapy (CBT) is recommended for SCZ (176), and CBT, interpersonal therapy, psychoeducation or another evidence-based therapy are recommended for BD and MDD (177, 178). Further, cognitive training has emerged as an evidence-based intervention for cognitive impairments in SCZ (188). The effectiveness of cognitive training on daily functioning is enhanced when provided together with psychosocial rehabilitation that promote employment, learning strategies and

adaptive living skills (189). Additional psychosocial interventions are considered important, including social skills training, family psychoeducation, and supported socialization (peer support groups) (190-192). Despite evidence of their positive effects on symptoms and functioning, these psychosocial interventions are inaccessible to large proportion of individuals with SMDs (190-192). Further, while many psychosocial approaches are aimed at increasing social network and social participation, there is a paucity of interventions that specially target the subjective feeling of loneliness (192, 193), which is further elaborated in the discussion of the findings in the current thesis. Finally, electroconvulsive therapy may be a treatment option for severe depression that has not responded to other treatments (178).

5.3 Cardiovascular disease comorbidity

Patients with SMDs have 15-20 years shorter life span compared to the general population, largely due to CVD (4, 34-37). The most common types of CVDs are coronary artery disease (CAD) and cerebrovascular disease, which involves reduced blood supply to the heart and brain, respectively (4). People with SMDs have on average 2-3 fold higher risk of CVD morbidity and mortality than the general population (4, 34-37). Moreover, patients with SCZ have a 3-fold greater risk of sudden cardiac death than the general population (194), and myocardial infarction accounts for over half of the cases (195). Studies indicate nearly twice as high risk of sudden cardiac death in BD and MDD compared to the general population (196, 197). The enhanced CVD risk in SMDs is largely attributed to raised levels of modifiable risk factors for CVD, including smoking, obesity, hypertension, type 2 diabetes (T2D), dyslipidemia as well as metabolic syndrome (MetS) (4, 82, 198, 199). MetS is a combination of metabolic abnormalities applied by clinicians to identify high-risk individuals for CVD at an early stage, enabling prevention of disease development (elaborated under the method section of study I) (200). Possible factors contributing to the raised level of CVD risk in SMDs are discussed after a presentation of temporal trends in CVD based on evidence that existed prior to this thesis.

5.3.1 Cardiovascular disease mortality and morbidity in the past decades

There has been a steady increase in life expectancy of the general population during the past decades (201). In the same time period, there has been several public health campaigns for health promotion and disease prevention (202), tobacco legislation has become stricter (203) and advances in medicine have been made (204-206). In particular, there has been improvement in hypertension treatment and control, increased use of statins to lower cholesterol, along with

development and timely use of thrombolysis (to dissolve blood clots in blood vessels) and stents (to widen blocked coronary arteries) to prevent infarction (204-206). These strategies appear to have contributed to improved public health. In the general population of Norway and other Western countries, the CVD mortality has decreased since the 1980s (206, 207). Similarly, the level of CVD related morbidity has reduced substantially over the last decades despite an increase in overweight and the prevalence of T2D in the general population (206, 208-210). Several studies suggest that the progress in life expectancy does not extend to patients with SMDs, and the mortality gap between patients and the general population has widened during the last decades (79, 211, 212). However, some data suggest that the longevity of patients with SMDs has improved over the past 20-30 years; however, this improvement is mainly due to a reduction in deaths from suicide and accidents, while CVD mortality show increasing trends (213). A recent Norwegian study replicated the findings of excess mortality in patients with SCZ compared to the general population, with CVD and cancer being the main causes of death (214). Altogether, current evidence suggests that CVD remains the leading cause of premature death in SMDs. However, at the time of planning the current PhD project, it was still unknown to what degree the level of CVD risk factors in patients with SMDs has remained high after several health promotion efforts the last decades. Recent findings suggest that the risk level is still higher in these patients compared to the general population. For instance, one study from England reported twice as high levels of CVD risk factors, including T2D, hyperlipidaemia and obesity, in patients with SCZ and BD compared to healthy controls (215). However, studies examining changes in CVD risk levels among patients during the past decade were lacking prior to this thesis.

5.3.2 Possible contributing factors

The etiology of CVD comorbidity in SMDs is poorly understood, but it is likely to involve an interplay of multiple genetic and environmental factors (4, 10). More specifically, the comorbid CVD appears to be associated with lifestyle factors, side-effects of pharmacological medication, inadequate somatic health care, loneliness and stressful experiences, which interact with genetic factors (4, 10, 216). These possible contributors to the CVD comorbidity are elaborated below.

Lifestyle factors

Unhealthy lifestyle factors, including tobacco smoking, excessive alcohol use, unhealthy diet and physical inactivity are all major contributors to CVD and are more prevalent in patients with SMDs compared to the general population (4, 10). In particular, studies suggest that 60-80 % of patients with SCZ smoke compared to 10-35 % in the general population (217, 218). The prevalence of smoking in BD and MDD is reportedly lower than in SCZ, yet still 2-3 times higher than in the general population (219-221). Similarly, smoking heavily (over 20 cigarettes a day) is more common in individuals with SMDs, and they are less likely to quit smoking (218, 219). Alcohol intake at hazardous levels and use of illegal drugs (especially cannabis, stimulant drugs and sedatives) in patients with SMDs (71-73), are also likely to exacerbate the risk of CVD (222). Furthermore, higher intake of saturated fat and salt and lower intake of fiber, vegetables and fruit are reported in patients with SMDS compared to the general population (217). Unhealthy diets are often accompanied by limited physical activity (10, 217).

Poor economy, largely as a result of unemployment, may contribute to unhealthy eating patterns and a sedentary lifestyle by restricting access to healthy food and training facilities (10, 223). In addition, depressive and negative symptoms, such as lack of initiative and motivation for activities, may limit the engagement in exercise and healthy dietary habits (10, 223). Furthermore, activities are often restricted during hospital admissions, and admissions of long duration can result in considerable reduced physical activity (10). Moreover, certain medications (e.g., antipsychotics and antidepressants) may increase appetite/food intake and lower physical activity (187). Additionally, disturbances of the reward system (mesolimbic pathways) and stress regulation (e.g., HPA axis) may increase the inclination to consume unhealthy/excessive food and use of substances to alleviate negative affective states (i.e., "self-medicate") (10, 224). In addition, personality variables associated with SMDs, including high levels of neuroticism (76, 77), can contribute to unhealthy lifestyle patterns (225). Yet another possible factor related to unhealthy lifestyle factors is loneliness (226), which is elaborated below.

Adverse effects of pharmacological treatment

In the 1950s, chlorpromazine was discovered as one of the first generation antipsychotics (FGAs), which provided better control of psychotic symptoms (especially positive symptoms) and agitation than other drugs used previously. The introduction of FGAs revolutionized psychiatric care by contributing to discharge from hospitals and allowed patients with SMDs to be treated in the community (227). However, FGAs have extrapyramidal side-effects, such as

tremor, muscle stiffness and tardive dyskinesia (involuntary, repetitive movements), which may cause considerable suffering and challenge the adherence to medication (228). Due to the burden of side-effects of FGAs, second generation antipsychotics (SGAs) was introduced in the 1990s. SGAs have a lower propensity to cause extrapyramidal symptoms (229). Some studies also indicate that SGAs are more effective at reducing negative, cognitive and depressive symptoms and prevent relapse than FGAs, while others find no clear beneficial effects of SGAs beyond lower risk of extrapyramidal side-effects (229, 230).

Despite the widespread use of SGAs, concerns have been raised regarding their potential harmful effects on the cardiovascular system (187). Many SGAs, especially clozapine and olanzapine, increase the risk of cardiometabolic side-effects, such as weight gain, dyslipidemia and diabetes (187, 231). SGAs have also been linked to raised blood pressure, but to a lesser extent than the above mentioned metabolic side effects (187, 231). Other psychotropic drugs commonly used in the treatment of SMDs are also related to elevated risk of cardiometabolic disturbances. Some antidepressants (including paroxetine and mirtazapine) and mood stabilizers (including lithium and valproate) are associated with weight gain, yet less so than clozapine and olanzapine (187). Most antidepressants and mood stabilizers have not been associated with dyslipidemia, although weight gain is a risk factor for lipid abnormalities (187). Evidence regarding the effect of antidepressants on diabetes is inconclusive, while certain mood stabilizers, especially valproate, have been associated with elevated risk of insulin resistance (187, 232). Some antidepressants are associated with increased blood pressure, while mood stabilizers do generally not seem to affect blood pressure (187, 232). Furthermore, antipsychotics and some antidepressant are associated with greater risk of life-threatening ventricular arrhythmia (especially torsades de pointes) and sudden cardiac death (187, 233).

In general, antipsychotics, and to a more restricted degree antidepressants and mood stabilizers, are associated with increased risk of cardiometabolic disturbances and arrhythmia (187, 233). These adverse effects appear to increase with higher dosages, polypharmacy and treatment of vulnerable individuals (e.g., young, old and genetically susceptible people) (187). Nevertheless, several large studies have reported that all-cause mortality is higher in patients not using antipsychotics (234, 235). Better somatic health care, reduced stress and lower suicide risk in patients receiving antipsychotics may possibly contribute to this finding of reduced mortality (234). However, the role of antipsychotics and the mechanisms through which they influence mortality continues to be debated (10). Likewise, the reasons for cardiometabolic side-effects of some antidepressant and mood stabilizers remain unclear (231).

Possible shared genetic and pathophysiological mechanisms

The biological mechanisms underlying the comorbidity between SMDs and CVD are complex and poorly understood. Emerging evidence indicates potential shared genetic and pathophysiologic factors influencing SMDs and CVD. Thus, it has been proposed that common genetic factors may predispose to both SMDs and CVD. In line with this hypothesis, genetic variants that increase the risk of T2D are found to also confer increased risk of SCZ (236-238). Recent studies have also revealed overlapping genetic loci between SCZ and other CVD risk factors, including body mass index (BMI), lipids, waist-to-hip ratio and blood pressure (131, 239). These findings point to shared genetic factors that may play a role in the CVD comorbidity in SCZ (10). Thus, some of the raised CVD risk may be inherent to the mental illness, which can help explain the early observations of increased diabetes risk in these patients in the pre-antipsychotic era (5, 6, 240). In addition, a vulnerability to metabolic disturbances is consistent with findings in unmedicated first-episode SCZ patients suggesting raised levels of insulin resistance, T2D, dyslipidemia, hypertension and obesity, compared to healthy controls (241-243). However, there are some discrepant findings, including indications of low BMI as a risk factor for SCZ (244, 245) and higher prevalence of both underweight and overweight in SCZ compared to the general population (246). The link between SCZ and low BMI was recently supported by genetic studies reporting a negative genetic correlation between SCZ and BMI (159, 247). Although the estimated genetic correlation is low ($r_g < -0.1$), the negative value may suggest that SCZ is genetically predisposed to lower BMI (247). Further, some studies report comparable levels of T2D and hyperglycemia in young unmedicated patients with SCZ and population samples (248). Nevertheless, several studies suggest increased risk of T2D in first-degree relatives of patients with SCZ (249-251), indicating a familial, possible genetic, link between T2D and SCZ. The conflicting findings regarding T2D risk may reflect the heterogeneity of SCZ, demonstrated at phenotypic, genetic and molecular levels (252). In support of this, recent molecular studies indicate abnormalities in glucose metabolism and insulin signaling pathways in subgroups of unmedicated patients with SCZ, suggesting an underlying metabolic vulnerability in some patients (252). Nevertheless, further investigation is necessary to elucidate the genetic relationship between SCZ and CVD risk factors.

Although there are few studies of drug-naïve first episode patients with BD and MDD, some recent findings do suggest that cardiometabolic disturbances extend to these diagnostic groups prior to pharmacological treatment (253-255). Likewise, family studies suggest higher

prevalence of T2D, hyperlipidemia and hypertension among first-degree relatives of people with MDD and BD (250, 256), which raises the possibility of a genetic susceptibility to CVD in these affective disorders. Moreover, evidence indicates some overlap in genetic risk factors that increase the liability to MDD and CVD (137, 257). For instance, Wray et al. discovered positive genetic correlations between MD and BMI and CAD (137). Although the genetic correlations were modest (rg=0.09-0.12), the results indicate that some of the genetic variants that predispose to MD overlap with those influencing CVD risk (137). Further, a systematic review of GWASs implicated potential overlapping genes associated with affective disorders (MDD and BD) and CVD risk factors (T2D, obesity, raised blood pressure and lipid levels) and CAD (258). These findings may suggest shared genetic mechanisms between MDD, BD and CVD; however, limited replication of some of the candidate genes demonstrates the need for future studies (258).

There is little research that focuses specifically on the putative genetic relationship between BD and CVD prior to this thesis. Two recent studies reported no significant genetic correlation between BD and CVD risk factors, using linkage disequilibrium score regression (LDSR) (159, 259). Importantly, this does not preclude genetic overlap between BD and CVD-related morbidity because a significant genetic correlation estimated with LDSR requires consistent effect directions of the shared variants between the phenotypes (159). As illustrated in Figure 2, the genetic relationship between two phenotypes can be characterized by a positive correlation, a negative correlation or genetic overlap without correlation (135). Two phenotypes that are not genetically correlated may still share several genetic variants if they possess a balanced mixture of agonistic and antagonistic allelic effect directions (Figure 2) (135). Increasing evidence suggests a pattern of mixed direction of effects among shared genetic variants between pairs of complex phenotypes (131, 140, 260). BD is a heterogeneous disorder with a complex genetic basis (138), and considerable individual variation in CVD risk factors is observed (82, 261), possibly indicating clinical subgroups with different vulnerability to CVD (elaborated under discussion of main findings). Thus, the absence of an overall genetic correlation between BD and CVD risk factors may be due to mixed effect directions of shared variants. Indeed, a recent study (published prior to study III of the current PhD project), revealed multiple shared loci between BD and BMI with a mixture of directional effects (262). The findings indicate that some genetic variants are associated with higher risk of both BD and obesity, while other variants are associated with higher risk of BD and lower risk of obesity, and vice versa.

The mixed effect directions 'cancel each other out', resulting in a non-significant genetic correlation between BD and BMI (262). However, whether BD shares genetic loci with other CVD risk factors or CAD remains unknown.

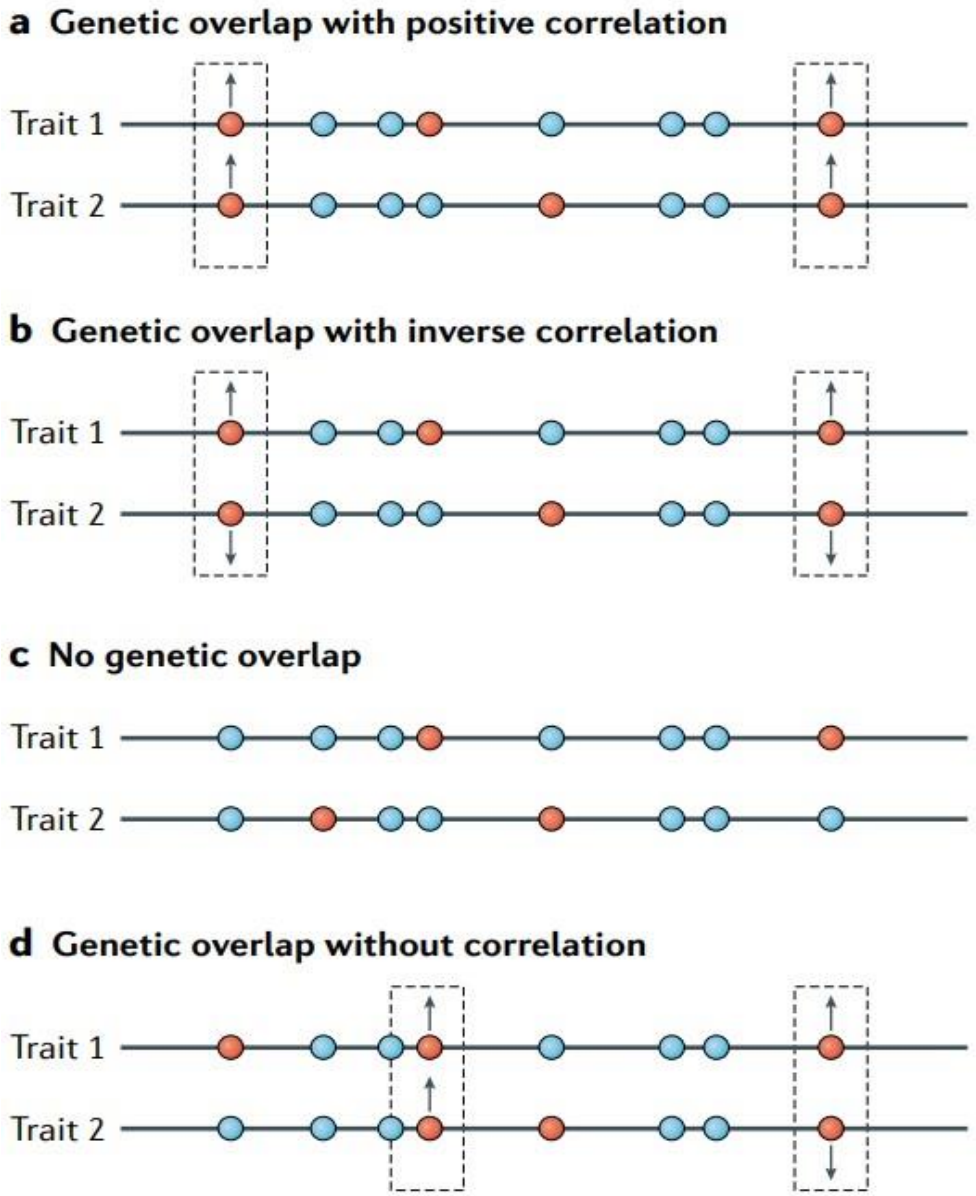

Figure 2. A comparison of genetic overlap and genetic correlation. The genetic relationship between two phenotypes can be characterized as a positive correlation, a negative correlation or an overlap without correlation. a) A positive correlation requires a majority of shared variants with agonistic allelic effects (arrows with the same directions). b) An inverse correlation requires a majority of shared variants with antagonistic allelic effects (arrows with opposite directions). c, d) Absent genetic correlation can indicate either no genetic overlap (c) or shared variants with a balanced mixture of agonistic and antagonistic effects (d). Genetic overlap exists when the same variant is associated with both phenotypes (dashed rectangles). The effect directions are only shown for shared variants. Figure reprinted from Smeland et al. 2020 (135).

Furthermore, findings suggest that there may be overlapping pathophysiology between SMDs and CVD. Dysregulation of the *HPA axis* have been implicated in both SMDs (160, 162) and CVD-related morbidity (263). Increased cortisol levels are reported in patients with SMDs (160, 162) and associated with CVD risk factors, including obesity, hypertension and dyslipidemia (264). Prolonged secretion of glucocorticoids can desensitize glucocorticoid receptors and disrupt the negative feedback mechanism responsible for terminating the HPA axis response to stress (265, 266). Such changes can sustain the HPA axis activation and interfere with regulation of *inflammation*, although the precise mechanisms involved need to be further elucidated (265, 266). Thus, HPA axis dysregulation can increase inflammation, thereby contributing to atherosclerosis (i.e., build-up of plaque and narrowing of arteries), which plays an important role in the development of CAD and other CVDs (263). Inflammation is also implicated in the pathogenesis of SMDs (171, 267) and may thus be a relevant mechanism linking SMDs to CVD (268). In addition, dysfunction of the *autonomic nervous system* is observed in patients with SMDs and is associated with elevated risk of CVD (269-271). For instance, individuals with MDD have higher levels of circulating catecholamines, indicating sympathetic activation, causing increased heart rate and blood pressure (270-272). Continued hyperactivity of the sympathetic system increases the risk of CVD (273). Patients with SMDs have also shown reduced heart rate variability, which is indicative of autonomic dysfunction (269, 270), and predicts increased risk of CVD (272). Furthermore, *neurotransmitters* (e.g., dopamine, serotonin and histamine) that are proposed to play a central role in the pathogenesis of SMDs (10, 120), also influence glucose and lipid metabolism as well as food intake and obesity (274, 275). Therefore, neurotransmitter imbalance may be another potential mechanism associated with the CVD comorbidity in SMDs (10, 258). Still, many aspects of the pathophysiology of the CVD comorbidity remain unclear.

Inadequate somatic health care

Even though patients with SMDs are at increased risk of CVD and other somatic diseases that require clinical attention, they are less likely to receive adequate physical health care than the general population (276, 277). Screening, assessment and treatment of CVD related morbidity in patients with SMDs fall below agreed standards and are well below that received by the general population (276, 277). For instance, regular monitoring of glucose, lipid levels and blood pressure is seldom, and patients with SMDs are less likely to receive adequate treatment of T2D, dyslipidaemia and hypertension (276-278). These health care disparities are likely the

result of several factors, such as patients' reluctance to seek somatic health care due to symptoms (e.g., affective or motivational symptoms, suspicion), problems communicating physical needs, poorer compliance with treatment and socioeconomic disadvantages (276). In addition, reduced pain sensitivity is reported in SCZ, despite suffering from painful acute medical conditions, such as myocardial infarction, which may result in severe conditions going undiagnosed (279). Apart from patient-related factors, poor collaboration between mental health and primary care providers appears to play an important role, causing confusion about who is responsible for the assessment of the physical health (e.g., the psychiatrist or the primary care physician) (276). Another contributing factor to inadequate somatic care may be a tendency to focus little on the physical health of patients in mental health clinics (276). Accordingly, there is an increased risk of serious somatic conditions remaining undetected and inadequately treated in SMD patients (276-278).

Loneliness

More recently, loneliness has emerged as a likely factor contributing to CVD in SMDs (103, 216). A number of studies indicate that loneliness is associated with increased risk for premature death and CVD morbidity, even after controlling for factors such as health-related behavior, age, gender, marital status and depressive symptoms (102, 280-283). A meta-analysis of longitudinal studies estimated that the influence of deficient social relationships on mortality is comparable with well-established risk factors such as smoking, and exceeds the risk associated with obesity and hypertension (281). Another meta-analytic review of longitudinal research suggests that loneliness is associated with ~30% increased risk of CAD (283). Moreover, loneliness predicts a number of CVD risk factors, including hypertension, obesity and MetS in population studies (284, 285) and studies of patients with SMDs (103, 216). Taken together with evidence of loneliness being a common issue in SMDs (90, 103-107), loneliness appears to represent an important mechanism that can contribute to increased CVD risk in SMDs. However, while current evidence suggests an association between loneliness and CVD comorbidity, the directionality of this association is unclear, and a bidirectional relationship is possible. For instance, stigma and reduced self-esteem associated with obesity can contribute to social withdrawal and increased loneliness (216). Further, it has been proposed that loneliness and social relationships influence CVD risk and mortality via multiple pathways, including indirectly by influencing health behaviour and psychological mechanisms, and through direct effects on physiological systems (e.g., neuroendocrine, immune and autonomic

nerve system) (100, 286). In particular, feeling lonely is associated with lifestyle factors (physical inactivity, unhealthy nutrition, smoking) and poorer treatment adherence and cooperation (226, 287). Loneliness is also accompanied by greater levels of perceived stress, depressive symptoms and diminished capacity for self-regulation (i.e., ability to regulate thoughts, feelings and behavior) (100, 288), rendering lonely individuals more vulnerable to stress (100). Finally, loneliness is associated with physiological changes, including activation of the HPA axis and the sympathetic nervous system along with increased inflammation (100, 286). Together, these processes can increase the risk of developing CVD in lonely individuals.

Loneliness may also be linked to CVD comorbidity in SMDs through a shared genetic basis with CVD and SMDs. Positive genetic correlations between loneliness and SMDs are reported, as described above (157, 158). In addition, a recent GWAS found a positive genetic correlation between loneliness and BMI, obesity and CAD (157). Although preliminary, these findings may suggest genetic contributions to the co-occurrence of loneliness, SMDs and CVD, which deserves further investigation.

Stressful life events

The CVD comorbidity is also likely related to stressful life events, including childhood trauma, that are frequently reported by individuals with SMDs (289). Several studies have shown that traumatic events are associated with cardiometabolic disturbances in the general population and among individuals with post-traumatic stress disorder (290, 291). More recently, studies focusing on SMD patients also suggest that childhood trauma is related to CVD comorbidity (292, 293). Furthermore, patients with SMDs are more likely to occupy lower socioeconomic positions (e.g., lower income level, educational attainment and employment status) than healthy controls (294, 295), which is associated with stressful conditions, including economic strain, insecure employment and discrimination (296). Additional stress comes from the symptoms of the SMDs. For instance, symptoms such as paranoia and hallucinations may be inherently stressful (297). The enduring exposure to stress, combined with limited availability of resources to alleviate stress (e.g., limited social support and coping strategies), can contribute to the elevated CVD risk in SMDs. Similar to loneliness, stress is proposed to increase the risk of CVD through indirect (e.g., lifestyle, sleep) and direct pathways involving dysregulation of the HPA axis, immune system and autonomic nervous system (298).

A conceptual framework

The overarching theoretical framework for understanding the comorbidity between SMDs and CVD used in the current PhD project is illustrated in Figure 3. This framework posits that genetic predisposition, together with environmental risk factors, such as stressors and trauma, can lead to brain dysfunctions influencing the development of SMDs and CVD, possibly through loneliness and lifestyle. There may also be a direct pathway from brain dysfunction to development of SMDs. The relationship between SMDs, CVD, and loneliness and lifestyle can be bidirectional (as indicated by the arrows). In addition, side-effects of medication and inadequate somatic health contribute to the cardiometabolic disturbances. In this model, we further postulate pleiotropy, i.e., that there may be some genetic variants jointly influencing cardiometabolic disturbances and brain functions that affect the risk of developing SMDs as well as behavioral and psychological risk factors (e.g., loneliness and lifestyle). This conceptual

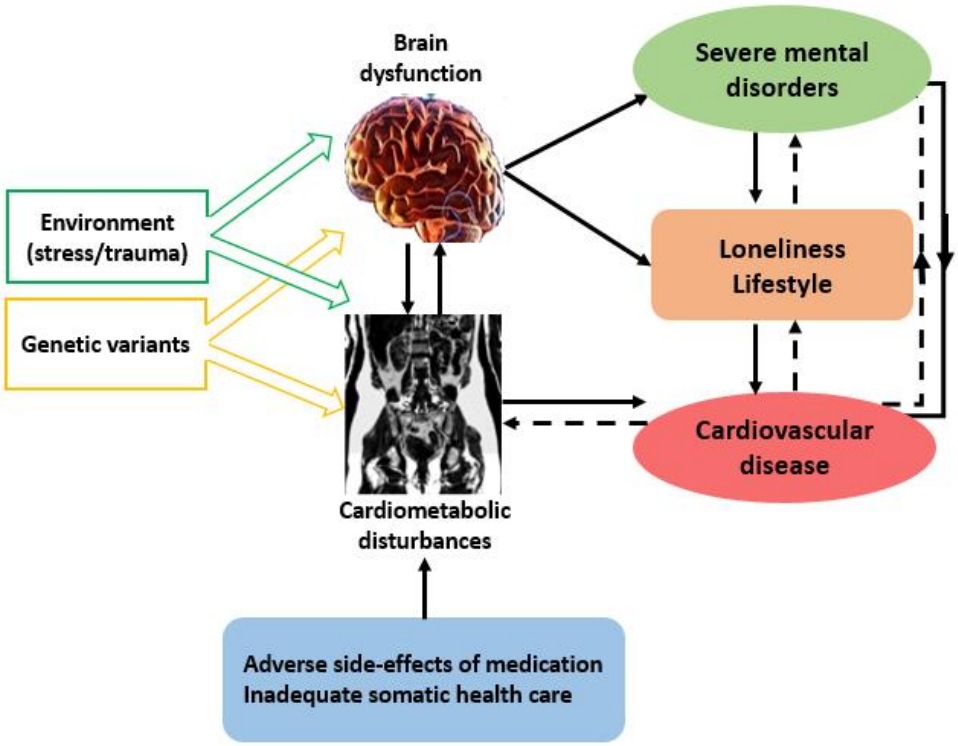

Figure 3. **Conceptual framework**. Genetic susceptibility and interplay with environmental risk factors, such as stress/trauma, can lead to brain dysfunctions influencing the development of SMDs and CVD, possibly through loneliness and lifestyle. SMDs may also develop directly from brain dysfunctions. Bidirectional relationships between the variables are possible, and there may be a direct link between SMDs and CVD (as indicated by the arrows). Other pathways (e.g. genes affecting cardiometabolic disturbances) are also possible. In addition, side-effects of medication and inadequate somatic health contribute to the CVD comorbidity.

framework builds on the idea that the genotype can modify the environmental risk for disease development. Thus, rather than simply influencing disease risk directly, genetic variants may influence risk indirectly through behavioral and psychological characteristics that put individuals at a higher environmental risk for disease development. This concept is based on findings of a genetic variant associated with smoking more and difficulties with smoking cessation (299). Individuals who carry this genetic variant display substantially higher risk of developing CVD and lung cancer (299). These results underscore the complex interplay between genetics and environmental factors and illustrate that genetic variants influencing the tendency to seek or avoid environmental risk (e.g., smoking), also influence the risk for developing disease. This provides an example of active gene-environment correlations in which individuals influence aspects of their environment in part based on their genetic propensities (300).

This perspective can be extended to include loneliness. While loneliness is not an environmental factor per se, it is a complex phenotype associated with psychological and behavioral aspects (100, 151) that may be related to a heightened environmental risk (e.g., poor social relationships, social isolation, lifestyle) (95, 100, 149, 226) for SMDs and CVD. As described above, recent findings implicate genetic variants influencing the propensity to loneliness and positive genetic correlations between loneliness and SMDs, BMI and CAD (157, 158). These observations warrant further investigation.

5.4 Novel statistical tools to assess genetic overlap

Most studies of genetic overlap between two phenotypes focus on estimating genetic correlations (25, 135, 157-159). While measures of genetic correlation can be useful to elucidate the overall degree of genetic overlap (301), they fail to capture polygenic overlap if the shared variants possess a balanced mixture of agonistic and antagonistic effect directions (135). Accordingly, to obtain a comprehensive understanding of the genetic relationship between traits, measures of genetic correlation should be complemented with tools that allow for the discovery of shared variants regardless of their effect directions (135). Two novel statistical tools, including bivariate causal mixture model (MiXeR) (302) and conditional/conjunctional false discovery rate (cond/conjFDR) (303), can discover shared variants irrespective of effect direction. MiXeR estimates the *total number* of shared genetic variants, thereby enabling the identification of shared genetic architecture beyond genetic correlation (302). MiXeR has

revealed substantial genetic overlap between SMDs and brain-related phenotypes (e.g., attention-deficit/hyperactivity disorder (ADHD), education) despite low or absent genetic correlation (135, 302) (Figure 4).

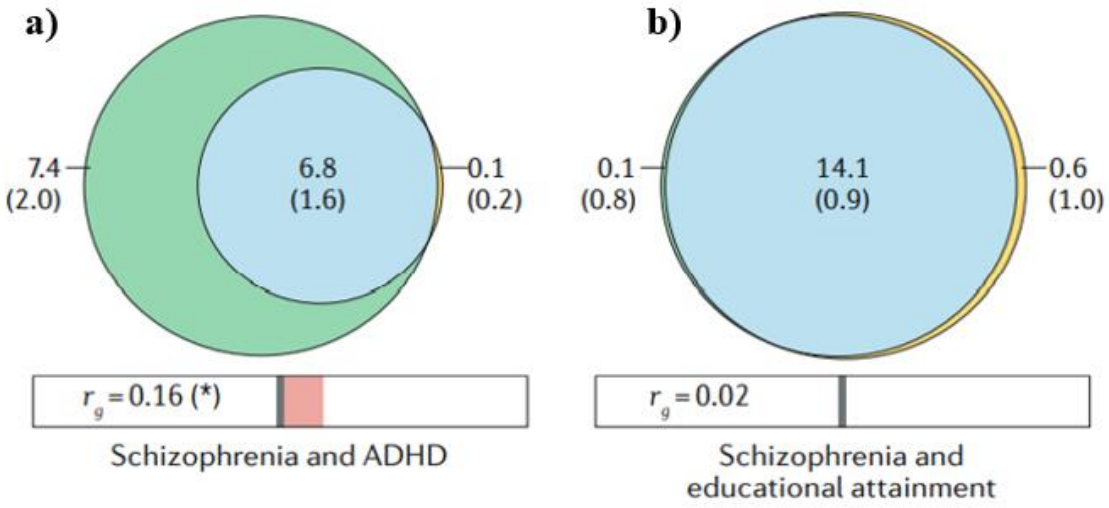

Figure 4. Venn diagrams of shared and unique variants. Venn diagrams showing polygenic overlap (blue) between a) schizophrenia (green) and attention-deficit/hyperactivity disorder (ADHD) (yellow), and b) educational attainment (yellow). The numbers indicate the estimated quantity of genetic variants (in thousands) per component, explaining 90% of SNP heritability in each phenotype, followed by the standard error. The size of the circles reflects the degree of polygenicity. r_g denotes the genetic correlation. Figures reprinted from Smeland et al. 2020 (135).

The cond/conjFDR approach can detect *individual* overlapping loci (303). The condFDR method builds on Bayesian statistics and increases the power to identify loci associated with a primary phenotype (e.g., BD) by leveraging associations with a conditional phenotype (e.g., BMI). ConjFDR is an extension of condFDR and can detect loci jointly associated with two phenotypes (303). The first step in the cond/conjFDR procedure is to construct conditional quantile–quantile (Q–Q) plots. The conditional Q-Q plots visualize overlap in SNPs associations (i.e., cross-trait enrichment) as successive leftward shifts from the null distribution (diagonal line in Figure 5) (262, 303). Figure 5a presents conditional Q-Q plot demonstrating genetic enrichment in BD conditional on associations with BMI, suggesting polygenic overlap. The reverse conditional Q-Q plot also display enrichment in BMI conditional on associations with BD (Figure 5b). The plots come from a recent study using cond/conjFDR uncovering several shared loci between BD and BMI with a mixture of directional effects (described above) (262). The results illustrate the utility of the cond/conjFDR approach to discover polygenic

overlap despite no significant genetic correlation. Together, MiXeR and cond/conjFDR provide novel avenues to investigate the genetic relationship between SMDs, loneliness and CVD.

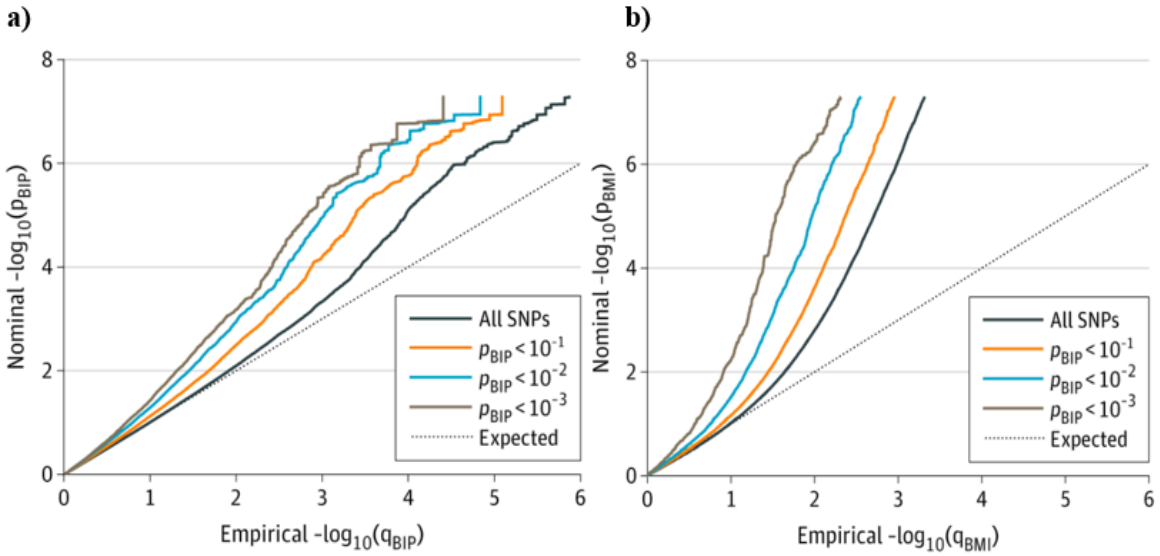

Figure 5. Conditional Q–Q plot displaying the a) nominal $-\log_{10}$p values of the single SNP association statistics versus their empirical distribution in bipolar disorder (BIP) below the standard GWAS threshold of $p < 5\times10-8$ as a function of significance of association with body mass index (BMI) at the level of $p \leq 0.1$, $p \leq 0.01$, $p \leq 0.001$, respectively. b) The reverse conditional Q-Q plots display the nominal $-\log_{10}$p values of the single SNP association statistics versus their empirical distribution in BMI below the standard GWAS threshold of $p < 5\times10-8$ as a function of significance of association with BIP at the level of $p \leq 0.1$, $p \leq 0.01$, $p \leq 0.001$, respectively. The blue line indicates all SNPs. The dashed line indicates the null hypothesis. Figure reprinted from Bahrami et al. 2020 (262).

5.5 Knowledge gaps

In summary, patients with SMD have a high risk of CVD, contributing to substantially reduced life expectancy. While the CVD risk has decreased in the general population during the last decade, *it is unknown whether patients with SMDs have experienced a reduction in CVD risk factors*. Thus, it is unknown whether recent health promotion efforts and preventive strategies have benefitted patients with SMDs in terms of CVD risk. Furthermore, the factors contributing to the CVD comorbidity remain poorly understood, yet lifestyle factors and side-effects of medication are likely contributors. Current evidence has also established a link between loneliness and increased CVD risk, and loneliness is highly prevalent in SMDs. Still, the mechanisms underlying the co-occurrence of loneliness and CVD in SMDs are unknown. Preliminary findings indicate that genetic susceptibility to both loneliness and CVD may contribute to the comorbidity. However, *whether loneliness shares genetic underpinnings with*

SMDs and CVD remains to be clarified. The genetic relationship between these phenotypes is likely complex and a genetic vulnerability to loneliness may differ across diagnostic groups, as suggested by different levels of genetic correlations. Moreover, *little research has focused on the putative genetic relationships between BD and CVD.* Although BD demonstrates no genetic correlation with CVD risk factors or CAD, genetic overlap between BD and CVD is possible. Genetic correlation (LDSR) can obscure genetic overlap if the shared variants have mixed directional effects (135, 159). In addition, measures of genetic correlation do not specify the individual genetic variants that may be involved (135, 159). These limitations of LDSR highlight the need for combining the genetic correlation measure with tools that allow for the discovery of genetic overlap and shared variants regardless of their effect directions, such as MiXeR (302) and cond/conjFDR (303).

6 AIMS

The main aim of the thesis was to increase knowledge about the CVD risk levels and possible underlying mechanisms in SMDs. Therefore, we investigated 1) CVD risk levels in two patient samples with SCZ and BD and healthy controls and the general population, 2) whether loneliness shares genetic variants with SMDs and CVD phenotypes, and 3) overlapping genetic variants between BD and CVD phenotypes.

The specific study aims were:
Study I: To investigate the level of CVD risk factors in patients with SCZ and BD recruited from 2002-2005 with patients recruited from 2006-2017. In addition, we compared the CVD risk levels in the most recent patient sample with healthy controls and the general population from the same time period (2006-2017).
Study II: To investigate shared genetic architecture (i.e., estimate the total number of shared variants) and identify specific loci shared between loneliness, SMDs and CVD phenotypes.
Study III: To investigate shared genetic architecture and identify specific loci shared between BD and CVD phenotypes.

While study I focused on examining potential temporal changes in CVD risk levels in SMDs, study II and III aimed at elucidating underlying mechanisms of the comorbidity. MiXeR (302). and cond/conjFDR (303) were used to assess potential genetic underpinnings of the observed association between SMDs, CVD and loneliness. While long-term longitudinal studies may be superior for identifying mechanisms underlying the association between the phenotypes, performing a longitudinal study was not feasible within the time frame of the PhD project. As an alternative, we analyzed large GWASs with MiXeR and cond/conjFDR. These tools can provide novel information about the genetic architecture of SMDs, CVD and loneliness, and their relationships. Investigating overlap in genetic variants can help reveal shared pathobiology and have implications for the understanding of CVD comorbidity, which can form the basis for improved prevention and treatment to reduce CVD risk in SMDs.

7 METHODS

7.1 Study design and ethics

Study I is based on data from the TOP study and Statistics Norway. The TOP study includes data from patients with SCZ and BD recruited from the major hospitals in the Oslo area; patients recruited from 2002-2005 (2005 sample) was compared with patients recruited from 2006-2017 (2017 sample). In addition, we used data from two reference groups: (1) healthy controls randomly recruited from the same catchment area and similar time period as the 2017 sample and (2) two larger samples from the Oslo general population obtained by Statistics Norway (224, 304-306) from similar time periods as the 2005 and 2017 samples. Study II and III are based on international GWASs. Written informed consent was obtained from all participants in the TOP study and the GWASs. The TOP study is conducted in accordance with the Helsinki Declaration and approved by the Regional Committee for Medical Research Ethic and the Norwegian Data Inspectorate. All GWASs were approved by the relevant ethics committees, and Regional Committees for Medical Research Ethics has evaluated the research protocol of the GWASs used and found that no additional institutional review board approval was necessary because no individual data were used.

7.2 Thematically organized psychosis research (TOP) study

Participants

The TOP study is an ongoing study of SMDs that have included participants since 2002. Participants are referred by their clinician (medical doctor or psychologist) and come from mental health clinics of the major hospitals in Oslo, currently covering a catchment area of 88% of the city's total population. These hospitals are located in different parts of the city, and are representative of the Oslo's variation in sociodemographic characteristics. To be eligible to the TOP study, the participants had to meet the inclusion criteria of a DSM-IV diagnosis of schizophrenia or other psychotic disorder (schizoaffective disorder, schizophreniform disorder, psychosis NOS or delusional disorder), BD type I, BD type II, BD NOS, age between 18-65 years and ability to give written informed consent. Participants were excluded in case of pronounced cognitive deficit (IQ below 70), severe somatic illness, brain damage, and not speaking a Scandinavian language. Healthy controls were randomly selected from statistical

records from the same catchment area and age range as patients. Since the beginning of the TOP study until May 2017, a total of 1281 patients with a diagnosis of SCZ (n=785) or BD (n=496), whom we also had CVD risk data from, were included. The first sample from 2002-2005 (2005 sample, n=161 SCZ and 109 BD) is described by Birkenæs et al. (307, 308). The characteristics of the sample recruited during the last decade (2017 sample) are presented in Table 1 in paper I (309). The 2017 sample comprised of 1011 patients, including 624 with SCZ and 387 with BD. The SCZ group consisted of patients with schizophrenia (n=474), schizophreniform (n=47), and schizoaffective disorder (n=103). The BD group consisted of patients with BD type I (n=245), BD type II (n=114), and BD NOS (n=28). The 2017 patient sample was compared with 922 healthy controls that were also recruited from 2006-2017. To compare the 2005 sample with the 2017 sample, we reanalysed data from Birkenæs et al. (307, 308) with some minor changes due to the updated dataset. Patients in the 2017 sample were younger than patients in the 2005 sample, with a mean (SD) age of 31.68 (10.49) versus 35.50 (11.07) years ($F(1, 1279)=27.59$, $d=0.35$, $p < 0.001$). The 2017 sample had a shorter duration of pharmacological treatment compared to patients in the 2005 sample (SCZ: $F(1, 696)=10.66$, $p=0.001$; BD: $F(1, 434)=9.33$, $p=0.002$). The duration of illness was also shorter among patients with BD in the 2017 sample than in in the 2005 sample ($F(1, 484)=5.85$, $p=0.016$). The clinical and demographic differences between the patient samples were small (all Cohen's $d < 0.2$ and phi < 0.1) (310).

Measurements

Clinical assessments

Consistent clinical assessment tools were applied during the whole recruitment period. A comprehensive diagnostic assessment was performed using the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (311), by trained clinical psychologists and medical doctors. Further information was retrieved, including demographic factors, self-reported diet, physical activity (hours per week), psychiatric history, medical history, and current use of psychotropic medication, tobacco, alcohol, and illicit drugs, from interviews and medical records. Psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (312). Depressive symptoms were measured with the Inventory of Depressive Symptoms (IDS-C) (313). General symptoms and functioning were rated using the Global Assessment of Functioning Scale (GAF), split version (symptoms, GAF-S; function, GAF-F) (314, 315). The inter-rater reliability of the symptom assessments is good to high, with an

Intraclass Coefficient (ICC) of 0.82 for PANSS ratings, 0.86 for GAF-S and 0.85 for GAF-F (316, 317). The inter-rater reliability of diagnosis is high, with overall agreement for diagnostic categories of 82 % with overall Cohen's kappa κ=0.77 (95% CI: 0.60 - 0.94) (95% CI: 0.60 - 0.94) (318).

Physical assessments and CVD risk factors

Physical examination was performed by a physician using the same protocol for both samples. BMI (weight in kg/height in m^2) was calculated from weighing the participants on calibrated digital weights wearing light clothing and no shoes. Waist circumference was measured midway between lowest rib and the iliac crest. Blood pressure was measured in sitting position after resting. Blood samples were collected after an overnight fasting of at least 8 hours and analyzed for fasting plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TGs). Blood samples were analyzed at the Department of Medical Biochemistry, Oslo University Hospital, on several routine instruments with standard tools (Integra 800, Abbot Architect, i2000, Cobas 8000 e602 and Cobas 8000 e801) from Roche Diagnostics, Basel, Switzerland (www.roche.com/about/business/diagnostics.html).

Metabolic Syndrome (MetS)

Different definitions of MetS exist (319). In study I, MetS was diagnosed based on the definition developed by the National Cholesterol Education Program, Adult Treatment Panel III in 2003 (320). Three or more of the following five criteria must be met for establishing a diagnosis of MetS. Cut off values for the individual variables are:

(1) FPG ≥ 5.6 mmol/L (100 mg/dL) or taking hypoglycemic medication,

(2) TGs ≥ 1.7 mmol/L (150 mg/dL),

(3) HDL-C < 1.0 mmol/L (40 mg/dL) (men) and < 1.3 mmol/L (50 mg/dL) (women),

(4) systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg or taking antihypertensive medication, and

(5) central obesity with waist circumference > 102 cm (40 in) (men) and > 88 cm (35 in) (women).

This definition is one of the most widely used due to its clinical usefulness (321, 322). Waist circumference was available for a limited number of patients in the 2005 sample in study I.

Therefore, we used a modified version of the MetS criteria (308) based on BMI≥30 as an alternative measure of central obesity when comparing the 2005 sample with the 2017 sample.

7.3 Statistics Norway sample

Statistics Norway (SSB, https://www.ssb.no/statbank/) is the national statistical institute of Norway responsible for providing official statistics. SSB has collected self-reported data on overweight and obesity (BMI ≥ 25) in the general population of Oslo in 2002 and 2005 (n=1285), and in 2008, 2012, 2015 and 2017 (n=3035) (224). Statistics Norway has also obtained data on self-reported daily smokers in Oslo in 2002-2005 (n=540) and in several intervals from 2006 to 2017 (n=4587) (Norhealth - an online database from the Norwegian Institute of Public Health: http://www.norgeshelsa.no/norgeshelsa/ (304)). Smoking data were merged into bins to get a sufficiently large sample to break down on county level, age groups and sex. SSB data from 2002-2005 was compared with the 2005 sample, and data from 2006-2017 was compared with the 2017 sample. The SSB sample was age-matched to the TOP sample.

7.4 Genomewide association study (GWAS) samples

For study II and III, we obtained GWAS results in the form of summary statistics (p-values and effect sizes). The GWASs analysed are described below. For further details about the inclusion criteria, genotyping and phenotype characteristics, see Supplementary Methods in paper II and III and the original GWAS publications (136-138, 157, 323-331).

GWAS samples in study II

Data on SCZ, BD and MD were retrieved from Psychiatric Genomics Consortium (PGC) (136-138). The SCZ dataset contained 49 non-overlapping case-control samples (34 241 cases with schizophrenia or schizoaffective disorder and 45 604 controls) and 3 family-based association studies (1235 parent affected-offspring trios) (136). The BD dataset consisted of 20 352 cases and 31 358 controls from 32 samples (138). Among the cases, 14 879 individuals were diagnosed with BD type I (BD1), 3421 with BD type II (BD2), 977 with schizoaffective disorder, bipolar type (SAB), and the remaining BD NOS (138). The MD dataset involved 135 458 cases and 344 901 controls (137). The term ‘MD’ is used instead of the diagnostic term ‘MDD’ as many (~56%) of the MD cases were identified by self-report, while the rest met

diagnosis criteria for a lifetime diagnosis of MDD (137). The GWAS of MD found strong support for the comparability of the MD cohorts that used different assessments methods (e.g., self-report vs. diagnostic interview), including high genetic correlation between the cohorts (137). A diagnosis of MDD (137), SCZ (136) or BD (138) was established according to international consensus criteria (DSM-IV, ICD-9, or ICD-10) assessed with semi-structured interviews by trained interviewers, clinician-administered checklists, or medical record review. Controls in most cohorts were screened for the absence of lifetime psychiatric disorders and randomly selected from the population. The TOP sample is part of the GWAS samples of SCZ and BD.

Loneliness data (n=452 302) were retrieved from the UK Biobank study based on self-reported responses to questions about (1) perceived loneliness, (2) the ability to confide in someone close, and (3) living alone and frequency of social interactions with family and friends (see Table 1 below) (157). Notably, GWAS data on perceived loneliness was used as a *primary* variable, while the remaining GWAS data sets (ability to confide, living alone and frequency of social interactions) were used to boost power for gene discovery. The three GWAS data sets were combined using a meta-analytical approach, multi-trait GWAS (MTAG) (332), which aims to increase the power to detect genetic loci associated with a primary variable by borrowing statistical power from additional variables. Using this approach, a "composite loneliness score" was computed by Day et al. (157). We used this composite score in our statistical analyses in study II (see below).

The UK Biobank recruited people from the general population consisting mainly of healthy individuals. Thus, only a minor fraction of participants has a psychiatric diagnosis, including 2483 with SCZ, 2123 with BD and 8276 with MDD (UK Biobank data field 41270). Although the number of participants with self-reported depression is higher (333), this did not significantly influence the finding of loneliness loci. A sensitivity analysis was performed by repeating the loneliness GWAS excluding individuals with self-reported depression (n=26 801, defined in response to an interview question ascertaining doctor diagnosed disorder), which did not lead to in any appreciable change in the findings of Day et al. (157). Anxiety disorders did not influence the results either as most individuals with self-reported anxiety disorder were removed when excluding people with self-reported depression, given the high comorbidity between these disorders (333). Therefore, the results are unlikely to be biased by psychiatric diagnoses that are far less prevalent than self-reported depression in the UK Biobank (Supplementary Table A-B in paper II). Thus, similar to Day et al., we did not exclude

participants with self-reported depression or other psychiatric diagnoses from the loneliness GWAS data. However, it is important to note that the UK biobank cohort (n=29 740) was excluded from the MD GWAS (137) to avoid sample overlap with the loneliness sample (157).

Further, we used data from GWASs on CVD risk factors, including BMI (n=339 224) (323), T2D (n=159 208) (327), TC (n=188 578) (325), HDL-C (n=188 578) (325), systolic blood pressure (SBP) (n=200 000) (324), diastolic blood pressure (DBP) (n=200 000) (324), along with CAD (n=185 000) (326). In addition, we used GWAS data on smoking (n > 200 000) for supplementary analysis (328). For MiXeR analysis, we used a larger BMI GWAS (n=795 640) (329) than for cond/conjFDR because MiXeR corrects for overlapping samples.

Table 1. Measure of loneliness and isolation in the UK Biobank

Items	Response options	Categorization
1) Do you often feel lonely?	Yes No Do not know Prefer not to answer	"Cases" (people who are likely to feel lonely), were identified as those who answered "yes". "Controls" (those who do not or are unlikely to feel lonely), were identified as people who answered "no".
2) How often are you able to confide in someone close to you?	Almost daily 2-4 times every week About once every week About once a months Once every few months Never or almost never Do not know Prefer not to answer	"Cases" were defined as those who answered "never or almost never". "Controls" were defined as those who answered "almost daily to once every few months".
3) a. How often do you visit friends or family or have them visit you? Instructions also stated participants to include meetings with friends or family outside of home. 3) b. Including yourself, how many people are living together in your household?	Almost daily 2-4 times a week About once a week About once a month Once every few months Never or almost never No friends/family outside household Do not know Prefer not to answer X number of people you live with Live alone Do not know Prefer not to answer	"Cases" were defined as those who lived alone and who indicated that they either never visited or had no friends or family outside their household. "Controls" were defined as those who either did not live alone, or had friends/family who visited at least once a week.
Items forming a validated composite measure of loneliness in the UK Biobank (Day et al. 2018) (157)		

GWAS samples in study III

To investigate genetic overlap between BD and CVD phenotypes in study 3, we used the same GWASs of BD (138), T2D (327), and lipids (TC, HDL-C, LDL-C) (325) as in study 2. We applied larger GWAS samples for SBP/DBP (n=757 601) (331), CAD (n=332 477) (330) and BMI (n=795 640) (329) including UK Biobank data in study 3 because sample overlap was not

an issue (i.e., no UK Biobank participants in the BD sample). We repeated the previously published cond/conjFDR analysis of genetic overlap between BD and BMI (262) to obtain a comprehensive overview of the genetic relationship between BD and CVD phenotypes. The GWAS samples used for study II and III were predominantly of European ancestry.

7.5 Statistical analyses

7.5.1 Statistical analyses for study I

Statistical analyses were performed using the statistical package SPSS, version 25 for Windows (IBM Corp, 2017) (334). All tests were carried out two-sided with the significance level set to 0.05. The distribution of data was investigated through histograms, skewness and kurtosis indicators. Variables that were not normally distributed were log transformed. To investigate sociodemographic and clinical differences between groups, we used a chi-square test for categorical variables, and univariate analysis of variance (ANOVA) for continuous variables. Univariate analysis of covariance (ANCOVA) and logistic regression were used to adjust for age as a potential confounder when comparing the CVD risks between groups (diagnostic groups, patients vs. controls). CVD risk levels in SCZ vs. BD were further investigated correcting for functioning level (GAF-F), symptom level (PANSS) and use of antipsychotics with adverse metabolic side effects as the diagnostic groups differed significantly in these variables. The prevalence of smoking and overweight/obesity between patients and the general population (SSB) were compared using chi-square test. The CVD risk factors in the 2005 sample and 2017 sample were compared with ANCOVA and logistic regression to adjust for differences in age, duration of illness and duration of pharmacological treatment (possible confounders). Additional analyses were performed to investigate CVD risk factors in subgroups, stratified by sex and age groups. Bonferroni correction was used to adjust for multiple testing when stratifying, dividing the p-value of 0.05 by the number of stratified groups. Effect sizes (Cohen's d, odds ratio and Phi) were reported and interpreted in line with guidelines (310, 335). Fasting blood samples were available from a subset of controls (n=222), which were compared with the fasting patients when considering levels of glucose and TGs (of which fasting status is of great importance).

7.5.2 Statistical analyses for study II and III

Imputation and quality control

Certain sets of nearby alleles at different loci occur together more often than expected. This tendency of some alleles to co-occur non-randomly due to proximity creates an association between them called linkage disequilibrium (LD) (336). Knowledge about the LD patterns can be used to select tag SNPs, i.e., SNPs used to represent a group of SNPs in high LD. Thus, tag SNPs can be applied to infer the nongenotyped SNPs through imputation (336). This procedure makes is possible to study variation across the whole genome without genotyping every SNP, increasing the power and cost-effectiveness of GWASs (336). The LD patterns that inform imputation is available in large reference samples that are densely genotyped (336), including samples from the 1000 Genomes Project (337, 338) and the Haplotype Reference Consortium (339). The GWASs used in study II and III applied such references panels genotyped at millions of sites (337-340) and used standard imputation tools (e.g., IMPUTE2 (341) and SHAPEIT (342)). Each GWAS data set has undergone stringent quality control (removing SNPs with high missingness and low imputation quality). Details of the specific quality control procedures and methods are available in the original GWAS publications (136-138, 157, 323-331).

Conditional Q-Q plots

To visualize the putative overlap in SNPs associations (i.e., cross-trait enrichment), we constructed conditional Q-Q plots. Enrichment exists when the proportion of SNPs associated with a phenotype (e.g., loneliness) increases as a function of the strength of the association with a secondary phenotype (e.g., SCZ) (303). Under the null hypothesis, the nominal p values will form a straight line when plotted against the empirical distribution. The conditional Q-Q plots visualize this cross-trait enrichment as successive leftward shifts from the null line (131, 303). Figure 6 below presents conditional Q-Q plots demonstrating genetic enrichment in loneliness conditional on associations with SMDs, suggesting polygenic overlap. Further information about this method is available in Supplementary Methods of paper II and III and a method review (303).

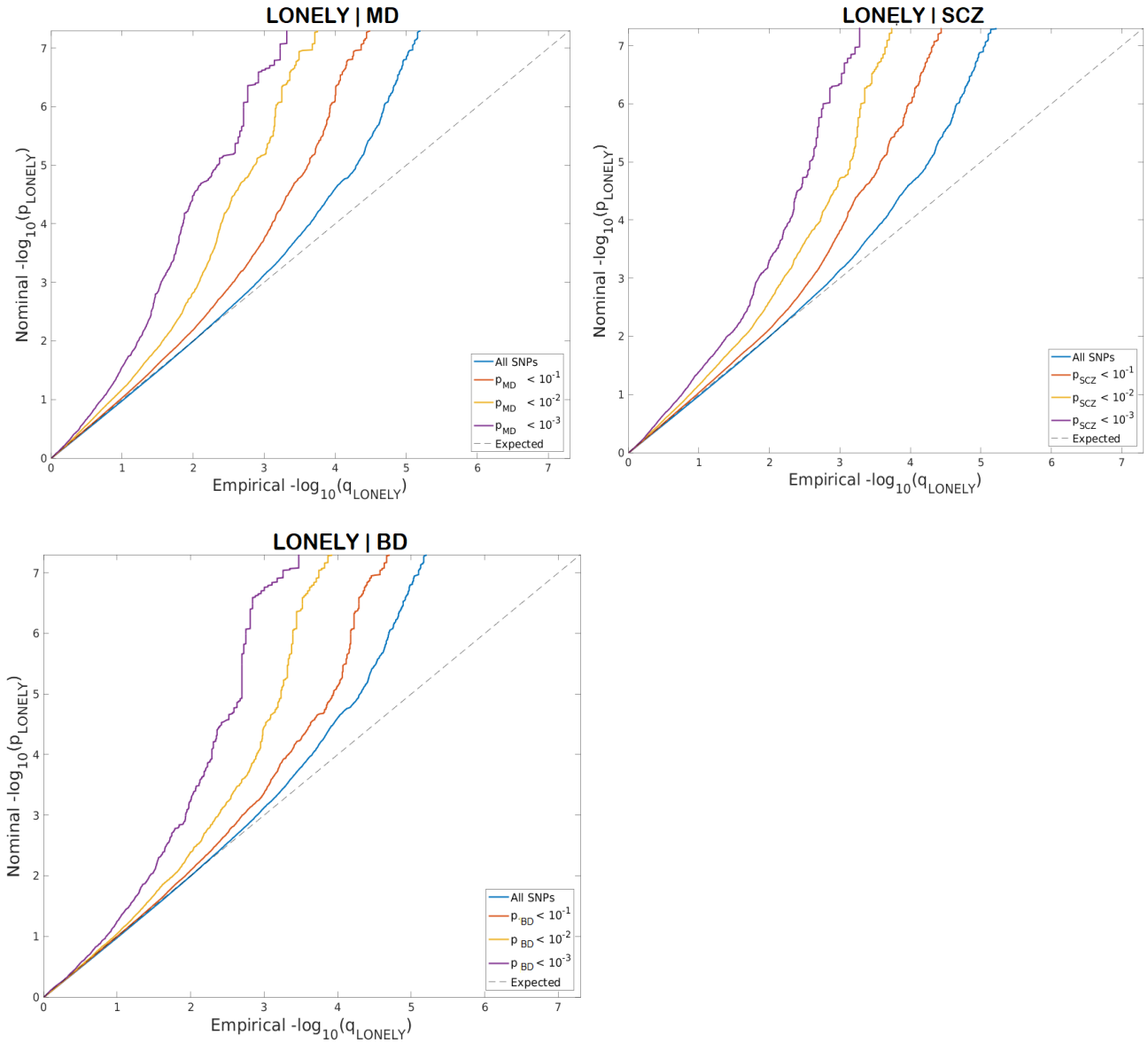

Figure 6. Polygenic overlap between loneliness and MD, SCZ and BD. Conditional Q-Q plots of nominal versus empirical −log10p values (corrected for inflation) in loneliness below the standard GWAS threshold of $p < 5 \times 10{-}8$ as a function of significance of association with MD, SCZ and BD at the level of $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively. The blue lines indicate all SNPs. The dashed lines indicate the null hypothesis. (These conditional Q-Q plots represent Supplementary Figure 1 in paper II.)

MiXeR

We applied the statistical tool MiXeR to estimate the total number of shared and unique trait-influencing variants (i.e., variants with 'pure genetic effects' not induced by LD) using GWAS summary statistics (302). This tool quantifies polygenic overlap irrespective of genetic correlation between phenotypes. The MiXeR results are presented as Venn diagrams of shared and unique variants (302). We assessed the model fit, i.e., the ability of the MiXeR model to predict the actual GWAS data, by inspecting a) modelled vs. actual conditional Q-Q plots, b) negative log-likelihood plots and c) calculating Akaike information criterion (AIC) (302). The conditional Q-Q plots illustrates optimal model fit by the model-based curves closely following the actual Q-Q curves. Support for the MiXeR model is a clearly defined minimum on the negative log-likelihood curve, as quantified by AIC criteria. A positive value of AIC provides support for the MiXeR model of polygenic overlap and suggests that the GWAS summary data has enough power to distinguish the estimated polygenic overlap, as shown in the MiXeR Venn diagrams, from the constrained models with minimal (π_{12}^{min}) and maximum (π_{12}^{max}) polygenic overlap (302). MiXeR is described further in the Supplementary Methods of paper II and III and by Frei et al. (302). We applied MiXeR for phenotypes that demonstrated most significant genetic overlap in conditional Q–Q plots (i.e., loneliness and SMDs and BMI in study II; BD and SBP, DBP, BMI and CAD in study III).

Conditional and conjunctional false discovery rate

The condFDR approach was used to identify specific genetic variants associated with SMDs, loneliness and CVD phenotypes (303). The method builds on an empirical Bayesian statistical framework and controls for the proportion of discoveries that are falsely rejected across all tests (131, 303, 343). CondFDR combines GWAS summary data from a trait of interest with data from a conditional trait, thereby increasing the power to discover significant SNPs that did not reach genome-wide significance in traditional GWASs. The condFDR approach re-ranks the test-statistics of a primary phenotype (e.g., loneliness) based on a conditional variable, i.e., the strength of the association with a secondary phenotype (e.g. SCZ) (131, 303). Next, we identified loci jointly associated with two phenotypes (e.g., both loneliness and SCZ) using the conjFDR approach. ConjFDR is defined as the maximum of two condFDR values, providing a conservative estimate of the FDR for a SNP association with both phenotypes (131, 303). In line with previous publications (262, 344-346), we used the standard thresholds condFDR<0.01 and conjFDR<0.05. In study III, we extended conjFDR to investigate overlap between three

sets of phenotypes, including loneliness, BMI and each SMD (trio conjFDR). Analyses were performed after excluding the major histocompatibility complex (MHC) and 8p23.1 regions because their intricate LD patterns may bias estimation (303). Furthermore, p-values were corrected for inflation using a genomic inflation control procedure (131). For details, see Supplementary Methods in paper II and III and method reviews (135, 303, 347).

Genomic loci definition

We defined the independent genomic loci according to FUMA, an online tool for functional mapping of genetic variants (http://fuma.ctglab.nl/)(348). *Independent significant SNPs* were defined as SNPs with condFDR<0.01 or conjFDR<0.05 and independent from each other at LD r^2<0.6. A subset of these SNPs that are in approximate linage equilibrium with each other at $r^2 < 0.1$ are defined as *lead SNPs*. *Distinct genomic loci* were identified by merging any physically overlapping lead SNPs (LD blocks <250 kb apart), and a SNP with the lowest p-value was selected as a lead SNP of the merged locus. The borders of the genomic loci were defined by identifying all SNPs in LD ($r^2 \geqq 0.6$) with one of the independent significant SNPs in the locus (348). The region with all these *candidate SNPs* is considered to be a distinct genomic locus.

Effect directions and genetic correlations

We evaluated the directional effects of the shared lead SNPs between the phenotypes by comparing their *z*-scores and odds ratios from the original publications (136-138, 157, 323-331). Genetic correlations were estimated using cross-trait LDSR, which quantifies the correlation coefficient of additive genetic effects for two phenotypes (e.g., SCZ and loneliness) using GWAS summary statistics (349).

Functional annotation

We used FUMA (348) to functionally annotate candidate SNPs in the genomic loci with a condFDR/conjFDR value<0.10 and an LD $r^2 \geqq 0.6$ with one of the independent significant SNPs. SNPs were annotated using three different tools, including Combined Annotation Dependent Depletion (CADD) (350), which predicts the deleteriousness of SNPs on protein structure/function; RegulomeDB (351), which predicts regulatory functions; and chromatin states that indicate the transcription/regulation effects at the SNP locus (277, 352). We also identified previously reported GWAS associations in the GWAS catalog (353) overlapping with

the identified loci. In addition, FUMA was used to map lead and candidate SNPs to genes and evaluate whether the genes were overrepresented in gene-sets associated with certain biological processes (348). In study III we also investigated whether the mapped genes were overrepresented in particular biological pathways using ConsensusPathDB (354). Analyses were corrected for multiple comparisons. For details, see Supplementary Methods of paper II and III.

8 SUMMARY OF RESULTS

Study I

The aim of the study was to compare CVD risk levels in patients with SCZ and BD recruited from 2002-2005 (2005 sample, n=270) with patients included in the time period 2006-2017 (2017 sample, n=1011) from the same geographical area in Oslo. We adjusted for differences in age, duration of illness and psychopharmacological treatment between samples using ANCOVA and logistic regression. The 2017 sample was also compared with healthy controls (n=922) and the general population (range=1285–4587, Statistics Norway) from the same area and time period. We found that patients with SCZ and BD in the 2017 sample have significantly higher levels of CVD risk factors compared to healthy controls and the general population. The analyses demonstrated no significant difference in CVD risk levels in SCZ between the 2005 and 2017 sample except for a small increase in FPG. Patients with BD in the 2017 sample had small to moderate reductions in the levels of TC, LDL-C, BP, hypertension and obesity, compared to the 2005 sample. There was no significant difference in self-reported diet and physical activity between the 2005 and 2016 samples. In conclusion, the results suggest no reduction in CVD risk in patients with SCZ and modest improvement in BD during the past decade despite several national health promotion efforts and increased clinical awareness.

Study II

The purpose of the study was to investigate overlapping genetic architecture and identify specific genetic loci shared between loneliness, SMDs and CVD phenotypes. We used the MiXeR and cond/conjFDR methods to analyse summary statistics from large GWASs of SCZ (n=82 315), BD (n=51 710), MD (n=450 619), loneliness (n=452 302) and CVD phenotypes (n=159 208 –795 640). We discovered substantial genetic overlap between loneliness, SMDs and BMI using MiXeR. Based on conjFDR <0.05, we identified 149 loci jointly associated with loneliness and SMDs (MD n=67, SCZ n=54 and BD n=28), and 55 distinct loci associated with both loneliness and CVD phenotypes, mainly BMI. Of the identified shared loci, 153 are novel loneliness loci. We also revealed genetic loci jointly associated with loneliness, SMDs and BMI. Most of the shared variants had consistent effect directions, in line with the estimated positive genetic correlations. Functional analyses indicated that the overlapping loci are linked to brain-expressed genes and involved in neuronal, metabolic and chromatin processes and the immune system. In conclusion, the study provides new insights into the shared genetic

architecture of loneliness, SMDs and CVD risk, indicating that common genetic variants may contribute to the observed clinical associations.

Study III

The aim of the study was to examine shared genetic architecture and detect specific genetic loci jointly associated with BD and CVD phenotypes, including CVD risk factors and CAD. We analysed recent large GWASs of BD (n=51 710) and CVD phenotypes (n=159 208–795 640) using MiXeR and cond/conjFDR. MiXeR indicated considerable polygenic overlap, estimating that most (82%) of the genetic variants underlying BD also influence BMI, while a smaller yet relevant fraction was estimated to also influence SBP/DBP (20-22%) and CAD (11%). Further, using conjFDR<0.05, we detected 129 shared loci between BD and CVD phenotypes, mostly BMI (n=69) (262), SBP (n=53) and DBP (n=53). Of the shared loci, 22 are novel BD loci. There was a pattern of mixed effect directions of the shared loci between BD and CVD phenotypes, in line with insignificant genetic correlations. Functional analyses implicated that the shared loci are linked to genes expressed in the brain and involved in neurodevelopment, lipid metabolism, chromatin and intracellular processes. In summary, the study discovered substantial genetic overlap between BD and CVD phenotypes, revealing common genetic mechanisms. The mixture of directional effects of the shared loci underlines the importance of environmental factors for the CVD comorbidity and suggests variation in genetic propensity to CVD across subsets of patients, possibly contributing to the observed variation in CVD risk among individuals with BD.

9 DISCUSSION

9.1 Main findings

By analysing large samples with a variety of methods, we elucidated the comorbidity between CVD and SMDs in three studies. First, we found significantly higher levels of CVD risk factors and limited improvement in CVD risk levels during the past decade in patients with SMDs compared to the general population and healthy controls. Second, we discovered polygenic overlap between loneliness, SMDs and CVD phenotypes. The analyses demonstrated that loneliness shares multiple genetic loci with SMDs and CVD phenotypes with mostly consistent allelic effect directions, in line with the estimated positive genetic correlations. Third, we identified several overlapping genetic loci with mixed effect directions in BD and CVD phenotypes, in agreement with the non-significant genetic correlations. Below, these findings are discussed in light of previous studies, methodical strengths and limitations, followed by a discussion of clinical implications and future directions.

9.2 Discussion of results

9.2.1 Limited improvement in CVD risk in SCZ and BD during the past decade

Study I suggests that the CVD risk levels have remained high in patients with SCZ and BD during the past decade, after correcting for age, duration of illness and pharmacological treatment. This is the first examination of temporal trends in CVD risk levels in SMDs from the same catchment area and, therefore, prior studies for direct comparison are lacking. Still, the current results agree with recent reports of raised levels of CVD risk factors, including FPG, BMI, wait circumference, dyslipidemia, hypertension and smoking in SMDs (215, 355-361). We also identified a higher prevalence of MetS, overweight, obesity and T2D in patients than in healthy controls and the general population, although the level of these risk factors were somewhat lower compared those reported in other studies (360, 362, 363). This variation in estimates across studies can be related to differences in sample composition, such as younger patients and shorter duration of illness and medication in the current study. Our findings are consistent with other studies of patients with lower age and shorter illness and treatment duration (364-367).

Subsequent studies confirm that the elevated CVD risk in individuals with SMDs is stable (368, 369). A national registry study of nearly 6 million individuals residing in Denmark from 2000 through 2016 found higher risk of most somatic diseases, including CVD, among individuals with SMDs compared to the general population (369). In the same cohort study, the life expectancy of people with SCZ remained unchanged while the life expectancy of individuals with affective disorders (grouped together, including BD and MDD) was slightly increased during the past decades (370, 371). Notably, the mortality owing to CVD and other somatic diseases increased in both diagnostic groups, while the mortality related to suicide and accidents (external causes) decreased over the 20 year-period (370, 371). Thus, a decrease in external causes of death - not a decline in CVD mortality - was responsible for the modest improvements in life expectancy in BD and MDD. Similarly, recent studies indicate that the level of CVD risk factors has remained high in MDD (372, 373). Altogether, the evidence suggests that patients with SMDs still lag behind the general population in cardiovascular health and life expectancy.

The current finding of limited reduction in CVD risk factors in SMDs differs from the development observed in the general population of Norway with decreased CVD risk and healthier lifestyle, including reduced daily smoking, increased physical activity and positive dietary changes (e.g., less sugar and more fruits and vegetables) (305, 374-376). Still, there is considerable room for improvement, and social inequalities in CVD risk and mortality are evident (377), as reflected by a greater decline in CVD risk and mortality in those with higher education (378). Possible explanations for the overall decrease in CVD risk in the general public include stricter tobacco legislation, such as a smoke-free policy in public buildings implemented in 2004, followed by multiple health campaigns, and smoking cessation programs (202, 203). More recently, food labels have been launched to facilitate healthier food choices (379, 380). For instance, the ‘Keyhole’ symbol was introduced in 2009 to help select food alternatives with less salt, sugar and saturated fat and more dietary fiber (380). However, the Keyhole label has not existed long enough to be considered an important factor behind the decline in CVD in the general population.

The public health initiatives described above seem to have been ineffective in SMDs, as suggested by high CVD risk levels and no improvement in lifestyle factors in our patient sample during the past decade. It is a public health concern that the level of CVD risk factors has remained fairly unchanged in people with SMDs in Norway, a high-income country with one of the top-ranked health care systems in the world (381). The limited CVD improvement in

these patients can partly be due to barriers for maintaining lifestyle changes in SMDs, such as reduced motivation and other affective or negative symptoms, substance use, impaired cognitive functioning, adverse side-effects of medication (i.e., drowsiness and fatigue) and socioeconomic issues (i.e., financial challenges and unemployment) (382, 383). In addition, loneliness and limited social support are possible contributing factors to the continuing high CVD risk levels in SMDs (103, 216). These challenges experienced particularly by individuals with SMDs, are difficult to change through public health initiatives.

Health care disparities can also help explain the sparse reductions in CVD risk in SMDs. Medical advances have emerged during past decades, such as improvements in hypertension treatment and control and increased use of statins in the general population (204, 205), probably contributing to the decline in hypertension and dyslipidemia (378). Studies of SMDs suggest inadequate treatment of hypertension, dyslipidemia and other metabolic disturbances (278). Many individuals with SMDs appear to be reluctant to seek somatic care (e.g., due to symptoms of the SMDs and stigma), experience difficulties communicating physical concerns and have poorer compliance with treatment (276, 277). In addition, stigma is widespread in SMDs and may act as an obstacle to access somatic care (384). Thus, medical conditions often remain undetected and undertreated in individuals with SMDs (278). Patients with SCZ may face greater barriers to somatic care and the benefits from health campaigns than patients with BD, possibly due to poorer motivation (385), cognitive function (83) and higher rate of antipsychotic medication with adverse side-effects (215). Such differences may, at least partly, explain why only the BD group demonstrated modest improvements in CVD risk in our sample.

Further, the limited CVD risk reductions may be related to a genetic propensity to CVD, as indicated by metabolic disturbances in drug-naïve patients and first-degree relatives (243, 250, 254, 255). However, recent GWASs do not provide clear evidence for a genetic susceptibility to CVD in SCZ and BD on a group level. Although overlapping loci between SCZ and CVD risk factors are discovered, their allelic effect directions are mixed (131, 239). Findings that occurred during the work with this thesis, implicate overlapping loci between SCZ and BMI with mostly opposite effect directions, in line with the estimated negative genetic correlation (262). BD was recently found to exhibit a more complex genetic relationship with BMI, as illustrated by shared genetic variants with a mixture of effect directions (262). Our results in study III corroborates these previous findings, suggesting common genetic variants with bidirectional effects in BD and multiple CVD phenotypes (elaborated below). Taken together, the GWAS results suggest that SCZ and BD are not associated with increased genetic

risk of CVD on average, and underscore the importance of environmental factors (e.g., lifestyle, psychotropic drugs) in explaining the CVD comorbidity. However, there may be subgroups of patients with a genetic liability to CVD, which are more prone to metabolic side-effects of medication and less likely to benefit from current prevention programs (386, 387). These unanswered questions deserver further research and are discussed in more detail under section 9.4.

In the last two decades, the mental health care sector has become increasingly aware of the CVD comorbidity, as reflected in updated clinical guidelines (179, 388) and improved education (389). In 2004, guidelines that emphasize the importance of cardiometabolic monitoring were introduced (390, 391). In particular, the guidelines stress the risk of cardiometabolic side-effects of SGAs and underscore the importance of baseline screening and regular metabolic monitoring in order to reduce the risk of developing diabetes, obesity and other CVD-related morbidity in SMDs (390, 391). The guidelines recommend that psychiatrists and other mental health care personnel assume a central role in the physical health monitoring, provide nutritional and physical activity counseling and refer to somatic health care professionals when required (390, 391). Norway followed up with similar guidelines and instigated educational activities to improve monitoring of CVD risk factors in SMDs (179). However, evidence suggests that the guidelines are difficult to implement in clinical practice (392), partly due to limited time or resources, little authoritative support, clinician's concerns over the quality of the guidelines and lack of ownership (393-395). In addition, severe psychiatric symptoms may attract greater clinical attention than metabolic screening (276). Our finding of limited improvement in CVD risk in SMDs during the past decade may reflect the gap between clinical practice and guidelines, indicating that CVD prevention in the health care system remains insufficient for SMDs, especially SCZ. The barriers to follow the guidelines represent important hinders to optimize health care to SMDs. The division of mental health clinics and somatic departments is another obstacle to provide better physical health care. Primary care and mental health care personnel have expressed confusion about who is responsible for the metabolic monitoring and treatment of metabolic conditions in patients with SMDs (393, 396). Thus, there is an urgent need for better collaboration and clarification of responsibilities between health care services.

In study I, the modest reductions in CVD risk were mainly observed in *female* patients with BD. Research has increasingly focused on sex differences in side-effects of psychotropic medication, (397, 398), indicating a greater propensity to cardiometabolic-side effects in

women (399). Clinicians may have begun to take these sex differences more into account in the medical treatment of BD. We found a trend (p=0.08) towards reduced use of the medications associated with most severe metabolic side-effects, including clozapine and olanzapine, only in female patients with BD during the last decade. However, this finding is preliminary and further studies are needed to determine if there truly are changes in drug prescription practice.

We discovered a higher level of CVD risk factors in patients with SCZ than in patients with BD. There was no difference in smoking between the two diagnostic groups, but the SCZ group reported lower physical activity levels and a less healthy dietary pattern than the BD group (details are provided in the Supplementary Material of paper I). These differences in lifestyle factors were small, yet may have influenced the variations in CVD risk factors between SCZ and BD. Other factors that may have contributed to the finding of higher CVD risk levels in SCZ include more frequent use of antipsychotic medication with adverse-side effects, higher symptom level and lower functioning level. After adjusting for these three clinical variables, several differences in CVD risk factors disappeared, whereas some risk factors (i.e., LDL-C, BP, obesity and waist circumference) were still greater in the SCZ group. Some recent studies also indicate higher CVD risk levels in SCZ compared to BD (400-402), while other studies provide inconsistent results, with similar level of MetS and higher rates of smoking and central obesity in SCZ (361), but lower lipid levels (357, 361). The inconsistent results highlight the need for further studies to determine whether CVD risk varies across diagnostic groups and, if so, why that is. We did not find statistically significant differences in CVD risk across BD subtypes, possibly related to underpowered subsamples.

Lastly, the current study found that the relative CVD risk increase is greater in younger patients with SCZ and BD (below 50 years) than in older patients, when compared to the general population. The same pattern is observed in other studies (403), and mortality from CVD occurs at an earlier age in individuals with SMDs compared to the general population (404, 405). Taken together, these results underscore the importance of earlier detection and prevention to reduce the burden of CVD comorbidity.

9.2.2 Polygenic overlap between loneliness, SMDs and CVD risk

In study II, we demonstrated substantial genetic overlap between loneliness, SMDs and CVD phenotypes. Using MiXeR, we found that a considerable proportion of the genetic architecture of loneliness also underlies SMDs and BMI. Still, larger GWASs are necessary to obtain more reliable MiXeR estimates for genetic overlap between loneliness and MD and BMI. Applying

conjFDR, we identified multiple loci shared with mostly consistent effect directions in loneliness and MD (96%) and SCZ (74%). These results are in line with the positive genetic correlations estimated in the current and other studies (157, 158, 406, 407). Further, many of the loci shared between BD and loneliness had mixed effect directions, with some genetic variants associated with increased risk of both BD and loneliness (62%), while the rest of the variants demonstrated opposite effect directions in BD and loneliness. The mixture of directional effects complies with the non-significant genetic correlation between BD and loneliness found in the present study and previous studies (157, 408). Further, we demonstrated polygenic overlap between loneliness and CVD risk factors, especially BMI, and CAD. The shared loci possessed mostly concordant effect directions (~70%), consistent with the positive genetic correlations (157, 408, 409). Altogether, the current findings corroborate and expand on prior evidence (157, 158, 406-409) by uncovering shared genetic architecture and specific loci between loneliness, SMDs and CVD risk.

The current results provide new insights into the genetic relationship between loneliness and SMDs and may suggest that the clinical association is partly explained by a common genetic basis. Thus, a genetic susceptibility to loneliness may also confer increased risk of SMDs, especially MD. Possible pathways linking loneliness to SMDs are illustrated in Figure 7. A genetic susceptibility to loneliness can involve a propensity to experience emotional pain

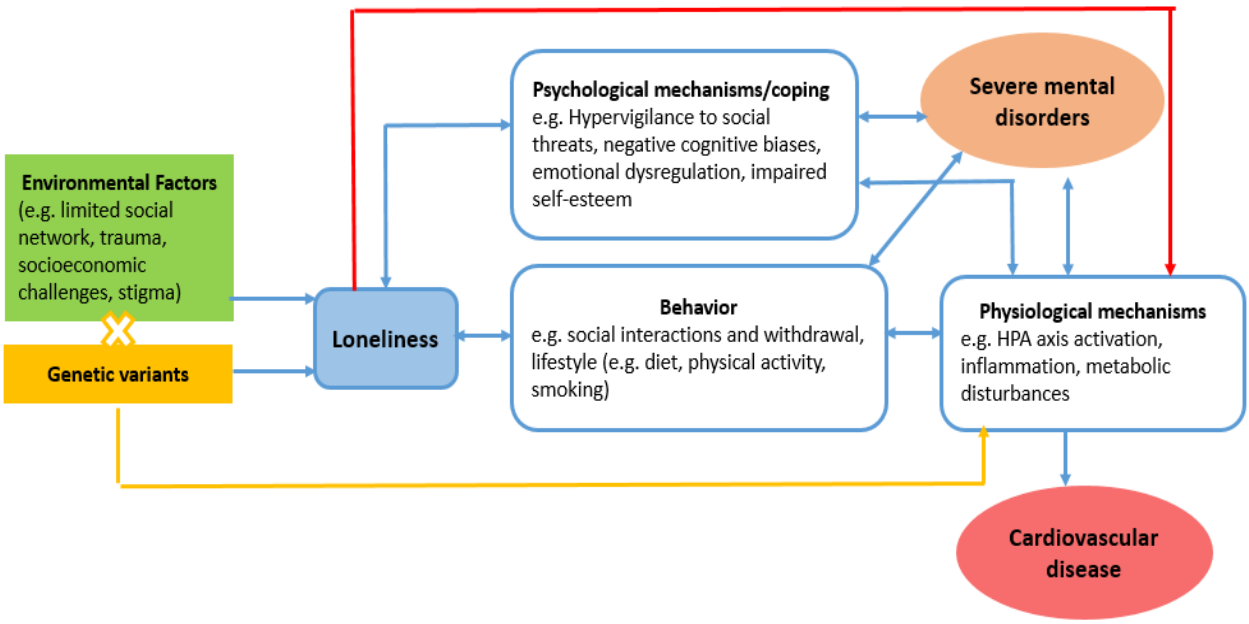

Figure 7. Possible pathways linking loneliness to SMDs and CVD. Environmental factors and shared genetic variants can affect the propensity to experience loneliness and develop SMDs and CVD through psychological, behavioural and physiological pathways. Bidirectional relationships are possible (as indicated by the arrows).

or distress in response to social isolation (410). The experience of loneliness elicits a hypervigilance for social threats, which may introduce negative cognitive biases (410). In particular, evidence indicates that lonely people attend more to negative social events, and anticipate and perceive social situations as more threatening (e.g., worry that others will ignore or reject them) than people who do not report feeling lonely (101, 151). In addition, lonely individuals have a tendency to adopt negative views of themselves (e.g., lower self-esteem) and blame themselves for failure and social exclusion (101, 411). These characteristics of loneliness resemble those of MD and, thus, the genetic overlap between loneliness and MD may reflect a genetic predisposition to negative cognitive biases. The cognitive biases may harm social interactions by influencing behaviour (e.g., exhibit less interest and trust), which may discourage others from seeking contact and, thus, exacerbate the isolation and elicit depressive symptoms (100, 410). In addition, loneliness is associated with difficulties regulating emotions (288), including diminished ability to down-regulate negative emotions, similar to what is seen in MD (412). Accordingly, the finding of polygenic overlap between loneliness and MD may indicate a genetic predisposition to cognitive biases, emotional dysregulation and maladaptive behavior patterns (Figure 7).

Further, we observed genetic overlap between loneliness and SCZ. As mentioned above, loneliness is associated with a heightened sensitivity to social threats, which can increase the feeling of insecurity (410). We may speculate that negative social expectations can increase the risk of paranoid thinking and, thereby, the propensity to develop a psychotic disorders. Accordingly, a genetic overlap between SCZ and loneliness may indicate shared genetic variants influencing the tendency to perceive the social world as unsafe, contributing to social isolation, thereby increasing the risk for both loneliness and psychotic disorders. Increasing evidence suggests a positive association between loneliness and psychotic symptoms, especially positive psychotic experiences involving paranoia (118, 119). Loneliness and negative symptoms are also correlated according to a recent meta-analysis (119). It is possible that some negative symptoms, such as amotivation and social withdrawal, may lead to social impairments and thereby contribute to loneliness (108, 119). However, other negative symptoms, such as lack of social interest, may involve a reduced need for social contact and thus be less associated with loneliness. Future investigations should assess the relationship between loneliness and different types of negative symptoms.

The genetic overlap between loneliness and BD may reflect some of the same processes as those proposed to underlie the genetic link between loneliness and MD and SCZ. BD is

associated with affective fluctuations, usually with more time spend in depression than in manic or hypomanic episodes (53, 413). Thus, it may be that depressive episodes as part of BD drive some of the observed genetic overlap between BD and loneliness. This hypothesis is consistent with recent findings suggesting that the genetic variants responsible for the overlap between loneliness and BD are largely involved in MD as well (409). We also speculate that individuals with BD who experience psychotic symptoms such as paranoia are more prone to social withdrawal and loneliness. In addition, uncritical social behaviour in a manic episode can impair social interactions and possibly contribute to loneliness. However, individuals who are more socially active in manic/hypomanic episodes may also feel less lonely. Importantly, research on loneliness across manic/hypomanic episodes in BD is scare and have so far provided inconsistent results (115). There is a need for investigation of loneliness across affective episodes and long-term clinical course to help identify underlying mechanisms. There may be heterogeneity in loneliness across BD subgroups, which would be consistent with the current finding of shared loci with mixed effect direction in BD and loneliness.

Using conjFDR, we discovered that loneliness shares a higher number of genetic loci with MD than with SCZ and BD. The finding of greatest genetic overlap with MD is consistent with clinical findings of a higher level of loneliness in MDD compared to SCZ and BD (108), although further studies comparing loneliness across different SMDs are necessary. More genetic overlap with MD than with SCZ and BD is also in agreement with reports of more robust associations between loneliness and depressive symptoms than between loneliness and psychotic, manic and hypomanic symptoms (93, 105, 118, 152, 414). Moreover, loneliness involves cognitive-affective features that seem particularly prominent in MD, as described above. Thus, some of the genetic overlap between loneliness and MD may be due to loneliness being an aspect of the phenomenology of MD. Nevertheless, there are conceptual and empirical distinctions between the loneliness and MD (100, 410, 414): while loneliness is a negative feeling arising when social relationships are perceived to be inadequate, depression is a diagnosis involving a more general dysphoric state. Factor analyses indicate that loneliness and depressive symptoms are related, yet separable (410). In addition, longitudinal data indicates that loneliness predicts increased depressive symptomatology above and beyond initial depressive symptoms (152, 414), indicating that the two constructs are associated, yet distinct. Further support for the distinction between loneliness and depression comes from a loneliness GWAS (157) demonstrating that the loneliness loci remained significant after excluding people with self-reported depression from the data set.

Further, by using conjFDR we discovered several shared loci between loneliness and CVD phenotypes. The majority of the shared SNPs had the same effect directions, in line with positive genetic correlations identified between loneliness and CVD risk factors and CAD. These findings corroborate previous genetic (157, 408) and clinical evidence of associations (102, 282, 283). Moreover, a recent study investigated the genetic association between loneliness and CAD using polygenic risk scores (PGRS), which estimates the overall genetic propensity to develop a given disease or trait, summarizing the effects of multiple risk alleles based on GWAS data (407). The study indicated that a genetic liability to loneliness was associated with increased risk for CAD. In particular, the analyses revealed that patients with a PGRS in the highest decile for loneliness have 50% greater risk of CAD compared to patients with scores in the lowest decile (407). Taken together, these results imply that a genetic susceptibility to loneliness is related to increased CVD risk (157, 407, 408). Multiple potential mechanisms may contribute to the link between loneliness and CVD risk (100), as illustrated in Figure 7. In particular, loneliness has been linked to activation of the HPA axis, increased sympathetic nervous system activation and inflammation (100, 286), which are implicated in the development of CVD (263). Loneliness may also have indirect effects on CVD through lifestyle, psychological coping and mental illness (100, 283). Our findings point to shared genetic architecture between loneliness and CVD phenotypes as one possible explanation for increased CVD risk associated with loneliness. It is unknown whether the genetic overlap reflects shared genetic variants influencing physiological factors directly e.g., HPA axis activation, inflammation) and/or indirectly through mechanisms such as lifestyle behavior, psychological coping and mental illness.

In the current study, we observed a positive genetic correlation between loneliness and tobacco smoking (cigarettes smoked per day) (rg=0.25), similar to previous findings (157, 408). However, no significant shared loci between loneliness and smoking were identified using conjFDR. The lack of significant overlapping loci is probably related to smoking GWAS power and heterogeneity or imprecision in phenotypic assessment (e.g., average or maximum number of cigarettes smoked per day) (415). Larger GWAS samples are likely to detect significant overlapping loci. The finding of a significant genetic correlation between loneliness and smoking indicates that some of the genetic variants predisposing to feeling lonely can also influence the inclination to smoke. Taken together with smoking GWAS findings (299, 415, 416), the current results illustrate the concept of genetic influence on environmental risk (e.g., smoking) for CVD.

We also used conjFDR to investigate loci jointly associated with loneliness, SMDs and BMI (three phenotypes), as loneliness demonstrated most genetic overlap between these phenotypes in conditional Q-Q plots. The analysis identified ten loci shared between both loneliness, BMI and MD (n=4), SCZ (n=5), and BD (n=1), with a majority of consistent effect directions. Whether this genetic overlap extends to other CVD risk factors, is unknown. Thus, future research is necessary to investigate whether the genetic overlap between loneliness and SMDs contributes to CVD comorbidity.

Gene-set analyses of the shared loci between loneliness and SMDs implicated genes involved in chromatin processes and brain functions, including synapses and dendrites.
The gene-set analyses of loneliness loci shared with SMDs and BMI also indicated genes related to metabolic mechanisms and immune system, which have been implicated in the pathophysiology of SMDs and CVD morbidity (252, 268). Gene-mapping of shared variants between loneliness and SMDs and CVD risk factors, indicated genes expressed in the brain. Thus, these results indicate the importance of brain-expressed genes in the shared genetic basis of SMDs, loneliness and CVD. These findings are consistent with brain dysfunction implicated in the pathophysiology of SMDs, and GWAS findings indicating neuronal genes involved in SMDs (136-138), loneliness (157, 408) and obesity (329). Thus, it seems likely that shared genetic variants, along with environmental factors, contribute to brain dysfunction that influences different mental (e.g., cognitive bias, emotional regulation) and behavioral (e.g., lifestyle, social withdrawal) tendencies that contribute to the development of both loneliness, SMDs and CVD. Other pathways are also possible; for example, shared genetic variants can influence metabolic mechanisms which increase the risk of overweight, which can impair self-esteem and contribute to development of loneliness and SMDs. Notably, the proposed pathways should be considered *preliminary*. Experimental investigations are necessary to determine the true causal variants underlying the shared genetic associations and clarify how the identified variants influence brain, metabolic and immune system development and function (for further information, see ‘Future directions’).

9.2.3 Bidirectional genetic overlap between BD and CVD risk

In study III, we discovered polygenic overlap between BD and CVD phenotypes. MiXeR estimated that most of the genetic variants underlying BD influences BMI (~82%), while a smaller, yet relevant proportion also underlies the genetic basis of SBP/DBP (~20%). We also observed genetic overlap between BD and CAD, but the degree of overlap is uncertain and a

larger CAD GWAS is necessary to yield more reliable MiXeR estimates (see further information under 'Methodological considerations'). The finding of greater genetic overlap between BD and BMI using MiXeR can possibly be related to BMI being more polygenic than blood pressure and CAD, as shown in the Venn diagrams (Figure 1 in paper III). Further, using the cond/conjFDR approach we increased the discovery of genetic loci and identified 129 loci shared between BD and CVD phenotypes. Twenty two of these loci are novel to BD. The shared loci demonstrated a pattern of mixed effect directions. Genetic variants with inconsistent effect directions "cancel each other out" (135), yielding non-significant genetic correlations between BD and CVD risk factors and CAD. Absent genetic correlations between BD and CVD risk factors are also reported previously (159, 259). Our findings comply with mixed effect directions of shared loci between SCZ and CVD risk factors (e.g., lipids, SBP) (131), except for the overlapping loci between SCZ and BMI that mainly possess opposite effect directions (262).

The current results indicate that BD on average is neither associated with increased nor decreased genetic risk of CVD. Although there was a slight preponderance of discordant effect directions of the shared loci between BD and CVD risk factors, the majority of the shared loci between BD and CAD possessed consistent effect directions (7/10). However, the low number of SNPs identified here explains only a small proportion of the overall risk of CVD. Accordingly, the present findings indicate that common genetic variants do not explain the increased CVD risk in BD. However, there may be other genetic factors that are not captured by current GWASs, including rare variants, which contribute to the elevated CVD risk. Furthermore, central drivers of the CVD comorbidity in BD likely involve environmental factors, such as unhealthy dietary patterns, physical inactivity, smoking and adverse side-effects of psychotropic agents (187, 417). In addition, loneliness can play a role (103, 216).

The mixture of effect directions of the shared loci can reflect variation in genetic propensity to CVD across BD subgroups. BD is a heterogeneous illness involving different subtypes, illness courses and severity (38) that may be differentially related to CVD comorbidity. Although the average level of CVD risk is higher in BD compared to the general population, the CVD comorbidity seems to be restricted to BD subgroups, as indicated by prevalence estimates for overweight (~50-75%), dyslipidemia (~25-40%), T2D (~5-20%) and hypertension (~35-60%) in BD (82, 261, 308). Our findings in study I also indicate that the elevated CVD risk is restricted to subsets of patients with BD (see for instance numbers for overweight (~50%), dyslipidemia (~25%), and hypertension (~30%)). These estimates can

indicate subgroups of patients with different susceptibility to CVD. For instance, patients with more depressive symptoms may constitute such a subgroup, as several studies suggest that increased depressive symptoms, rather than mania, are associated with higher level of obesity, dyslipidemia, blood pressure and T2D (418-424). Still, a study found that a history of manic or hypomanic episode was the main predictor of CVD (425). However, this study consisted of only 129 patients (425), and several studies emphasize the link between depressive symptoms and greater CVD risk in BD (418-424). Nevertheless, the relationship is complex, as depression can take different forms, with atypical or melancholic features, involving decreased appetite and weight loss and increased appetite and weight gain, respectively (19). Thus, some patients lose weight, while other patients gain weight during a depressive episode, while most patients experience weight loss during a manic episode (426). The mixture of effect directions of the shared variants between BD and BMI (262) are in line with the clinical variation in weight changes across affective episodes of BD. Furthermore, recent findings indicate a genetic susceptibility to weight gain in MD (262). BD type II is genetically correlated with MD (138) and, thus, this subtype of BD may also involve increased genetic susceptibility to weight gain. By contrast, BD type I demonstrates more genetic overlap with SCZ (138), which is found to be associated with reduced genetic risk of weight gain (262). Thus, BD type I may involve a decreased genetic risk of weight gain. Identifying potential subgroups with different genetic risk to CVD can increase the understanding of CVD comorbidity in BD and help improve risk prediction and prevention. We did not investigate these potential variations in CVD comorbidity across BD subtypes as this requires larger GWAS samples of clinical subtypes.

Functional analyses of the loci shared between BD and CVD implicated biological processes and pathways associated with neurodevelopment, lipid metabolism, hormones, chromatin and intracellular processes. Gene-mapping of the shared variants indicated genes expressed in the brain. These findings are in line with brain dysfunction implicated in the pathophysiology of BD (120) and more recently linked to shared genetic variants between BD and BMI (258, 262). Moreover, lipid biology may be involved in the pathogenesis of BD, as proposed for SCZ (346), consistent with observations of white-matter abnormalities and myelin dysfunction in these disorders (427, 428). Furthermore, functional analyses of the shared loci between BD and SBP suggested genes involved in stress-related pathways, including cortisol synthesis and secretion. Similarly, recent findings indicate overlapping genetic variants between BD and CVD risk factors that are associated with processes involved in HPA axis regulation, including corticotrophin-releasing hormone (258, 262). Shared genetic variants

associated with the HPA axis appear plausible given evidence of HPA axis dysregulation in BD (163), obesity and hypertension (264).

Taken together, the current findings indicate that brain-related mechanisms may play a role in CVD comorbidity in BD. The results can be interpreted within the conceptual framework proposed earlier: It is possible that shared genetic variants, together with environmental factors, influence brain function that affects mental processes (e.g., affective symptoms) and behavior (e.g., lifestyle) and, thereby, the development of BD and comorbid CVD. In addition, there may be shared variants between BD and CVD morbidity that influence metabolic processes (258, 262) which affect CVD risk and brain function, contributing to development of BD. However, separate pathways underlying BD and CVD are also likely given the mixed effect directions of the shared loci. It is important to note that the pathways proposed here should be considered *preliminary*, and further studies are needed to detect the causal variants underlying the shared associations, and to determine how the genetic variants influence BD and CVD morbidity (see below).

9.2 Methodological considerations

9.2.4 Samples, assessment methods and study design

TOP study

Strengths of study I include the large and well-characterized sample of SCZ and BD recruited from in- and outpatient clinics in Oslo. All participants underwent comprehensive clinical assessments performed by trained physicians/psychologists. The diagnostic evaluations have good agreement, and the inter-rater reliability of symptom scores underscores the quality of the assessments (429, 430). The assessment methods have remained consistent throughout the study period, and the 2005 and 2017 samples were recruited from the same catchment area, yielding samples that are suitable for comparison.

Furthermore, the TOP sample is considered fairly representative of the target population. The Norway health care system is publicly funded and based on catchment areas, which reduces the likelihood of sociodemographic differences influencing the recruitment. Nevertheless, the most severely affected patients may not be included because they cannot give informed consent or are unable to undergo a thorough assessment that requires attention and effort over several hours. However, the patients were considered for inclusion after an *acute* phase of psychosis or affective symptoms had settled and they had entered a more stable phase.

Patients at the opposite end with high functioning may decline participation because they are occupied with employment or other obligations. Thus, the TOP sample may not include the patients with the highest and lowest functional levels. In addition, the TOP sample mainly consists of Caucasian participants and further investigations of non-Caucasian and multi-ethnic samples are warranted.

Further strengths of study I include over 900 healthy controls recruited by random selection from statistical records within the same period and catchment area as patients. It has, however, been argued that the controls may be particularly healthy, possibly involving a subset of the population that is more health conscious than nonparticipants. By comparing results that we obtained from the general population (Statistics Norway), smoking and overweight/obesity appeared to be less prevalent in the healthy TOP controls. Thus, the CVD risk levels in the control group may represent an underestimation of the risk levels in the population at large. Nevertheless, the patients demonstrated significantly higher levels of smoking and overweight/obesity compared to both the general population and healthy controls.

The cross-sectional design of study I prevents us from drawing causal inferences, and we cannot rule out that the observed associations are influenced by confounding factors not taken into account. However, the patient sample is thoroughly investigated, both in terms of demographic, psychological, behavioural and somatic characteristics, which allowed us to adjust for some of the most likely confounders. In particular, we adjusted for difference in age and duration of illness and psychopharmacological treatment when comparing the 2005 and 2017 samples. In addition, we controlled for other covariates, including functional level, symptom levels and use of antipsychotics with adverse metabolic side effects, when comparing CVD risk factors across diagnostic groups. Furthermore, we found that substances abuse/dependence was more prevalent in patients with SCZ in the 2017 sample than in the 2005 sample (supplementary material in paper I), but this difference did not influence the results. We did not, however, have data on loneliness in the TOP sample, and we were thus prevented from assessing the prevalence of loneliness in these patients with SCZ and BD and how loneliness is related to their CVD risk. We had data on some variables associated with loneliness, including whether the patients were married/cohabiting, which did not differ between the 2005 and 2017 samples. Another limitation is that we used crude self-reported measures of lifestyle (e.g., self-reported number of hours of physical activity per week; self-reported diet). Although investigating loneliness and lifestyle behaviour was not the aim of study I, data on loneliness

and more precise lifestyle measures would have been useful to elucidate factors associated with CVD risk.

Furthermore, it is a limitation that the study periods of the 2005 and 2017 samples are close, which may reduce the chance of detecting significant differences between the samples. Therefore, we performed supplementary analyses comparing the 2005 sample with a sample from 2014-2017, which mainly supported our original findings (details are provided in the supplementary material of paper I). Some of the reductions in BD, however, disappeared (LDL-C, hypertension, overweight and obesity), while the SCZ sample from 2014-2017 demonstrated a small reduction in low HDL-C. These results need to be replicated in larger samples to decide whether the CVD risk level has started to decrease in SCZ.

A strength of study I is the presence of data from all or the vast majority of patients (ca. 90-95%). Missingness at this level in large samples does not appear to significantly distort estimates, provided that the data is missing at random (431), which is likely to be the case in the TOP sample. Therefore, we did not impute data in patients. However, the availability of certain CVD data, including blood pressure, fasting blood samples and information on daily smoking, were restricted to a subset of healthy controls. Importantly, missing data in the controls was mainly due to a change in the study protocol. Thus, missing information was not due to participants or investigators systematically avoiding assessment owing to characteristics of the participants (431).

Finally, a limitation is that the BD 2017 sample may not have been large enough to detect statistically significant differences in CVD risk across subtypes of BD.

GWASs

In contrast to the cross-sectional design of study I, analyzing GWAS data provides an opportunity to elucidate aspects of disease etiology and genetic risk factors underlying the association between SMDs, loneliness and CVD. Furthermore, the currently analyzed GWASs were large and have undergone stringent quality control (136-138, 157, 323-331). Nevertheless, the methods used to assess the phenotypes have advantages and disadvantages. For instance, loneliness was assessed with the question “Do you often feel lonely?” (157). This item bears resemblance to a question recently recommended to use at a minimum to measure loneliness in large-scales studies (“How often do you feel lonely?”) (432), although the UK Biobank measure does not provide the opportunity to rank the frequency of loneliness. Indirect measures of loneliness are also recommended due to the stigma associated with loneliness that can make

some people hesitant to disclose that they feel lonely (95, 432). While the UK Biobank did not use any of the proposed indirect items (e.g., "How often do you feel that you lack companionship?") (95, 432), participants were asked about their ability to confide in someone close (157). Studies suggest that lonely individuals perceive themselves as less able to confide and have fewer people to confide in than non-lonely individuals (433, 434), providing support for this item as an indirect probe of loneliness. Further, to increase power, the loneliness GWAS included data on frequency of contact with family and friends and living alone (157). This information concerns objective rather than subjective social isolation. However, lonely individuals tend to have less frequent contact with friends and close relatives (98, 99) and are more likely to live alone than people who are not lonely (97). The loneliness GWAS also gives support for an association between subjective and objective aspects of social isolation on a genetic level: The genetic loci associated with perceived loneliness overlapped with those detected in the broader analysis (including perceived loneliness, ability to confide, frequency of contact and living alone) (157). Still, loneliness and objective isolation are distinct, and the loneliness assessment in the UK Biobank is limited by not using the best-validated loneliness items (95, 432).

The currently analyzed SMDs GWASs are based on different ascertainment methods. The MD GWAS included both samples with a formal diagnosis of MDD and samples with self-reported depression (137). These subsamples may involve clinically and/or genetically heterogeneous groups. However, the methods applied by these MD cohorts were thoroughly reviewed, and the comparability of the cohorts were supported (e.g., high genetic correlation between the MD samples) (137). Furthermore, a variety of methods was used to establish a diagnosis of SCZ and BD (see method description above) (136, 138), yet consistent diagnostic criteria were applied and quality control was performed to assess the diagnostic procedures. Still, genetic heterogeneity were observed among BD GWAS cohorts (138), and variation in polygenic effects were discovered between BD subtypes (i.e., BD type I vs. type II) (138). This genetic heterogeneity across BD cohorts and subtypes is consistent with our findings of mixed effect directions of shared variants between BD and loneliness, and between BD and CVD phenotypes. The complex genetic architecture and the clinical heterogeneity may contribute to the inconsistency in GWAS findings for BD (138). Still, the heterogeneity poses a challenge for GWASs and highlights the need for careful and consistent clinical assessment of patients and controls (138). In addition, there is a need for larger GWAS samples in which different clinical subtypes are more evenly represented. The BD GWAS (138) is mainly comprised of

BD type I (73%), whereas BD type II (17%) and SAB (5%) constitute a smaller proportion of the sample.

The GWASs of CVD phenotypes also include some variation in assessment methods that may be more or less precise. For instance, a BMI GWAS was based on measured or self-reported weight and height (323). In addition, the CAD GWAS (330) (used for study III) identified cases defined by self-report, hospital records or death registries. Moreover, the CAD phenotype was broad (including myocardial infarction, chronic ischemic heart disease, angina and revascularization procedure) (330). Heterogeneity may exist within this broadly defined CAD phenotype. However, there was strong concordance between GWAS signals for the broad and stricter definitions of CAD (330).

The GWAS samples of SMDs and CVD phenotypes are considered representative, while the GWAS sample of loneliness from the UK Biobank does not appear to be representative of the general population due to evidence of a "healthy volunteer bias" (333, 435). Lower levels of both mental illness and risk factors for somatic disease are reported in the UK Biobank than in the general population (333, 435). Thus, the UK Biobank is not suitable for deriving at prevalence and incidence rates (435). Nevertheless, the GWAS findings from the UK Biobank can be generalizable. Likewise, the current findings of genetic overlap between loneliness, SMDs and CVD phenotypes probably have external validity, although larger and more ethnically diverse samples are necessary to ensure that the genetic discoveries are broadly applicable. The GWAS data used in this PhD project are primarily retrieved from populations of European descent. This is a standard approach to limit the confounding effects of population stratification, defined as the presence of systematic differences in allele frequencies between subpopulations due to different ancestry (436). If not properly accounted for, population stratification can cause false positive associations or failure to detect true associations between the genotype and phenotype (436). Although analysing GWAS samples of mainly European ancestry limits this confounding effect, some degree of population stratification may still occur (e.g., not 100% homogeneous ancestral samples). Accordingly, the GWASs used in the current PhD project controlled for population stratification, and we used a genomic inflation control procedure to correct for spurious enrichments (e.g., inflated p-values) due to population stratification (131).

As noted earlier, loneliness involves cognitive-affective features that may be difficult to separate from symptoms of MD. Thus, the genetic overlap between loneliness and MD may in part be due to loneliness being an aspect of the phenomenology of MD. Nevertheless, there are

distinctions between loneliness and MD (100, 410, 414) and the loneliness GWAS indicated that the loneliness risk loci remain significant after removing depressed individuals from the analysis (157). Furthermore, both loneliness and MD are associated with personality traits, especially neuroticism (437, 438). Individuals with higher levels of neuroticism are more likely to report feeling lonely and have a higher risk for MDD (437, 438). Similarly, neuroticism is genetically correlated with loneliness and MD (157, 408). Thus, some of the genetic overlap discovered between loneliness and MD may possibly be driven by shared genetic effects with neuroticism. We did not correct for personality variation, but a recent study did (409). This study confirmed that loneliness and MD share a genetic basis and indicated that the genetic factors responsible for this overlap also influence neuroticism (409). However, the genetic overlap between loneliness and MD remained significant after correction for neuroticism (409). Thus, the genetic association between loneliness and MD cannot be fully explained by neuroticism.

9.2.5 Statistical methods and analytical tools

The statistical tests used in study I are commonly used, while the statistical tools used in study II and II are more novel and are therefore granted more attention below.

Statistical tests for investigating group differences

In study I, we used ANCOVA and logistic regression to analyze potential difference in CVD risk factors between groups (e.g., 2005 sample vs. 2017 sample; patients vs. controls) and to adjust for potential confounding factors. One of the advantages of these parametric statistical tests is that they have more power than non-parametric tests (439, 440). Thus, ANCOVA and logistic regression are more likely to detect statistically significant differences if those differences truly exist compared to non-parametric statics. However, parametric tests build on a set of assumptions about the data that restricts their use. In particular, ANCOVA assumes normality of the distribution and homogeneity of the variance across groups (441). The distribution of some CVD variables in the TOP sample was skewed, and therefore log transformation was performed in order to bring the data closer to a normal distribution. Logistic regression does not make assumptions about the distribution of the values, but is similar to ANCOVA in that this method is sensitive to high correlations between the covariates (multicollinearity), which can lead to unreliable estimates (441).

We performed multiple tests, which can increase the risk of type 1 error (i.e., false positives). To limit the likelihood of type 1 error, we used Bonferroni correction when stratifying by sex and age groups. Some might argue that Bonferroni correction should have been applied to a greater degree across tests, but since the Bonferroni method can be overly conservative (442), we used this method to control for multiple testing when considered appropriate.

Statistical tools for assessing genetic overlap

In study II and III we applied the cond/conjFDR approach and MiXeR to examine genetic overlap. Cond/conjFDR boosts power to detect significant SNPs by leveraging the combined power from two GWASs (303). MiXeR complements cond/conjFDR by quantifying the total number of shared and unique trait-influencing variants and provides an easily interpretable illustration of shared and unique genetic architecture in Venn diagrams (302). Both cond/conjFDR and MiXeR have the advantage of allowing for discovery of genetic variants irrespective of effect directions and genetic correlation between the phenotypes (135, 302, 303). Using these tools, we discovered polygenic overlap and several shared loci between BD and loneliness (study II) and between BD and CVD phenotypes (study III), despite non-significant genetic correlations. These results in particular highlight the utility of cond/conjFDR and MiXeR to uncover polygenic overlap in the absence of genetic correlations.

Standard GWASs control for multiple testing given the high number of variants tested and uses a genome-wide significance threshold of $p < 5 \times 10^{-8}$ to avoid false positive results. This approach controls for *any* single false positive result, but may be too strict and can result in failure to detect true associations (443). Cond/conjFDR provides an alternative approach by controlling for the *expected proportion* of false discoveries among the discoveries instead of guarding against any false positive result. The benefit of this method is increased power while still adjusting for false positives (303). Multiple testing is not an issue when applying MiXeR as this tools estimates the *total number* of genetic variants influencing phenotypes (i.e. it does not test each individual SNP) (302).

The cond/conjFDR approach and MiXeR have some limitations. As mentioned previously, some sets of nearby genetic variants tend to co-occur, i.e., they are in high LD with each other (336). Therefore, the finding of an association between a given SNP and a phenotype (e.g., SCZ) may be the result of this SNPs being in high LD with the true causal variant. Although we excluded intricate LD regions (MHC and 8p23.1) and selected a subset of SNPs

that are independent from each other (at $r^2 < 0.1$, i.e., lead SNPs), complex correlations among SNPs can bias the FDR estimates. Accordingly, the cond/conjFDR approach cannot detect the causal variants underlying the shared genomic associations (303). This implicates that the overlapping loci could result from both shared and separate causal variants, or mediated pleiotropy (130, 303). The latter refers to a scenario where a variant influences one trait (e.g., loneliness) through another trait (e.g., MD). Similar to the condFDR framework, the MiXeR model cannot pinpoint the causal genetic variants. However, the MiXeR bypasses the difficulty of detecting the exact localization of causal variants by aiming at estimating their overall amount (302). The actual number of variants estimated to influence the phenotypes of interest (here: SMDs, loneliness and CVD) is potentially higher as the MiXeR model clump together variants in high LD with each other (302).

Furthermore, the cond/conjFDR estimates are influenced by the GWAS power of the phenotypes. In particular, cross-trait enrichment will be more difficult to identify if one or both of the analysed GWASs are inadequately powered (303). Differences in GWAS power can contribute to the finding of greater genetic overlap between loneliness and MD than between loneliness and BD and SCZ using cond/conjFDR in study II. Similarly, the use of a larger GWASs of BMI and SBP/DBP in study III can contribute to the finding of a higher number of shared loci between BD and these CVD risk factors compared to the other CVD phenotypes.

The MiXeR model requires even larger GWAS power than the cond/conjFDR approach because MiXeR aims to estimate the total amount of genetic overlap (302). In study II, we observed uncertainty of the MiXeR estimates for loneliness, MD and BMI, suggesting that larger GWASs are needed to obtain more reliable MiXeR estimates. Study III also indicated some caution in interpreting the MiXeR estimates of polygenic overlap between BD and CAD. This may also indicate that a larger CAD GWAS is required to obtain better model fit. It can also be difficult to reliably estimate the amount of genetic overlap between BD and CAD because CAD have lower polygenicity than the CVD risk factors investigated, as illustrated by the Venn diagrams (Figure 1 in study III). Phenotypes with low polygenicity involve a smaller number of variants that can be shared with another trait compared to traits with higher polygenicity. In addition, due to the intricate biology of low polygenic phenotypes, their genetic effects are distributed in a complex way and the MiXeR model is too simplistic to capture this complexity (Oleksandr Frei, personal communication, 24.06.20).

We applied FUMA (348), an online platform for functional mapping of genetic variants. The shared SNPs were mapped to genes, and biological resources and repositories were used

to provide insight into potential biological mechanisms of the prioritized genes. However, the identified genes are not necessarily the genes by which the causal variants exert their phenotypic effect. Thus, the proposed biological functions and pathways associated with the shared variants are preliminary. Nevertheless, the FUMA findings can help generate hypotheses that are testable in experiments (348).

9.3 Clinical implications

Study I demonstrated that the level of CVD risk factors has remained high in SCZ and BD during the past decade. The findings implicate that most patients with SMDs have not benefitted from recent health promotion and disease prevention efforts. The results underscore the need for more effective prevention and targeted interventions. Routine screening and monitoring of cardiometabolic status should be better implemented, and more focus on life-style factors should be a part of the treatment of SMDs. More integrated care through closer collaboration between primary care physicians and psychiatrists and psychologists is warranted.

Study II revealed that both SMDs and CVD risk factors share considerable genetic architecture with loneliness, indicating that the clinical association may in part have genetic underpinnings. Thus, a genetic susceptibility to loneliness may also increase the risk of SMDs and CVD, and vice versa. Together with the clinical and epidemiological data discussed above, the current findings underscore that loneliness is a psychosocial factor of importance for SMDs and CVD. At present, interventions that effectively reduce loneliness in people with SMDs are limited (93, 444). Still, there is a wide range of psychosocial interventions aiming to increase social contact and support in SMDs, including group therapies, social skills training, online social interventions, peer support groups and Assertive Community Treatment (93, 445). However, these approaches have generally proven ineffective in reducing loneliness in SMDs (193, 444). Evidence-based interventions that specifically target the subjective feeling of loneliness are lacking, though promising developments have emerged (93, 193, 444). The most promising approaches involve attempts to change social thinking and appraisal. These interventions address cognitive biases and attributions styles (e.g., blaming oneself for social exclusion) in an effort to change the way individuals think about themselves and their social relationships (193, 444). Such interventions are consistent with the loneliness model proposed by Hawkley and Cacioppo (100) described in the introduction. However, targeting an individual's cognitions without considering the wider social context in which the individual lives, may have limited effect (193). Thus, the cognitive approaches to loneliness should be

considered within a broader societal context, including improving opportunities for social interactions and inclusion, education and employment (193, 444). In addition, effectively reducing loneliness in people with SMDs should address their specific barriers to social participation and meaningful relationships, such as symptoms, social anxiety, social skills and stigma (444-446). Our results underline the importance of an integrated approach to patients with SMDs by focusing on formation and maintenance of meaningful social bonds. The findings are also relevant for the social distancing measures implemented during the current covid-19 pandemic. The social distancing is important to reduce the spread of corona virus, but may increase feelings of loneliness, perhaps especially among those with SMDs (447, 448). Our results indicate that people with SMDs may have a genetic propensity for loneliness, which can make them particularly vulnerable to negative effects of the isolation enforced in several countries (447, 448). Reducing loneliness has the potential to provide a broader benefit on psychosocial functioning, quality of life and recovery in individuals with SMDs (193, 444). In addition, limiting loneliness in SMDs may improve cardiovascular health, but these proposed benefits of reducing loneliness remain to be tested.

Further, the discovery of overlapping genetic variants with mixed effect directions in BD and CVD risk factors in study III have important clinical implications. The findings may suggest variation in genetic propensity to CVD across subgroups of patients with BD, possibly underlying the observed variation in CVD between individuals with BD (82, 261, 308). Furthermore, the CVD comorbidity is likely to be associated with environmental risk factors, including physical activity, nutrition, smoking and medication, in CVD comorbidity (187, 417). The environmental risk factors and genetic susceptibility interact and influence the development of comorbid CVD. Moreover, genetic mechanisms may influence the likelihood of exposing oneself to environmental risk factors, such as smoking (299, 415, 416). A new GWAS identified a positive genetic correlation between smoking initiation and BD, and revealed that a considerable proportion of the genetic architecture of BD is associated with smoking (449). Recent data also suggest a positive genetic correlation between smoking and SCZ, MD and CVD risk (416). This evidence indicates that there may be some genetic variants influencing the tendency to seek or avoid environmental risk (e.g., smoking) that also influence the risk for SMDs and CVD.

Taken together, the current results underscore the need for more targeted lifestyle interventions to prevent comorbid CVD. In particular, there is a need for more personalized lifestyle interventions focusing on the barriers for maintaining a healthy lifestyle, such as

motivational challenges and other psychiatric symptoms, medication side-effects and socioeconomic issues (10). In addition, better risk prediction tools allowing for earlier detection and prevention of CVD comorbidity are necessary. Current PGRSs for SMDs have poor sensitivity and specificity (136-138, 449), which limits clinical utility of these scores for risk prediction. PGRS for CAD and T2D appears to have more predictive power and have shown potential clinical utility (450, 451). Larger GWAS samples are necessary to improve risk prediction and stratification for SMDs and CVD morbidity. In addition, improved prevention requires more tailored pharmacological treatment according to individual risk.

9.4 Future directions

Further research

Despite decades of research, the underlying pathobiology of SMDs has proven difficult to uncover, which has hampered the development of effective treatment with less metabolic side-effects. Similarly, the mechanisms underlying the CVD comorbidity are elusive, although the results presented in this thesis have provided new insights that can inform future investigations. More research is needed to elucidate the mechanisms responsible for the CVD comorbidity in SMDs to improve prevention and treatment. In particular, larger GWAS samples are necessary to uncover more of the polygenic architecture of SMDs and CVD-related morbidity. Similarly, larger well-characterized samples are needed to investigate potential differences in genetic propensity to CVD across clinical subgroups (e.g., BD type I vs. BD type II). Future studies are also necessary to clarify whether a shared genetic basis between loneliness and SMDs explains part of the CVD comorbidity. Methods such as Mendelian randomization analyses can be used to assess possible causal relationships (452). Furthermore, increasing GWAS samples sizes will increase the pool of risk alleles from which to estimate PGRS, which can improve risk prediction and stratification. These developments combined with novel statistical tools to analyse the GWAS data can yield clinically relevant discoveries and facilitate precision medicine (i.e., more targeted and tailored interventions) (135). Genetic risk factors should be combined with other factors (e.g., lifestyle, loneliness, medications) to further improve risk prediction tools, which may inform clinical trials to select individuals that are more likely to develop CVD and respond to novel therapies. Furthermore, experimental studies are necessary to identify the specific causal variants underlying the identified shared genetic associations and their biological functions. Causal variants can be identified using fine-mapping approaches that

limit the ‘noise’ from correlated variants, and the functions of the causal variants can be investigated via experiments involving cell-based systems, model organisms (e.g., rodents) and computational modeling (for further details see Tam et al. (453)). Functional characterization of the causal variants may shed light on central pathophysiological mechanisms, which can help identify potential targets for prevention and treatment (e.g., psychotropic agents with less adverse side-effects). Overall, further research should aim at providing greater knowledge to optimize prevention and treatment of CVD comorbidity in SMDs tailored to individual disease risk. There is a need for a better understanding of how to efficiently reduce CVD risk through lifestyle changes, development of medications with less cardiometabolic side-effects, loneliness interventions and greater health care utilization and provision for individuals with SMDs.

10 CONCLUSION

This thesis has provided new insights into CVD comorbidity in SMDs. The level of CVD risk factors has remained high in patients with SMDs during the past decade, although patients with BD showed modest reductions in CVD risk levels. The limited improvement in CVD risk suggests that most patients with SMDs have not benefitted from recent medical advances and health promotion efforts. Further, the thesis found polygenic overlap between loneliness, SMDs and CVD risk factors, thus providing novel insights into their shared genetic architecture. The results suggests that a genetic susceptibility to loneliness may also contribute to increased risk of SMDs and CVD, which may underlie some of the clinical association between loneliness and these disorders. The findings further indicate that SMDs differ in their relationships with loneliness, with a larger fraction of the genetic architecture underlying MD also influencing loneliness, when compared to BD and SCZ. In addition, we discovered extensive genetic overlap between BD and CVD phenotypes, implicating shared genetic molecular mechanisms. However, the shared loci possessed bidirectional effects, which highlights the importance of environmental causes of the raised CVD risk in BD. In addition, the mixed effect directions may suggest variation in genetic vulnerability to CVD across subgroups of BD, possibly underlying some of the heterogeneity of CVD comorbidity in BD. Overall, the findings underscore the need for further research to dissect the relationship between SMDs and CVD through a multidisciplinary approach focusing on genetic and environmental risk factors. Such an integrated approach can provide meaningful clinical discoveries and pave the way for improved prediction tools, earlier detection and prevention.

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Errata

Study II

Reference **# 52** (and the corresponding reference # 6 in Supplementary Method) "*Davis KAS, et al. Mental health in UK Biobank: development, implementation and results from an online questionnaire completed by 157 366 participants. BJPsych Open. 2018;4:83–90. doi: 10.1192/bjo.2018.12*." should be the updated version "*Davis KAS, Coleman JRI, Adams M, Allen N, Breen G, Cullen B, et al. Mental health in UK Biobank - development, implementation and results from an online questionnaire completed by 157 366 participants: a reanalysis. BJPsych Open. 2020;6(2):e18-e.*» **Importantly, the numbers cited in study II from the original reference are correct**. Davis et al. 2020 performed a re-analysis that only resulted in a decreased alcohol use disorder prevalence and, thus, a decrease in total psychiatric disorder prevalence in the UK Biobank. This supports the use of the UK Biobank as a population sample consisting of mainly healthy individuals.

Study I

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Cardiovascular risk remains high in schizophrenia with modest improvements in bipolar disorder during past decade

Rødevand L, Steen NE, Elvsåshagen T, Quintana DS, Reponen EJ, Mørch RH, Lunding SH, Vedal TSJ, Dieset I, Melle I, Lagerberg TV, Andreassen OA. Cardiovascular risk remains high in schizophrenia with modest improvements in bipolar disorder during past decade

Objective: While CVD risk has decreased in the general population during the last decade, the situation in patients with schizophrenia (SCZ) and bipolar disorder (BD) is unknown.
Methods: We compared CVD risk factors in patients with SCZ and BD recruited from 2002–2005 (2005 sample, N = 270) with patients recruited from 2006–2017 (2017 sample, N = 1011) from the same catchment area in Norway. The 2017 sample was also compared with healthy controls (N = 922) and the general population (N range = 1285–4587, Statistics Norway) from the same area and period.
Results: Patients with SCZ and BD in the 2017 sample had significantly higher level of most CVD risk factors compared to healthy controls and the general population. There was no significant difference in the prevalence of CVD risk factors in SCZ between the 2005 and 2017 samples except a small increase in glucose in the 2017 sample. There were small-to-moderate reductions in hypertension, obesity, total cholesterol, low-density lipoprotein, systolic and diastolic blood pressure in the BD 2017 sample compared to the 2005 sample.
Conclusion: Despite major advances in health promotion during the past decade, there has been no reduction in the level of CVD risk factors in patients with SCZ and modest improvement in BD.

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Key words: schizophrenia; bipolar disorder; general population; cardiovascular risk; life expectancy

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Significant outcomes

- We found no improvement in CVD risk in patients with SCZ while patients with BD had small-to-moderate reductions in several risk factors during the past decade.
- The striking increase in CVD risk factors in patients with SCZ and BD compared to the general population is a major clinical problem in psychiatry.

Limitations

- The study periods of the 2005 and 2017 samples are close, which may reduce the chance of detecting differences between the samples.
- Fasting blood samples and information on daily smoking were retrieved from a subset of healthy controls, although a sufficiently large number for comparison with patients.

Introduction

Severe mental disorders (SMD) such as schizophrenia and bipolar disorder are associated with substantially decreased life expectancy compared to the general population (1, 2). About 60% of the excess mortality among patients with SMD is caused by somatic diseases, especially cardiovascular disease (CVD) (3, 4). The remaining 40% is due to accidents

and suicides (5). The risk of dying from CVD is estimated to be 2–3 fold greater in these patients compared with the general population (2, 6), and several studies have reported at least 2 times higher prevalence of the metabolic syndrome (MetS) (7, 8). MetS is widely applied by clinicians to identify high-risk individuals for CVD at an early stage, enabling prevention of disease development (9).

There has been a steady increase in life expectancy in the general population the last decades (10). During the same time period, there has been several public health campaigns for health promotion and disease prevention (11) and tobacco legislation has become stricter (12). These strategies appear to have been effective in improving public health (13). In the Norwegian population, the risk of dying from CVD has more than halved the past 20 years (14). Similarly, the level of CVD related morbidity has decreased substantially over the last decades despite an increase in overweight and the prevalence of type 2 diabetes (13, 15). Similar trends are observed in other Western countries (16, 17).

Several epidemiological studies suggest that there has been no progress in life expectancy among patients with SMD and that the mortality gap between patients and the general population has increased during the last decades (18, 19). A recent study from Finland, however, reported that the longevity of patients with schizophrenia has improved during the past 30 years, largely due to decrease in suicidal death, while CVD morality has increased in these patients (20). A recent Norwegian study confirm the increased mortality in patients with schizophrenia compared to the general population, with CVD and cancer being the most common causes of death (21). Still, it is unknown to what degree the elevated level of CVD risk factors in patients with schizophrenia and bipolar disorder has sustained after several health promotion efforts.

Preliminary findings suggest that the risk level is still higher in these patients compared to the general population. A recent study from England found doubled levels of CVD risk factors, including type 2 diabetes, hyperlipidemia and obesity, in patients with schizophrenia and bipolar disorder compared to individuals without psychiatric disorders (22). However, this and other studies did not investigate change in CVD risk among patients over time. Thus, there is a need for clinical studies focusing on the development of CVD risk in representative patient samples.

Birkenæs et al. (2006) reported a doubled rate of CVD risk factors, including hypertension, obesity, dyslipidemia, type 2 diabetes, and smoking in a representative sample of Norwegian SMD patients compared to the general population (23, 24). The same level of CVD risk factors were found in individuals with schizophrenia and bipolar disorder (24). These findings are largely confirmed by international studies (7, 8, 25). In the present study, the primary aim was to determine whether the level of CVD risk factors has remained high in patients with schizophrenia and bipolar disorder during the past decade. To examine temporal trends, we compared risk levels among patients included in 2002–2005 (23, 24) with patients included in 2006–2017 from the same catchment area. To examine differences from the rest of the population, we compared the CVD risk level in patients with healthy controls and the general population.

Material and methods

Overall design

The study includes data from two patient samples of schizophrenia or other psychotic disorders (SCZ) and bipolar disorders (BD) recruited from the major hospitals in the Oslo area; the first sample was recruited in 2002–2005 (2005 sample) and the second in 2006–2017 (2017 sample). In addition, we used data from two reference groups: (i) healthy controls randomly recruited from the same catchment area and similar time period as the 2017 sample and (ii) two larger samples from the Oslo general population obtained by Statistics Norway (26, 27) from similar time periods as the 2005 and 2017 samples.

Participants in the thematically organized psychosis (TOP) study

The present study was part of the Thematically Organized Psychosis (TOP) study, an ongoing study in Oslo, Norway. Participants are recruited from psychiatric inpatient and outpatient units at the major hospitals in the Oslo area. These Oslo hospitals collectively cover a catchment area of 88% of Oslo's total population, are located in different parts of the city and are representative of the city's variation in sociodemographic characteristics. Eligible participants were those who met the inclusion criteria of a DSM-IV diagnosis of schizophrenia, other psychotic disorder or bipolar disorder I, bipolar disorder II or bipolar disorder not otherwise specified (NOS), age between 18–65 years and ability to give written informed consent. Exclusion criteria were presence of a pronounced cognitive deficit (IQ below 70), severe somatic illness, brain damage, and not speaking a Scandinavian language. Healthy controls were randomly selected from statistical records from the same catchment area and age range as patients.

The TOP study is conducted in accordance with the Helsinki Declaration and approved by the Regional Committee for Medical Research Ethic and the Norwegian Data Inspectorate. All participants have signed informed consent.

From the start of the TOP study in October 2002 through May 2017, a total of 1281 patients from whom we had CVD risk data and with a diagnosis of bipolar disorders ($N = 496$), schizophrenia or other psychotic disorder ($N = 785$) were included. The characteristics of the first sample from 2002–2005 (2005 sample, $N = 161$ SCZ and 109 BD) are published previously (23, 24). The characteristics of the patients included during the last decade (2017 sample) are presented here: $N = 1011$ patients, 387 with BD and 624 with SCZ. The BD group included patients with BD I ($N = 245$), BD II ($N = 114$), and BD NOS ($N = 28$). The SCZ group consisted of patients with schizophrenia ($N = 474$), schizophreniform ($N = 47$), and schizoaffective disorder ($N = 103$). In addition, 922 healthy controls were recruited from 2006 to 2017 to compare with the 2017 sample of patients.

Demographic and clinical characteristic of patients in the 2017 sample are summarized in Table 1 (more details in supplementary material). Psychotropic drug use of the 2017 sample is presented in Table S1. For the comparisons between the 2005 and 2017 sample, we reanalyzed data from Birkenæs et al. (23, 24). with some minor changes due to the updated dataset. Patients from the 2017 sample were younger than patients from the 2005 sample, with a mean (SD) age of 31.68 (10.49) vs. 35.50 (11.07) years ($F(1, 1279) = 27.59$, $d = 0.35$, $P < 0.001$). The duration of pharmacological treatment was significantly shorter among patients in the 2017 sample compared to patients in the 2005 sample (SCZ: $F(1, 696) = 10.66$, $P = 0.001$; BD: $F(1, 434) = 9.33$, $P = 0.002$). Among patients with BD, duration of illness was shorter in the 2017 sample ($F(1, 484) = 5.85$, $P = 0.016$). All effect sizes were small (Cohen's $d < 0.2$ and phi $\phi < 0.1$) (28). For more details, see supplementary material.

Clinical assessments

The clinical assessment tools were the same during the whole recruitment period. A comprehensive diagnostic interview was conducted with Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), Axis 1 (29). Additional information was collected through interviews and treatment records to determine demographic factors, self-reported diet, physical activity (hours per week), psychiatric history, medical history, and current use of psychotropic medication, tobacco, alcohol, and illicit drugs. Psychotic symptoms were rated using the Positive and Negative Syndrome Scale (PANSS) (30). Depressive symptoms were assessed with the Inventory of Depressive Symptoms (IDS-C) (31). General symptoms and functioning were measured by the Global Assessment of Functioning Scale (GAF), split version (symptoms, GAF-S; function, GAF-F) (32, 33).

The inter-rater reliability of the symptom assessments in the TOP study is good, with an Intraclass Coefficient (ICC) of 0.82 for PANSS symptoms, 0.86 for GAF-S and 0.85 for GAF-F (34, 35). The inter-rater reliability is also satisfactory for diagnosis, with overall agreement for diagnostic categories of 82% and overall $\kappa = 0.77$ (95% CI: 0.60–0.94) (36).

Physical assessments and CVD risk factors

All participants underwent a physical examination performed by a physician, with the same protocol for both samples. Body mass index (BMI: weight in kg/height in m^2) was calculated from weighing the participants on calibrated digital weights wearing light clothing and no shoes. Waist circumference was measured midway between lowest rib and the iliac crest. Blood pressure (BP) was recorded in sitting position after resting.

Blood samples were drawn after an overnight fast of at least 8 h and analyzed for fasting plasma glucose (FPG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides (TGs).

Fasting venous blood samples were analyzed at the Department of Medical Biochemistry, Oslo University Hospital, on several routine instruments: Integra 800, Abbot Architect, i2000, Cobas 8000 e602 and Cobas 8000 e801 (Roche Diagnostics, Basel, Switzerland: www.roche.com/about/business/diagnostics.html) using standard methods controlled by internal and external quality control samples. Until 2012, LDL was calculated by the Friedewald formula, thereafter analyzed by an enzymatic colorimetric method.

Statistics Norway sample

Statistics Norway (SSB, https://www.ssb.no/statbank/) has obtained self-reported data on overweight and obesity (BMI ≥ 25) in the general population of Oslo in 2002 and 2005 ($N = 1285$), and in 2008, 2012, 2015 and 2017 (37) ($N = 3035$). Statistics

Table 1. Demographic and clinical characteristics of 2017 sample

Characteristics	All patients		Male		Female	
	Schizophrenia (*N* = 624)	Bipolar disorder (*N* = 387)	Schizophrenia (*N* = 369)	Bipolar disorder (*N* = 152)	Schizophrenia (*N* = 255)	Bipolar disorder (*N* = 235)
Male, % (*N*)	59.2 (369)	39.3 (152)***				
Caucasian, % (*N*)	80.6 (502)	89.9 (347)***	77.2 (285)	89.4 (135)**	85.5 (218)	90.2 (212)
Outpatients, % (*N*)	74.7 (461)	92.4 (352)***	69.8 (257)	93.3 (139)***	81.9 (204)	91.8 (213)*
Employed/student, % (*N*)	19.8 (123)	42.6 (164)***	19.8 (73)	43.7 (66)***	19.8 (50)	41.9 (98)***
Married or cohabiting, % (*N*)	14.8 (92)	34.8 (133)***	12.5 (46)	30.2 (45)***	18.1 (46)	37.8 (88)**
Substance abuse†, % (*N*)	26.0 (162)	23.5 (91)	36.9 (114)	31.6 (48/152)	18.9 (48)	18.3 (43)
Age, mean (SD)	30.6 (9.6)	33.5 (11.6)***	29.6 (8.4)	34.0 (12.2)***	32.0 (10.9)	33.1 (11.2)
Education, mean (SD)	12.8 (2.6)	14.3 (3.0)***	12.5 (2.7)	14.2 (3.1)***	13.2 (2.8)	14.3 (3.0)***
Treatment duration, mean (SD)	4.5 (6.5)	5.7 (6.7)*	4.0 (5.7)	4.4 (5.7)	5.3 (7.4)	6.4 (7.2)
Illness duration, mean (SD)	7.0 (7.5)	11.5 (9.8)***	6.6 (7.1)	10.3 (9.6)***	7.5 (8.1)	12.2 (9.9)***
GAF symptom, mean (SD)	42.5 (11.5)	56.9 (11.6)***	41.9 (11.3)	57.0 (11.8)***	43.5 (12.0)	56.9 (11.5)***
GAF function, mean (SD)	43.1 (11.1)	54.4 (12.9)***	42.3 (10.4)	54.1 (13.5)***	44.1 (12.0)	54.7 (12.6)***
IDS-C, total mean (SD)	18.2 (12.4)	17.2 (11.8)	17.3 (11..3)	14.8 (11.0)*	19.3 (13.6)	18.8 (12.1)
PANSS, total mean (SD)	64.1 (16.7)	45.7 (10.3)***	65.9 (16.2)	46.4 (11.1)***	61.6 (17.0)	45.2 (9.7)***

Categorical variables were compared using the Chi-square test, and continuous variables were compared using ANOVA. GAF, Global Assessment of Functioning; IDS, Inventory of Depressive Symptomatology, PANSS, Positive and Negative Syndrome Scale. *P* value *< 0.05. **<0.01. ***<0.001.
†Substance abuse includes both abuse and dependence of substances.

Norway has also collected data on self-reported daily smokers in Oslo in 2002–2005 ($N = 540$) and in several intervals from 2006 to 2017 ($N = 4587$) (Norhealth – an online database from the Norwegian Institute of Public Health: http://www.norgeshelsa.no/norgeshelsa/ (26)). Smoking data were merged into bins to get a sufficiently large sample to break down on county level, age groups and sex. We used SSB data from 2002–2005 to compare with the 2005 sample, and data from 2006–2017 to compare with the 2017 sample. To match the age span in the TOP Study, we used SSB data on overweight/obesity from individuals aged 18–65 years and data on smoking from individuals aged 16–74 years (the most similar age group available).

Metabolic syndrome

Currently, several different definitions of MetS are being used in the literature (38). In this study, MetS was diagnosed according to the definition proposed by the National Cholesterol Education Program, Adult Treatment Panel III in 2003 (39) (supplementary material). This definition is widely used due to its clinical utility (9, 40). Waist circumference was available only for a limited number of patients in the 2005 sample. Consequently, we used a modified version of the MetS criteria (Birkenes et al., 2007 (24)), based on BMI ≥ 30 as an alternative measure of central obesity, when comparing the two samples.

Statistical analysis

Data was analyzed using statistical package SPSS, version 25 for Windows (IBM Corp, 2017) (41). All statistical tests were carried out two-sided with the significance level set to 0.05. The distribution of data was investigated through histograms and skewness indices. Variables that were not normally distributed were log transformed before being entered into statistical analyses. In the comparisons of sociodemographic and clinical variables between groups, we used a chi-square test for categorical variables, and univariate analysis of variance (ANOVA) for continuous variables. Univariate analysis of covariance (ANCOVA) and logistic regression were used to adjust for age as a potential confounder when comparing the CVD risks between groups (diagnostic groups, patients vs. controls). Age was considered a confounder in accordance with the analyses of the 2005 sample (23, 24). In supplementary analyses of SCZ vs. BD we adjusted for functioning level (GAF-F), symptom level (PANSS) and use of antipsychotics with adverse metabolic side effects as the diagnostic groups differed significantly in these variables. A chi-square test was used to compare the prevalence of smoking and overweight/obesity between patients and the general population with data from SSB as we had access to percentage and total numbers, not raw data.

Further, in the comparison of CVD risk factors between the 2005 and 2017 sample, we used ANCOVA and logistic regression to adjust for differences in age, duration of illness and duration of pharmacological treatment (possible confounders). We also examined the CVD risk in subgroups, stratified by sex and age groups (18–35 years, 36–50 years, 51–65 years), in line with the analyses of the 2005 sample (23, 24). Bonferroni correction

was used to control for multiple test when stratifying, dividing the *P*-value of 0.05 by the number of stratified groups. A $P < 0.025$ (0.05/2) was considered statistically significant when stratifying by sex, and a $P < 0.008$ (0.05/6) was regarded significant when stratifying by sex and age groups (two sexes × three age groups).

We reported the effect size, Cohen's d, from ANCOVA, using Cohen's guidelines of 0.2, 0.5, and 0.8 as small, medium and large, respectively. The computed effect size from logistic regressions was odds ratio where values of 1.5, 2.5 and 4.3 were considered small, medium and large, respectively. The effect size ϕ was obtained from Chi-square test, where values of 0.1, 0.3 and 0.5 are considered small, medium and large, respectively (Cohen, 1988 (28)).

As fasting vs. non-fasting status is mainly of importance for glucose and TGs, fasting levels of glucose and TGs in patients were compared with the restricted number of fasting controls that were available ($N = 222$).

Results

CVD risk factors of the 2017 sample

Table 2 shows CVD risk factors in patient with SCZ and BD in the 2017 sample. In general, the level of CVD risk factors was significantly higher in patients with SCZ than in patients with BD. More specifically, age-adjusted BMI, waist circumference, TGs, FPG, BP and TC were higher (all *P*'s < 0.01), and obesity, central obesity, hypertension, low-HDL and MetS were more prevalent among the patients with SCZ (all *P*'s < 0.05). HDL-C was lower in patients with SCZ than in patients with BD ($P < 0.001$).

After adjustments for additional covariates, including functioning level (GAF-F), symptom level (PANSS) and use of antipsychotics with adverse metabolic side effects, the differences in CVD risk factors between diagnostic groups disappeared except for obesity, waist circumference, LDL-C and diastolic BP that remained significantly higher in the SCZ group ($P < 0.05$).

Comparison of CVD risk factors between 2005 and 2017 samples

Table 2 also presents the results of the comparison of CVD risk factors in the 2005 sample with the 2017 sample, adjusting for age, duration of illness and duration of psychopharmacological treatment. Among patients with SCZ, there was no significant difference in the level of CVD risk factors except from FPG being slightly higher in the 2017 sample ($P = 0.042$). Among patients with BD, there were significant lower levels of TC, LDL-C, systolic, and diastolic BP in the 2017 sample compared to the 2005 sample (all *P*'s < 0.01). The rate of obesity

Table 2. Cardiovascular risk factors of 2005 sample vs. 2017

	Schizophrenia			Bipolar disorder		
Variable	2005 sample ($N = 161$)	2017 sample ($N = 624$)	Effect size	2005 sample ($N = 109$)	2017 sample ($N = 387$)	Effect size
Daily smoking	53.5 (83/155)	47.2 (282/597)	1.359	45.9 (50/109)	42.5 (161/379)	1.16
Obesity†	21.5 (32/149)	23.8 (132/555)	0.809	23.6 (25/106)	12.9 (46/357)	2.131*
Overweight†	59.7 (89/149)	54.8 (304/555)	1.083	57.5 (61/106)	51.5 (184/357)	1.118
Hypertension	47.1 (66/140)	37.7 (215/571)	1.392	50.9 (54/106)	30.6 (110/359)	1.916**
Low-HDL-C	37.5 (57/152)	31.6 (165/522)	1.311	22.1 (23/104)	24.8 (88/355)	1.032
MetS‡	36.6 (52/142)	23.9 (120/503)	1.108	29.8 (31/104)	14.5 (50/346)	1.831
Type 2 diabetes	1.9 (3/161)	1.6 (10/624)	1.197	4.6 (5/109)	2.3 (9/387)	1.849
BMI†	26.1 (25.3, 27.0)	26.6 (26.1, 27.0)	−0.044	26.2 (25.3, 27.1)	25.7 (25.1, 26.1)	0.204
Waist, cm	93.1 (87.7, 98.5)	92.9 (91.5, 94.2)	0.065	94.4 (87.1, 101.8)	88.9 (87.4, 90.4)	0.326
Systolic BP, mm HG	121.5 (119.0, 124.0)	120.2 (119.0, 121.5)	0.087	126.8 (123.7, 129.9)	118.0 (116.2, 119.8)	0.608**
Diastolic BP, mm HG	79.4 (77.6, 81.2)	77.4 (76.4, 78.3)	0.186	81.8 (79.5, 84.1)	75.7 (74.4, 77.0)	0.636**
Cholesterol, mmol/L	5.3 (5.1, 5.4)	5.1 (5.0, 5.2)	0.214	5.4 (5.2, 5.6)	5.0 (4.8, 5.0)	0.526**
HDL-C, mmol/L	1.3 (1.2, 1.3)	1.3 (1.3, 1.4)	0.092	1.5 (1.4, 1.5)	1.4 (1.4, 1.5)	0.041**
LDL-C, mmol/L	3.2 (3.1, 3.4)	3.2 (3.1, 3.3)	0.093	3.3 (3.1, 3.5)	3.0 (2.9, 3.1)	0.421**
Glucose, mmol/L	5.1 (4.9, 5.2)	5.2 (5.1, 5.3)	−0.131*	5.3 (5.1, 5.5)	5.1 (5.0, 5.2)	0.227
Triglycerides, mmol/L	1.8 (1.6, 2.0)	1.6 (1.4, 1.7)	0.172	1.5 (1.3, 1.7)	1.3 (1.2, 1.4)	0.202

Mean (95% CI) levels and percentages (*N*) of cardiovascular risk factors for the two patient samples. Effect sizes are reported in Cohen's d for continuous variables and odds ratio for categorical variables. All values except from percentages (*N*) are adjusted for age, duration of treatment and duration of illness with ANCOVA and logistic regression. BMI, body mass index; BP, blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low high density lipoprotein cholesterol; MetS, Metabolic syndrome. **P* value < 0.05. **<0.01.

†Weight in kg/height in m^2.

‡In the comparison of MetS between samples, BMI ≥ 30 was used an alternative measure of central obesity due to waist measurements for a limited number of patients in 2005 sample.

and hypertension was also lower among patients with BD in the 2017 sample than in the 2005 sample ($P = 0.011$ and $P = 0.007$, respectively) (Fig. 1a). There was no significant difference between the samples in MetS, overweight, central obesity, low-HDL-C or type 2 diabetes. The effect sizes were small except from medium effect sizes for BP and TC in the BD group ($d = 0.53$ for TC; $d = 0.61$ for systolic BP, and $d = 0.64$ for diastolic BP).

We made the same comparisons between the two samples with stratification by age and sex to investigate whether the above-mentioned changes were restricted to certain age groups or sexes (Tables S2 and S3). After Bonferroni correction, the stratification analyses show that most of the changes were restricted to female BD patients, including reduced levels of obesity, hypertension, systolic and diastolic BP, and TGs levels in female patients with BD aged 18–50 years. Reduction in diastolic BP and HDL-C were evident in male patients with BD. Within the SCZ subgroups, there were no statistical significant differences between the 2005 and 2017 sample. There was a nominal significant decrease in daily smoking and increase in FPG among 18–35-year-old male patients ($P = 0.040$ and $P = 0.041$, respectively) with SCZ.

CVD risk factors in the 2017 sample compared with healthy controls

Table 3 and Fig. 1a shows CVD risk factors in patients compared to healthy controls. The CVD risk level was generally significantly higher in patients compared to controls. The level of age-adjusted BMI, waist circumference and TGs were significantly higher and HDL-C was significantly lower in both diagnostic groups than in controls ($P < 0.001$–0.029). Among patients with SCZ, TC and LDL-C levels were also higher compared to controls ($P < 0.001$). The prevalence of daily smoking, overweight, central obesity, low-HDL, MetS and type 2 diabetes were increased in both diagnostic groups compared to controls ($P < 0.001$–0.005). In addition, the prevalence of obesity and hypertension was higher in patients with SCZ ($P < 0.001$, $P = 0.015$, respectively). Effect sizes (odds ratio) were highest for type 2 diabetes, MetS and daily smoking.

Stratification analyses show that the level of CVD risk factors was higher in both male and female patients compared to healthy controls, aged 18–50 years (Table S4). Comparisons with controls aged 51–65 years were not possible because of limited number of of controls in this age group. Most differences between SCZ and controls remained significant after Bonferroni correction, while several differences between the BD and control subgroups were not significant after Bonferroni correction (more details in supplementary material).

CVD risk factors in the 2017 sample compared with the general population samples

For comparison we included data from two general population samples of Oslo that were matched on geographical area with our patient sample.

Statistics Norway sample: Analyses show a considerably higher prevalence of daily smokers among patients in the 2017 sample compared with the Statistics Norway sample (χ^2 (1, 5562) = 551.35, $\phi = 0.32$, $P < 0.05$) (Fig. 1b). The graph also illustrates a significant decline in the prevalence of daily smokers in the Statistics Norway sample during the past decade (χ^2 (1, 5127) = 38.69, $\phi = 0.09$, $P < 0.05$). The reduction was statically significant for both sexes ($P < 0.05$). In contrast, there was no reduction in daily smoking among patients.

Figure 1b also illustrates that overweight and obesity were more frequent in patients of the 2017 sample than in the Statistics Norway sample (χ^2 (1, 3977) = 146.17, $\phi = 0.20$, $P < 0.05$). Although not significant the level of overweight and obesity has non-significantly decreased in the Statistics Norway sample (from 36.5% to 35.5%) and in patients with SCZ (from 59.7% to 54.8%) from the 2005 to the 2017 sample, while it has significantly decreased in patients with BD (from 57.5% to 51.5%). Despite these minor changes, the prevalence of overweight and obesity has remained considerably higher in both diagnostic groups in the 2017 sample compared to the Statistics Norway sample (Fig. 1b).

Discussion

The main finding of the present study was significantly higher levels of CVD risk factors in patients with SMD compared to the general population. While there was no significant improvement in CVD risk factors in SCZ during the past decade, there were small to moderate improvements in BD, including lower levels of TC, LDL-C, BP, hypertension and obesity. Taken together, the current findings suggest a limited improvement in CVD risk in patients with SMD during the last 10 years.

To the best of our knowledge, this is the first investigation of changes in CVD risk factors in patients with SCZ and BD from the same catchment area during the past decade. Although there

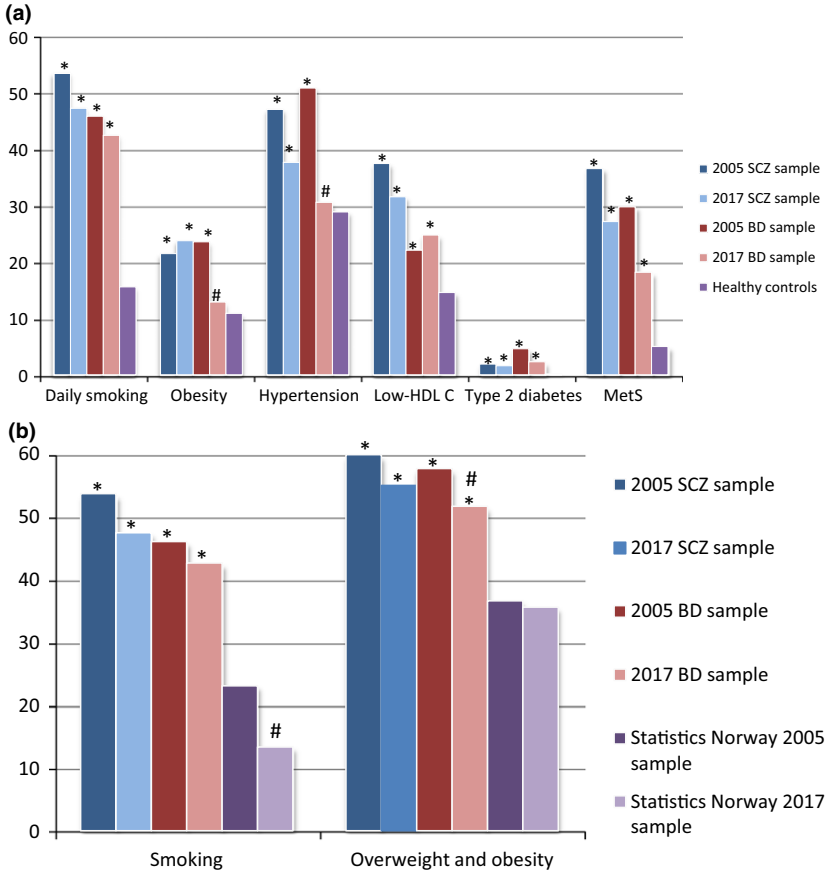

Fig. 1. (a) Level (%) of CVD risk factors in 2005 sample vs. 2017 sample and healthy controls. For all *P*-value levels, 2005 sample and 2017 sample are compared within each diagnostic group, and patient samples are compared with healthy controls. The level of all risk factors were significantly higher in both patients with SCZ and BD than in controls, except from hypertension and obesity that were not more frequent in the BD 2017 sample compared to controls. Results are from logistic regression with adjustments for age, duration of illness and duration of pharmacological treatment. $^{*}P$ value < 0.05 comparing patients and healthy controls. $^{\#}P$ value < 0.05 comparing patient 2005 sample and 2017 sample. HDL-C, high density lipoprotein cholesterol; MetS, Metabolic syndrome. (b) Daily smoking, overweight and obesity (%) in the Statistics Norway sample and 2005 sample and 2017 sample. Daily smoking and overweight/obesity are significantly more prevalent in patients compared to the Statistics Norway sample, as indicated by $^{*}P$ value of <0.05. Smoking has declined in the Statistics Norway sample from 2005 to 2017, and obesity has declined in BD patients, as indicated by $^{\#}P$ value < 0.05.

are no previous studies for direct comparison, the findings are in line with recent cross-sectional studies showing elevated levels of CVD risk factors, including waist circumference, BMI, lipids and FPG (42–46), although some variation in severity exists (47, 48). Similarly to other studies, we found increased prevalence of MetS, overweight, obesity, type 2 diabetes, low-HDL, hypertension and daily smoking in patients compared to healthy controls and the general population (22, 48–50). The frequency of MetS, overweight, obesity and type 2 diabetes were, however, somewhat lower in the present sample (49, 51, 52), possibly due to differences in sample characteristics such as lower age and shorter duration of illness and medication. Our results are in line with other studies of younger patients with shorter illness and treatment duration (53–56).

In the present study, we were able to statistically control for age, illness duration and pharmacological treatment duration in the comparison of the 2005 and 2017 samples. Moreover, the samples were from the same catchment area, and recruited and examined with the same procedures. This allowed us to investigate the time-dependent differences in CVD risk in SMD patients. The comparison of the two samples showed no improvement in CVD risk factors in the SCZ group and some reductions in the BD group. These findings of limited improvements in CVD risk factors suggest that public health efforts (11), and awareness in the health care system (57, 58) to reduce CVD risk have had no appreciable effect in patients with SCZ and modest effects in patients with BD. Further, due to the novel data collected in the Norwegian health surveys with random sampling from

Table 3. Cardiovascular risk factors in 2017 sample vs. healthy controls

		Schizophrenia ($N = 624$)		Bipolar disorder ($N = 387$)	
CVD variable	Healthy controls ($N = 922$)	Statistic	Effect size	Statistic	Effect size
Daily smoking	15.3 (61/399)	$\chi^2 = 115.7$	4.914***	$\chi^2 = 74.5$	4.172***
Obesity (BMI≥30)†	10.9 (20/183)	$\chi^2 = 21.8$	2.753***	$\chi^2 = 9.2$	1.203
Overweight (BMI≥25)†	39.9 (73/183)	$\chi^2 = 33.7$	2.099***	$\chi^2 = 27.2$	1.671**
Central obesity‡	17.1 (123/719)	$\chi^2 = 109.7$	3.106***	$\chi^2 = 63.7$	2.041***
Hypertension§	28.9 (44/152)	$\chi^2 = 14.8$	1.634*	$\chi^2 = 19.1$	1.106
Low-HDL¶	14.6 (127/870)	$\chi^2 = 55.8$	2.744***	$\chi^2 = 18.4$	1.921***
MetS	5.0 (10/201)	$\chi^2 = 68.6$	6.469***	$\chi^2 = 18.9$	2.966**
Type 2 diabetes	0.1 (1/922)	$\chi^2 = 13.8$	16.971**	$\chi^2 = 19.4$	20.915**
BMI†	24.5 (23.8, 25.2)	$F = 21.3$	0.363***	$F = 5.0$	0.191*
Waist, cm	85.8 (84.8, 86.8)	$F = 81.9$	0.449***	$F = 9.0$	0.218**
Systolic BP, mm HG	118.6 (116.2, 120.9)	$F = 2.0$	0.110	$F = 0.6$	0.099
Diastolic BP, mm HG	76.4 (74.7, 78.0)	$F = 1.0$	0.012	$F = 2.9$	0.194
Cholesterol, mmol/L	4.9 (4.8, 4.9)	$F = 24.6$	0.136***	$F = 3.9$	0.058
HDL-C, mmol/L	1.5 (1.5, 1.6)	$F = 87.3$	−0.511***	$F = 11.5$	−0.215**
LDL-C, mmol/L	2.9 (2.8, 2.9)	$F = 51.4$	0.300***	$F = 0.4$	0.028
Glucose, mmol/L	5.1 (5.0, 5.2)	$F = 1.5$	0.118	$F = 1.1$	−0.050
Triglycerides, mmol/L	1.0 (0.9, 1.2)	$F = 55.2$	0.622***	$F = 18.5$	0.375***

Percentages (*M*) and mean (95% CI) values of metabolic risk variables for healthy controls. Logistic regression was used to adjust for age differences between controls and patients when comparing categorical CVD variables. ANCOVA was used to adjust for age differences when comparing continuous CVD variables. Reported effects sizes are Cohen's d computed from ANCOVA, and odds ratio from logistic regression. BMI, body mass index; HDL-C, high density lipoprotein cholesterol, LDL-C, low high density lipoprotein cholesterol; BP, blood pressure; MetS, Metabolic syndrome. *P value < 0.05. **<0.01. *** <0.001.

†Weight in kg/height in m^2.

‡Waist > 102 cm (males), < 88 cm (females).

§Systolic blood pressure ≥130 mm HG and/or diastolic blood pressure ≥85 mm HG or taking antihypertensive.

¶Low-HDL < 1.0 mmol/L (males), <1.3 mmol/L (females).

2005 to 2017 (Statistics Norway), we were able to compare our patient results with risk levels in the general population collected during the same time period and from the same geographical area as the patients.

Our finding of limited improvement in CVD risk in SMD patients differs from the changes seen in the general population with reduced CVD risk and healthier life-style with increase in physical activity, better diet and reduction in daily smoking (27, 59, 60). Possible reasons for the improvement in the general population are tobacco control policies, including ban on smoking inside public places (2004), cessation programs and several health campaigns since 2003 (11, 12). Additionally, food labels was introduced in 2009 to help consumers make healthier food choices (61). These public health efforts appear to have been ineffective in SMD, as indicated by high level of CVD risk and no significant improvement in life-style factors in our sample of patients with SMD (details in supplementary material). It is of public health concern that patients with SMD in Norway, a country with one of the highest ranked health care systems in the world (62), show little change in CVD risk factors. The question is why patients with SMD, and SCZ in particular, show limited improvement. One explanation may be that there are several inherent obstacles to life-style change in SMD, including low motivation, symptom load, reduced cognitive functioning, financial challenges, and sedentary side effects of medication (i.e. drowsiness and fatigue) (63–65). These challenges are difficult to influence through public health efforts.

Moreover, treatments with antihypertensiva and statins have increased in the general population during the past decades (66, 67), possibly contributing to the reductions in hypertension and dyslipidemia (15). Evidence suggests undertreatment of hypertension, dyslipidemia and other metabolic conditions in SMD (68). Patients with SMD report difficulties getting access to primary care, problems communicating physical needs and poorer compliance with treatment (69). Accordingly, there is an increased risk of serious conditions remaining undetected and inadequately treated in SMD patients compared to the general population (68). Patients with SCZ may be even more limited in their ability to access somatic care and benefit from health campaigns than patients with BD, possibly due to poorer motivation (70) and cognitive function (71) and more frequent use of antipsychotics with adverse side effects (22). These differences may contribute to explaining why the improvement that we found was restricted to the BD group. The sparse reductions in CVD

risk can also be due to a genetic vulnerability to CVD in SMD patients (72). Drug naïve patients and first degree relatives show increased risk of metabolic disturbances (73). These results may point to a shared genetic risk for psychotic disorders and CVD, as indicated by reports of overlapping genes between CVD risk factors and SMD (74).

During the last 10–20 years, there has been increased focus on the comorbid CVD risk and side effects of medications in the health care sector, with revised guidelines (57, 58) and better education and training (69). In 2004, guidelines that stress the importance of metabolic monitoring in patients with SMD were published (75, 76). American Diabetes Association et al. recommended regular monitoring of weight, waist circumference, glucose, lipids and BP, and nutritional and physical activity counseling (75). In Norway, similar recommendations were presented and educational activities aimed at improving monitoring of CVD health in SMD, were initiated (58). The level of CVD risk in our patient sample could indicate that these changes in guidelines and education have been insufficient for SMD patients, especially for SCZ. This may partly be due to difficulties in implementing the guidelines (77), including limited time or resources, low organizational support, severity of psychiatric illness, and clinician's concerns over the quality of the guidelines (78–80). These barriers to apply the guidelines should be taken into account in the development of more effective implementations strategies. Moreover, studies indicate uncertainty among primary care and mental health providers over who is responsible for the metabolic monitoring and treatment of metabolic abnormalities in patients with SMD (78, 81). Thus, the responsibilities of primary and secondary care need to be clarified, preferably through better collaboration between health services.

The reductions in CVD risk that we found in the BD group were mainly restricted to female patients. There has been an increasing number of studies focusing on sex inequalities in metabolic side effects of psychotropic drugs (82, 83), with women being more prone to antipsychotic-induced weight gain and metabolic disturbances (84). Clinicians might be more cautious during psychopharmacological treatment of women. In line with this hypothesis, we found a lower level in the use of clozapine and olanzapine only among female patients with BD, but this was on the border of statistical significance ($P = 0.08$).

We found higher levels of several CVD risk factors in SCZ compared to BD. Consistent with this finding, self-reported physical activity levels were lower and self-reported diet was less healthy in SCZ than BD (details in supplementary material). Although the differences in these life-style factors were small, they may contribute to the observed differences in CVD risk between the two diagnostic groups. In addition, more frequent use of antipsychotics with metabolic side effects, higher symptom level and lower level of functioning in the SCZ group may play a role. Recent findings suggest that higher levels of unhealthy lipids are associated with more severe symptoms and poorer functioning in SCZ (85). Consistent with this, after adjusting for symptom level, functioning level and use of antipsychotics with adverse metabolic side effects, several differences in CVD risk factors between the diagnostic groups disappeared, while obesity, waist, LDL-C and diastolic BP remained significantly higher in the SCZ group. Some recent studies also suggest greater risk levels among patients with SCZ compared to BD (86–88). Other studies report mixed findings, including similar rates of MetS and greater prevalence of smoking and central adiposity in SCZ, but lower levels of TC and LDL-C (50). One study reported slightly higher prevalence of lipid abnormalities in patients with BD than SCZ (44). Accordingly, more studies are needed to investigate whether there is a clear difference in CVD risk between the two diagnostic groups.

Strengths of the current study are the large representative sample of patients with SCZ and BD recruited from the same catchment area and assessed with the same methods. We also had access to daily smoking data and BMI from a large sample of the general population (Statistics Norway) from the same geographical area and time period as patients. It is a limitation that the time periods of the two compared patient samples are close, which may reduce the chance of detecting differences between the samples. Therefore, we did subanalyses comparing the 2005 sample with a sample from 2014–2017, which generally confirmed our original findings (supplementary material). However, there was a significant reduction in low HDL-C in the SCZ group from 2014–2017. This may indicate that there are improvements in the SCZ group in more recent years. However, due to smaller sample size, these results need to be replicated, and future studies should address if the CVD risk levels have started to decrease in SCZ.

Another limitation is the lack of waist circumference from the 2005 sample, which left us with BMI as the measure of obesity when comparing samples. However, BMI is commonly employed as a measure of obesity and found to predict CVD risk

(89). In the assessment of CVD risk in the 2017 sample we used both BMI and waist circumference. A third limitation was that fasting blood samples and information on daily smoking were retrieved only from a subset of healthy controls, although a sufficiently large number for comparison. Finally, methods for glucose and lipid analyses have changed somewhat during the years; however, without noticeable implications for estimated levels.

Despite major advances in cardiovascular health promotion and disease prevention during the past decade, both in the general population and the mental health care system, the level of CVD risk factors remained high in patients with SCZ and BD, with some improvements in the BD group. Our finding of limited improvements in CVD risk in patients highlights the need for more targeted interventions and improved prevention strategies. Moreover, better screening and monitoring of metabolic status should be implemented. Closer collaboration between mental health and primary care providers may contribute to improve monitoring practices. Strengthening accreditation is suggested to promote the collaboration between primary and secondary health services (90). In addition, more focus on life-style factors, including physical activity and nutrition, should be better integrated in the treatment of individuals with SMD.

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Declaration of interests

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Supporting Information

Additional Supporting Information may be found online in the Supporting Information section at the end of the article:
Table S1. Psychotropic Drug Use of Sample 2017, % (*N*)
Table S2. Cardiovascular risk factors of SCZ 2005 sample versus 2017
Table S3. Cardiovascular risk factors of BD 2005 sample versus 2017
Table S4. Cardiovascular risk factors of healthy controls vs. 2017 sample
Table S5. Cardiovascular Risk Factors of 2005 sample versus 2014-2017 sample
Table S6. Cardiovascular Risk Factors in 2014-2017 sample versus controls

Supplementary material

Cardiovascular risk remains high in schizophrenia with small-to-moderate improvements in bipolar disorder during the past decade

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Content:

Demographic and clinical characteristic of the 2017 sample

There were more men in the SCZ group (59.2 %) than in the BD group (39.3 %, $p < 0.001$). Patients with SCZ were somewhat younger than patients with BD, with a mean (SD) age of 30.6 (9.6) years versus 33.5 (11.6) years ($p < 0.001$, partial eta squared = 0.018), respectively. The mean age (SD) of patients, 31.7 (10.5) years, was significantly lower compared to the mean age (SD) of the healthy controls, 33.6 (9.2) years ($p < 0.001$, partial eta squared = 0.010). Self-reported physical activity level (hours per week) were significantly lower in patients with SCZ ($M = 3.19$, $SD = 3.26$) than in patient with BD ($M = 4.30$, $SD = 5.32$) ($F (1, 918) = 9.86$, $p < 0.001$, partial eta squared = 0.016). Self-reported diet of patients with BD was more healthy compared to the diet of SCZ patients ($\chi^2 (1, 930) = 5.52$, $p = 0.019$, phi = 0.077). Individuals with BD were more often Caucasian of Norwegian origin, had higher education and were more likely to be outpatients, full- or part time employed, and living in a stable relationship. In addition, scores on Global Assessment of Functioning (GAF) were higher, and scores on Positive and Negative Syndrome Scale (PANSS) were lower among patients with BD compared to SCZ. Patients with BD had a longer duration of pharmacological treatment and duration of illness than the SCZ group.

Comparison of demographic and clinical characteristics of the 2005 sample and 2017 sample

Patients from the 2017 sample were more likely to be part- or full time employed than patients from the 2005 sample (SCZ: $\chi^2 (1, 784) = 4.60$, $p = 0.032$, BD: $\chi^2 (1, 494) = 4.60$, $p = 0.032$). Patients with BD in 2017 sample had less education ($F (1, 473) = 4.32$, $p = 0.038$) and lower GAF-scores (GAF-F: $F (1, 488) = 5.83$, $p = 0.016$; GAF-S: $F (1, 489) = 5.69$, $p = 0.017$) compared to BD in the 2005 sample. Among patients with SCZ, substances abuse/dependence was more prevalent in the 2017 sample than in the 2005 sample ($\chi^2 (1, 785)$

= 4.39, p = 0.036). All effect sizes were small (Cohen's d < 0.2 and phi < 0.1). There were no significant differences between the 2005 and 2017 sample in the level of depressive symptoms (IDS), PANSS scores, gender, ethnicity, hospitalization, self-reported physical activity level and diet or the proportion of patients with BD type 1 versus BD type 2.

Metabolic syndrome (MetS)

For establishing the diagnosis of MetS, at least 3 out of 5 criteria must be present. Cut off values for the individual variables are:

(1) FPG ≥ 5.6 mmol/L (100 mg/dL) or taking hypoglycemic medication,

(2) TGs ≥ 1.7 mmol/L (150 mg/dL),

(3) HDL-C < 1.0 mmol/L (40 mg/dL) (men) and < 1.3 mmol/L (50 mg/dL) (women),

(4) systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 85 mm Hg or taking antihypertensive medication, and

(5) central obesity with waist circumference > 102 cm (40 in) (men) and > 88 cm (35 in) (women).

Supplementary table 1. Psychotropic Drug Use of Sample 2017, % (N)

	All patients		Male		Female	
Characteristics	Schizophrenia (N=624)	Bipolar disorder (N=387)	Schizophrenia (N=369)	Bipolar disorder (N=152)	Schizophrenia (N=255)	Bipolar disorder (N=235)
Minimum 1 antipsychotic	87.3 (545)	53.7 (208)***	87.5 (323)	55.3 (84)***	87.1 (222)	52.8 (124)***
Minimum 2 antipsychotic	26.4 (165)	6.7 (26)***	27.6 (102)	5.9 (9)***	24.7 (63)	7.2 (17)***
Weight-inducing antipsychotics[a]	62.8 (392)	43.7 (169)***	63.4 (234)	46.1 (70)**	62.0 (158)	42.1 (99)***
Lithium	2.1 (13)	18.1 (70)***	1.6 (6)	16.4 (25) ***	2.7 (7)	19.1 (45)***
Minimum 1 antiepileptic	12.8 (80)	35.4 (137)***	9.8 (36)	36.2 (55)***	17.3 (44)	34.9 (82)***
Weight-inducing antiepileptics[b]	4.5 (28)	14.2 (55)***	4.1 (15)	19.1 (29)***	5.1 (13)	11.1 (26)*
Minimum 1 antidepressant	27.7 (173)	32.3 (125)	24.7 (91)	25.7 (39)	32.2 (82)	36.6 (86)
Weight-inducing antidepressants[c]	11.5 (72)	10.6 (41)	10.3 (38)	10.4 (16)	13.3 (34)	10.6 (25)

Percentages (N) of patients using medication.
[a]Clozapine, olanzapine, risperidone and quetiapine
[b]Valproate and carbamazepine
[c] Paroxetine, mirtazapine, mianserine and venlafaxine
*p value < 0.05. ** < 0.01. *** < 0.001.

Supplementary table 2. Cardiovascular risk factors of SCZ 2005 sample versus 2017

	Women		Men	
Variables	2005 sample	2017 sample	2005 sample	2017 sample
All ages	N = 67	N = 255	N = 94	N = 369
Daily smoking	50.8 (33/65)	46.4 (116/250)	55.6 (50/90)	47.8 (166/347)
Obesity (BMI≥30)[a]	20.0 (12/60)	20.7 (48/232)	22.5 (20/89)	26.0 (84/323)
Overweight (BMI≥25)[a]	48.3 (29/60)	48.7 (113/232)	67.4 (60/89)	59.1 (191/323)
Hypertension	36.8 (21/57)	24.7 (59/239)	54.2 (45/83)	47.0 (156/332)
Low HDL C	38.1 (24/63)	31.7 (69/218)	37.1 (33/89)	31.6 (96/304)
Metabolic syndrome	29.3 (17/58)	21.5 (45/209)	41.7 (35/84)	25.5 (75/294)
Type 2 diabetes	3.0 (2/67)	2.8 (7/254)	1.1 (1/94)	0.8 (3/369)
BMI[a]	25.4 (5.1)	26.0 (6.0)	26.6 (4.5)	27.0 (5.1)
Systolic BP, mm HG	116.5 (14.5)	114.4 (15.1)	125.2 (13.6)	124.1 (12.6)
Diastolic BP, mm HG	76.6 (10.4)	74.7 (11.6)	81.1 (11.3)	79.3 (9.6)
Cholesterol, mmol/L	5.2 (1.1)	5.1 (1.1)	5.3 (1.1)	5.1 (1.1)
HDL-C, mmol/L	1.4 (0.3)	1.5 (0.4)	1.1 (0.4)	1.2 (0.4)
LDL-C, mmol/L	3.1 (0.8)	3.1 (1.0)	3.3 (0.9)	3.3 (0.9)
Glucose, mmol/L	5.1 (1.1)	5.1 (0.8)	5.1 (0.8)	5.3 (1.0)
Triglycerides, mmol/L	1.4 (1.1)	1.2 (0.8)	2.0 (1.5)	1.8 (1.3)
18-35 y	N = 41	N = 174	N = 60	N = 289
Daily smoking	53.7 (22/41)	42.9 (73/170)	63.8 (37/58)	40.6 (136/269)
Obesity (BMI≥30)[a]	16.2 (6/37)	19.0 (30/158)	20.7 (12/58)	23.6 (60/254)
Overweight (BMI≥25)[a]	37.8 (14/37)	45.6 (78/158)	60.3 (35/58)	53.9 (137/254)
Hypertension	27.0 (10/37)	17.8 (29/163)	51.7 (30/58)	44.7 (115/257)
Low HDL C	34.2 (13/38)	30.7 (47/153)	39.3 (22/56)	28.6 (69/241)
MetS	17.1 (6/35)	16.9 (25/138)	35.2 (19/54)	19.9 (46/231)
Type 2 diabetes	2.4 (1/41)	1.7 (3/174)	1.7 (1/60)	0.3 (1/289)
BMI[a]	24.3 (5.0)	25.4 (5.9)	25.8 (4.3)	26.4 (5.0)
Systolic BP, mm HG	113.7 (13.1)	112.6 (13.6)	123.0 (11.4)	123.8 (12.0)
Diastolic BP, mm HG	74.6 (8.4)	73.1 (11.3)	79.2 (9.8)	78.3 (9.7)
Cholesterol, mmol/L	4.9 (1.0)	4.8 (0.9)	5.1 (1.1)	5.0 (1.0)
HDL-C, mmol/L	1.4 (0.4)	1.5 (0.4)	1.2 (0.4)	1.2 0.3()
LDL-C, mmol/L	2.9 (0.8)	2.9 (0.9)	3.2 (0.8)	3.2 (0.9)
Glucose, mmol/L	4.9 (1.1)	5.0 (0.5)	5.0 (0.9)	5.3 (1.0)
Triglycerides, mmol/L	1.2 (0.7)	1.1 (0.7)	1.8 (1.2)	1.7 (1.2)
36-50 y	N = 20	N = 62	N = 30	N = 72
Daily smoking	47.4 (9/19)	52.5 (32/61)	37.9 (11/29)	38.6 (27/70)
Obesity (BMI≥30)[a]	33.3 (6/18)	21.1 (12/57)	28.6 (8/28)	38.7 (24/62)
Overweight (BMI≥25)[a]	72.2 (13/18)	54.4 (31/57)	78.6 (22/28)	80.6 (50/62)
Hypertension	58.8 (10/17)	36.2 (21/58)	56.5 (13/23)	55.2 (37/67)
Low HDL C	47.4 (9/19)	36.2 (17/47)	34.5 (10/29)	44.8 (26/58)
MetS	50.0 (9/18)	26.1 (12/46)	53.8 (14/26)	48.3 (28/58)
Type 2 diabetes	5.0 (1/20)	4.8 (3/62)	0 (0/30)	2.8 (2/72)
BMI[a]	28.6 (4.9)	26.4 (5.7)	28.8 (4.7)	29.4 (4.9)
Systolic BP, mm HG	122.3 (16.2)	118.4 (16.8)	131.7 (18.4)	125.3 (15.1)
Diastolic BP, mm HG	82.1 (13.2)	77.7 (10.8)	86.0 (14.7)	83.2 (8.6)
Cholesterol, mmol/L	5.6 (1.0)	5.6 (1.2)	5.9 (1.1)	5.5 (1.3)
HDL-C, mmol/L	1.4 (0.3)	1.5 (0.5)	1.2 (0.3)	1.2 (0.6)
LDL-C, mmol/L	3.3 (0.8)	3.5 (1.2)	3.9 (0.9)	3.5 (1.2)
Glucose, mmol/L	5.4 (1.0)	5.3 (1.2)	5.3 (0.8)	5.4 (1.3)
Triglycerides, mmol/L	1.9 (1.4)	1.3 (0.8)	2.3 (1.8)	2.1 (1.5)
51-65 y	N = 6	N = 19	N = 4	N = 8
Daily smoking	40.0 (2/5)	57.9 (11/19)	66.7 (2/3)	37.5 (3(8)
Obesity (BMI≥30)[a]	0 (0/5)	35.3 (6/17)	0 (0/3)	0 (0/7)
Overweight (BMI≥25)[a]	40.0 (2/5)	58.8 (10/17)	100 (3/3)	57.1(4/7)
Hypertension	33.3 (1/3)	50.0 (9/18)	100 (2/2)	50.0 (4/8)
Low HDL C	33.3 (2/6)	27.8 (5/18)	25.0 (1/4)	20.0 (1/5)
MetS	40.0 (2/5)	41.2 (7/17)	50.0 (2/4)	20.0 (1/5)
Type 2 diabetes	0 (0/6)	5.3 (1/19)	0 (0/4)	0 (0/8)
BMI[a]	24.9 (4.6)	29.1 (6.1)	28.0 (1.5)	24.4 (3.4)
Systolic BP, mm HG[b]	126.6 (.)	120.0 (19.8)	141.9 (14.1)	126.4 (11.5)
Diastolic BP, mm HG[b]	70.0 (.)	79.6 (14.1)	99.3 (3.5)	82.1 (12.5)
Cholesterol, mmol/L	5.7 (0.8)	5.6 (0.7)	5.8 (0.2)	6.2 (0.8)
HDL-C, mmol/L	1.4 (0.2)	1.5 (0.4)	1.0 (0.3)	1.5 (0.5)
LDL-C, mmol/L	3.3 (0.5)	3.5 (0.7)	3.4 (1.2)	4.3 (1.0)
Glucose, mmol/L	5.6 (1.4)	5.7 (1.0)	4.9 (0.2)	5.0 (0.7)
Triglycerides, mmol/L	2.2 (1.6)	1.6 (1.1)	3.1 (0.4)	0.7 (2.1)

CVD risk levels in SCZ 2005 sample and 2017 sample. For categorical risk factors, percentages (%) are from chi-square test and p-values are from logistic regression with adjustment for differences in age, duration of treatment and duration of illness. Mean (SD) values of continuous variables have been adjusted for the same covariates with ANCOVA.

[a] Weight in kg/height in m^2.

[b] Statistical significant difference and SD are not computed as data is available from only one female patient aged 51-65 years.

*p < 0.025. **p < 0.008. Abbreviations: BMI = body mass index, BP = blood pressure, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, MetS = Metabolic syndrome

Supplementary table 3. Cardiovascular risk factors of BD 2005 sample versus 2017

	Women		Men	
Variables	2005 sample	2017 sample	2005 sample	2017 sample
All ages	N = 65	N = 235	N = 44	N = 152
Daily smoking	38.5 (25/65)	43.1 (100/232)	56.8 (25/44)	41.5 (61/147)*
Obesity (BMI≥30)[a]	28.6 (18/63)	11.9 (26/218)**	16.3 (7/43)	14.4(20/139)
Overweight (BMI≥25)[a]	50.8 (32/63)	45.4 (99/218)	67.4 (29/43)	61.2 (85/139)
Hypertension	43.5 (27/62)	15.1 (33/218)**	61.4 (27/44)	54.6 (77/141)
Low HDL C	21.7 (13/40)	25.9 (56/216)	22.7 (10/44)	23.0 (32/139)
MetS	25.0 (15/60)	12.7 (27/212)	36.4 (16/44)	26.7 (36/135)
Type 2 diabetes	7.7 (5/65)	3.0 (7/235)	0 (0/44)	1.3 (2/152)
BMI[a]	26.2 (5.8)	25.2 (4.9)	26.1 (3.6)	26.3 (3.5)
Systolic BP, mm HG	123.2 (18.1)	112.7 (12.9)**	131.2 (19.0)	125.9 (17.2)
Diastolic BP, mm HG	79.6 (9.7)	72.2 (10.4)**	84.8 (11.6)	81.4 (13.8)**
Cholesterol, mmol/L	5.2 (1.1)	4.9 (1.0)	5.6 (1.3)	5.0 (1.0)
HDL-C, mmol/L	1.7 (0.5)	1.6 (0.4)	1.2 (0.3)	1.2 (0.3)*
LDL-C, mmol/L	3.0 (1.1)	2.9 (0.9)	3.7 (1.1)	3.1 (0.8)
Glucose, mmol/L	5.3 (1.7)	5.1 (1.0)	5.3 (0.7)	5.2 (0.8)
Triglycerides, mmol/L	1.4 (1.7)	1.1 (0.6)	1.7 (0.9)	1.5 (0.9)
18-35 y	N = 34	N = 150	N = 19	N = 96
Daily smoking	41.2 (14/34)	38.1 (56/147)	68.4 (13/19)	41.8 (38/91)
Obesity (BMI≥30)[a]	26.5 (9/34)	11.3 (16/142)	10.5 (2/19)	9.0 (8/89)
Overweight (BMI≥25)[a]	47.1 (16/34)	39.4 (56/142)	57.9 (11/19)	52.8 (47/89)
Hypertension	30.3 (10/33)	9.2 (13/141)**	47.4 (9/19)	53.3 (48/90)
Low HDL C	20.0 (6/30)	27.0 (38/141)	31.6 (6/19)	21.6 (19/88)
MetS	19.4 (6/31)	10.9 (15/138)	21.1 (4/19)	14.0 (12/86)
Type 2 diabetes	11.8 (4/34)	2.0 (3/150)	0 (0/19)	0 (0/96)
BMI[a]	25.5 (5.9)	24.8 (5.1)	26.1 (3.5)	25.3 (3.2)
Systolic BP, mm HG	117.5 (13.1)	110.1 (9.9)**	127.6 (13.6)	122.6 (15.8)
Diastolic BP, mm HG	77.2 (8.7)	70.1 (9.3)**	79.2 (8.7)	79.5 (14.3)
Cholesterol, mmol/L	4.9 (0.8)	4.6 (0.8)	5.2 (1.5)	4.8 (0.9)
HDL-C, mmol/L	1.2 (0.2)	1.3 (0.3)	1.1 (0.3)	1.2 (0.3)
LDL-C, mmol/L	2.7 (0.7)	2.7 (0.7)	3.3 (1.2)	3.0 (0.7)
Glucose, mmol/L	5.3 (2.0)	5.0 (1.2)	5.2 (0.8)	5.1 (0.6)
Triglycerides, mmol/L	1.2 (1.0)	1.1 (0.5)**	1.7 (1.0)	1.4 (0.9)
36-50 y	N = 19	N = 67	N = 17	N = 34
Daily smoking	36.8 (7/19)	52.2 (35/67)	58.8 (10/17)	38.2 (13/34)
Obesity (BMI≥30)[a]	33.3 (6/18)	10.2 (6/59)	18.8 (3/16)	18.8 (6/32)
Overweight (BMI≥25)[a]	50.0 (9/18)	52.5 (31/59)	81.3 (13/16)	75.0 (24/32)
Hypertension	44.4 (8/18)	22.0 (13/59)	64.7 (11/17)	51.6 (16/31)
Low HDL C	26.3 (5/19)	27.1 (16/59)	17.6 (3/17)	33.3 (10/30)
MetS	16.7 (3/18)	17.2 (10/58)	47.1 (8/17)	30.0 (9/30)
Type 2 diabetes	0 (0/19)	6.0 (4/67)	0 (0/17)	0 (0/34)
BMI[a]	25.6 (5.1)	25.6 (4.0)	25.7 (3.5)	27.0 (3.6)
Systolic BP, mm HG	126.0 (16.8)	114.8 (13.1)**	133.7 (22.4)	126.1 (14.9)
Diastolic BP, mm HG	79.8 (7.8)	75.8 (12.0)	88.9 (12.8)	80.8 (11.4)
Cholesterol, mmol/L	5.7 (1.3)	5.1 (1.0)	6.0 (1.2)	5.5 (1.1)
HDL-C, mmol/L	1.8 (0.5)	1.5 (0.4)	1.2 (0.2)	1.3 (0.3)
LDL-C, mmol/L	3.4 (1.4)	3.1 (0.9)	4.1 (1.1)	3.4 (0.8)
Glucose, mmol/L	4.8 (0.4)	5.0 (0.7)	5.4 (0.4)	5.0 (0.3)
Triglycerides, mmol/L	1.1 (0.4)	1.2 (0.8)**	1.7 (1.2)	1.7 (0.9)
51-65 y	N = 12	N = 18	N = 8	N = 22
Daily smoking	40.0 (2/5)	57.9 (11/19)	25.0 (2/8)	45.5 (10/22)
Obesity (BMI≥30)[a]	27.3 (3/11)	23.5 (4/17)	25.0 (2/8)	33.3 (6/18)
Overweight (BMI≥25)[a]	63.6 (7/11)	70.6 (12/17)	62.5 (5/8)	77.8 (14/18)
Hypertension	81.8 (9/11)	38.9 (7/18)	87.5 (7/8)	65.0 (13/20)
Low HDL C	18.2 (2/11)	12.5 (2/16)	12.5 (1/8)	40.0 (8/20)
MetS	54.5 (6/11)	6.3 (1/16)	50.0 (4/8)	47.4 (9/19)
Type 2 diabetes	8.3 (1/12)	0 (0/18)	0 (0/8)	9.1 (2/22)
BMI[a]	29.0 (6.6)	28.0 (6.4)	26.8 (4.3)	28.2 (3.5)
Systolic BP, mm HG	144.2 (21.2)	122.7 (23.5)	147.1 (18.7)	134.5 (19.9)
Diastolic BP, mm HG	90.4 (10.6)	74.8 (9.6)**	91.5 (10.2)	84.7 (10.8)
Cholesterol, mmol/L	6.2 (1.0)	6.3 (1.1)	5.9 (1.1)	5.1 (1.0)
HDL-C, mmol/L	1.5 (0.5)	1.9 (0.4)	1.4 (0.4)	1.2 (0.3)
LDL-C, mmol/L	3.8 (0.8)	3.9 (1.1)	3.8 (0.9)	3.1 (0.8)
Glucose, mmol/L	6.1 (1.5)	5.4 (0.5)	5.8 (0.8)	5.8 (1.4)
Triglycerides, mmol/L	2.8 (3.4)	1.0 (0.4)	1.7 (0.9)	1.8 (0.9)

CVD risk levels in BD 2005 sample and 2017 sample. For categorical risk factors, percentages (N) are from chi-square test and p-values are from logistic regression with adjustment for differences in age, duration of treatment and duration of illness. Mean (SD) values of continuous variables have been adjusted for the same covariates with ANCOVA.

[a] Weight in kg/height in m^2.

* $p < 0.025$. ** $p < 0.008$. Abbreviations: BMI = body mass index, BP = blood pressure, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, MetS = Metabolic syndrome

Supplementary table 4. Cardiovascular risk factors of healthy controls vs. 2017 sample

	Women			Men		
Variables	Healthy controls	SCZ	BD	Healthy controls	SCZ	BD
All ages	N = 423	N = 255	N = 235	N = 499	N = 369	N = 152
Daily smoking	12.4 (24/194)	46.4 (116/250)**	43.1 100/232)**	18.0 (37/205)	47.8 (166/347)**	41.5 (61/147)**
Obesity (BMI≥30)[a]	9.5 (8/84)	20.7 (48/232)**	11.9 (26/218)	12.1 (12/99)	26.0 (84/323)**	14.4(20/139)
Overweight (BMI≥25)[a]	40.5 (34/84)	48.7 (113/232)	45.4 (99/218)	39.4 (39/99)	59.1 (191/323)**	61.2 (85/139)**
Central obesity	22.4 (70/313)	44.9 (93/207)**	34.8 (72/207)**	13.1 (53/406)	29.8 (93/213)**	24.1 (33/137)*
Hypertension	14.5 (10/69)	24.7 (59/239)**	15.1 (33/218)	41.0 (34/83)	47.0 (156/332)*	54.6 (77/141)
Low HDL C	15.9 (63/397)	31.7 (69/218)**	25.9 (56/216)**	13.5 (64/473)	31.6 (96/304)**	23.0 (32/139)**
MetS	2.4 (2/84)	21.5 (45/209)**	12.7 (27/212)	6.8 (8/117)	25.5 (75/294)**	26.7 (36/135)*
Type 2 diabetes	0.2 (1/423)	2.8 (7/254)*	3.0 (7/235)*	0 (0/499)	0.8 (3/369)	1.3 (2/152)
BMI[a]	24.2 (3.7)	26.1 (6.0)**	25.3 (5.1)	24.8 (4.0)	27.0 (5.2)**	26.2 (3.6)
Waist, cm	80.6 (12.4)	87.9 (15.5)**	85.2 (13.7)**	89.8 (11.4)	96.4 (15.2)**	94.1 (10.8)**
Systolic BP, mm HG	113.7 (12.6)	114.9 (15.6)	112.5 (12.7)	122.3 (10.5)	124.4 (12.8)	125.3 (16.4)
Diastolic BP, mm HG	73.8 (9.0)	74.6 (11.8)	71.9 (10.5)	78.6 (8.0)	79.3 (9.6)	80.4 (13.5)
Cholesterol, mmol/L	4.9 (0.9)	5.1 (1.0)*	4.9 (1.0)	4.9 (1.0)	5.2 (1.1)**	4.9 (1.0)
HDL-C, mmol/L	1.7 (0.4)	1.5 (0.4)**	1.6 (0.4)**	1.4 (0.4)	1.2 (0.4)**	1.2 (0.3)**
LDL-C, mmol/L	2.7 (0.8)	3.1 (1.0)**	2.9 (0.8)	4.0 (0.9)	3.4 (1.0)**	3.1 (0.8)
Glucose, mmol/L	4.9 (0.4)	5.1(0.8)	5.0 (1.0)	5.2 (0.4)	5.3 (1.0)	5.2 (0.4)
Triglycerides, mmol/L	0.8 (0.4)	1.2 (0.8)**	1.1 (0.4)**	1.2 (0.9)	1.7 (1.3)**	1.5 (1.0)**
18-35 y	N = 266	N = 174	N = 150	N = 309	N= 289	N = 96
Daily smoking	12.7 (15/118)	42.9 (73/170)**	38.1 (56/147)**	17.4 (20/115)	40.6 (136/269)**	41.8 (38/91)**
Obesity (BMI≥30)[a]	8.0 (4/50)	19.0 (30/158)	11.3 (16/142)	10.3 (6/58)	23.6 (60/254)	9.0 (8/89)
Overweight (BMI≥25)[a]	34.0 (17/50)	45.6 (78/158)	39.4 (56/142)	37.9 (22/58)	53.9 (137/254)**	52.8 (47/89)
Central obesity	17.9 (37/207)	37.9 (53/140)**	29.6 (40/135)**	10.4 (28/269)	24.9 (60/241)**	16.5 (14(85)
Hypertension	11.9 (5/42)	17.8 (29/163)**	9.2 (13/141)	36.2 (17/47)	44.7 (115/257)**	53.3 (48/90)
Low HDL C	18.4 (46/250)	30.7 (47/153)**	27.0 (38/141)	11.0 (32/292)	28.6 (69/241)**	21.6 (19/88)
MetS	1.7 (1/60)	16.9 (25/138)	10.9 (15/138)	5.2 (4/77)	19.9 (46/231)**	14.0 (12/86)
Type 2 diabetes	0 (0/266)	1.7 (3/174)	2.0 (3/150)	0 (0/309)	0.3 (1/289)	0 (0/96)
BMI[a]	23.5 (3.8)	25.7 (6.0)**	24.9 (5.2)	24.4 (4.2)	26.5 (5.1)**	25.7 (3.5)
Waist, cm	78.7 (13.1)	85.9 (15.0)	83.8 (13.4)**	88.1 (14.5)	94.2 (11.0)**	92.1 (0.8)**
Systolic BP, mm HG	113.1 (7.8)	113.0 (13.6)	110.5 (9.7)	121.5 (10.3)	124.1 (12.4)	122.8 (15.7
Diastolic BP, mm HG	72.7 (7.4)	73.2 (11.1)	70.2 (9.3)	78.8 (8.5)	78.1(9.7)	79.7 (14.8)
Cholesterol, mmol/L	4.7 (0.9)	4.8 (0.9)	4.6 (0.8)	4.7 (1.0)	5.0 (1.0)**	4.9 (0.9)
HDL-C, mmol/L	1.7 (0.5)	1.5 (0.4)**	1.6 (0.4)**	1.4 (0.3)	1.2 (0.4)**	1.2 (0.3)**
LDL-C, mmol/L	2.5 (0.7)	2.9 (0.9)**	2.7 (0.7)	2.8 (0.9)	3.2 (0.9)**	3.0 (0.8)
Glucose, mmol/L	4.9 (0.4)	4.9 (0.5)	5.0 (1.1)	5.1 (0.4)	5.2 (0.9)	5.1 (0.6)
Triglycerides, mmol/L	0.9 (0.4)	1.2 (0.7)**	1.1 (0.6)**	1.1 (0.9)	1.7 (1.2)**	1.4 (0.9)
36-50 y	N = 130	N = 62	N = 67	N = 174	N = 72	N=34
Daily smoking	8.3 (5/60)	52.5 (32/61)**	52.2 (35/67)**	20.8 (16/77)	38.6 (27/70)	38.2 (13/34)
Obesity (BMI≥30)[a]	12.9 (4/31)	21.1 (12/57)	10.2 (6/59)	12.8 (5/39)	38.7 (24/62)**	18.8 (6/32)
Overweight (BMI≥25)[a]	51.6 (15/31)	54.4 (31/57)	52.5 (31/59)	38.5 (15/39)	80.6 (50/62)**	75.0 (24/32)**
Central obesity	30.5 (29/95)	52.9 (27/51)**	40.7 (22/54)	17.6 (23/131)	50.8 (32/63)**	28.1 (9/32)
Hypertension	12.5 (3/24)	36.2 (21/58)*	22.0 (13/59)	44.1 (15/34)	55.2 (37/67)	51.6 (16/31)
Low HDL C	13.2 (16/121)	36.2 (17/47)**	27.1 (16/59)	16.9 (28/166)	44.8 (26/58)**	33.3 (10/30)
MetS	4.2 (1/24)	26.1 (12/46)*	17.2 (10/58)	7.7 (3/39)	48.3 (28/58)**	30.0 (9/30)
Type 2 diabetes	0.8 (1/130)	4.8 (3/62)	6.0 (4/67)	0 (0/174)	2.8 (2/72)	0 (0/34)
BMI[a]	25.5 (3.5)	26.3 (5.5)	25.6 (4.4)	25.6 (3.6)	29.0 (5.0)**	26.8 (3.6)
Waist, cm	83.5 (9.7)	90.3 (15.2)**	86.5 (13.4)	93.5 (11.7)	104.8 (15.0)**	97.9 (9.9)
Systolic BP, mm HG	112.2 (9.8)	119.0 (18.7)	113.5 (13.7)	123.4 (10.6)	125.0 (14.6)	126.6 (14.3)
Diastolic BP, mm HG	73.6 (8.0)	77.1 (12.3)	74.8 (12.4)	79.2 (7.5)	82.9 (8.2)	80.6 (10.7)
Cholesterol, mmol/L	5.1 (0.9)	5.5 (1.2)	5.1 (1.0)	5.3 (1.0)	5.6 (1.2)	5.4 (1.1)
HDL-C, mmol/L	1.7 (0.4)	1.6 (0.5)**	1.6 (0.4)	1.3 (0.3)	1.2 (0.6)**	1.2 (0.3)
LDL-C, mmol/L	3.0 (0.8)	3.4 (1.2)**	3.4 (1.3)	3.3 (0.8)	3.5 (1.1)	3.4 8(0.8)
Glucose, mmol/L	5.1 (0.9)	5.3 (1.2)	5.0 (0.8)	5.4 (1.3)	5.3 (0.5)	5.1 (0.4)
Triglycerides, mmol/L	0.7 (0.2)	1.3 (0.7)**	1.2 (0.8)**	1.2 (0.9)	2.0 (1.5)**	1.7 (1.2) **
51-65 y[b]	N = 27	N = 19	N = 18	N = 16	N = 8	N = 22
Daily smoking	25.0 (4/16)	57.9 (11/19)	57.9 (11/19)	7.7 (1/13)	37.5 (3(8)	45.5 (10/22)
Obesity (BMI≥30)[a]	0 (0/3)	35.3 (6/17)	23.5 (4/17)	50.0 (1/2)	0 (0/7)	33.3 (6/18)
Overweight (BMI≥25)[a]	33.3 (1/3)	58.8 (10/17)	70.6 (12/17)	100 (2/2)	57.1(4/7)	77.8 (14/18)
Central obesity	36.4 (4/11)	81.3 (13/16)	55.6 (10/18)	33.3 (2/6)	12.5 (1/8)	50.0 (10/20)
Hypertension	66.7 (2/3)	50.0 (9/18)	38.9 (7/18)	100 (2/2)	50.0 (4/8)	65.0 (13/20)
Low HDL C	3.8 (1/26)	27.8 (5/18)	12.5 (2/16)	26.7 (4/15)	20.0 (1/5)	14.3 (3/21)
MetS	0 (0/17)	41.2 (7/17)	6.3 (1/16)	100 (1/1)	20.0 (1/5)	40.0 (8/20)
Type 2 diabetes	0 (0/27)	5.3 (1/19)	0 (0/18)	0 (0/16)	0 (0/8)	9.1 (2/22)
BMI[a]	24.7 (3.2)	28.4 (6.1)	28.1 (6.0)	24.6 (3.5)	30.6 (2.4)	28.2 (3.5)
Waist, cm	90.2 (12.5)	99.2 (14.7)	95.2 (14.2)	93.2 (11.4)	94.5 (6.5)	103.2 (9.8)
Systolic BP, mm HG	147.4 (42.5)	118.0 (19.0)	124.3 (21.5)	135.1 (7.1)	127.8 (11.5)	135.0 (19.5)
Diastolic BP, mm HG	92.2 (15.0)	80.0 (13.3)	75.4 (9.2)	84.5 (12.5)	84.5 (12.5)	84.9 (10.6)
Cholesterol, mmol/L	6.0 (1.1)	5.6 (0.7)	6.2 (1.2)	6.3 (0.9)	6.3 (0.8)	5.1 (0.9)
HDL-C, mmol/L	1.8 (0.4)	1.6 (0.4)	1.8 (0.5)	1.4 (0.4)	1.4 (0.5)	1.2 (0.3)
LDL-C, mmol/L	3.5 (1.1)	3.4 (0.7)	3.5 (0.8)	3.8 (1.0)	4.3 (0.7)	3.1 (0.8)
Glucose, mmol/L[c]	. (.)	5.6 (1.2)	5.3 (0.5)	4.2 (.)	5.5 (0.7)	5.8 (1.4)
Triglycerides, mmol/L[c]	. (.)	1.5 (1.0)	1.2 (0.6)	1.3 (.)	2.2 (0.4)	1.8 (0.9)

CVD risk levels in healthy controls and 2017 sample. For categorical risk factors, percentages (N) are from chi-square test and p-values are from logistic regression with adjustment for age. Mean (SD) values of continuous variables are adjusted for age with ANCOVA.

[a] Weight in kg/height in m^2.

[b] Due to small sample size of controls between 51-65 years, metabolic risk factors in this age group are not statistically compared with SCZ and BD.

[c] Missing/only one fasting blood samples from healthy controls

*p < 0.025. **p < 0.008.. Abbreviations: BMI = body mass index, BP = blood pressure, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, MetS = Metabolic syndrome

Stratified analysis of healthy controls and BD 2017 sample, Bonferroni corrected

Several differences in CVD risk factors between controls and BD 2017 sample did not reach significance level after Bonferroni correction. After stratifying by sex with accompanying Bonferroni correction, the significant difference in MetS and BMI between controls and BD 2017 sample disappeared ($p > 0.025$). When stratifying by both sex and age groups, significant differences disappeared in overweight, central obesity, low HDL, MetS and TGs in males aged 18-35 years, low HDL, MetS, HDL-C and FG in males aged 36-50 years, and daily smoking, LDL and FG in males aged 51-65 years ($p > 0.008$). Within the female group, significant difference in MetS and low HDL C disappeared in the age group 36-50 individuals after Bonferroni correction ($p > 0.008$).

CVD risk factors in the 2014-2017 sample compared with the 2005 sample, controls and the general population

As the difference in time between the two samples was short and the duration of the samples was different, we did supplementary analysis comparing the 2005 sample with a sample of similar duration from 2014-2017. The results were mainly in line with the original findings, except from fewer significant reductions in the BD group. Specifically, the reductions in LDL-C, hypertension, overweight and obesity did not reach statically significance, while daily smoking was significantly reduced to 28.4 % (odds ratio = 2.29, $p = 0.013$) in patients with BD from 2014-2017. Among patients with SCZ, there was a significant reduction in low HDL-C (odds ratio = 2.414, $p = 0.006$) in the 2014-2017 sample. No significant difference was found in self-reported physical activity and diet between samples ($p > 0.05$). Moreover, the CVD risk level was higher in patients from 2014-2017 compared to controls and the general population from the same time period. Several of the differences between patients with BD and controls, however, did not reach statistical significance, which is probably related to reduced statistical power. For more details, see Supplementary table 5 and 6.

Supplementary table 5. Cardiovascular Risk Factors of 2005 sample versus 2014-2017 sample

	Schizophrenia			Bipolar disorder		
Variable	2005 sample (N=161)	2014-2017 sample (N=109)	Effect size	2005 sample (N=109)	2014-2017 sample (N=96)	Effect size
Daily smoking	53.5 (83/155)	46.7 (49/105)	1.362	45.9 (50/109)	28.4 (27/95)	2.290*
Obesity[a]	21.5 (32/149)	27.1 (26/96)	0.689	23.6 (25/106)	14.4 (13/90)	1.972
Overweight[a]	59.7 (89/149)	55.2 (53/96)	1.116	57.5 (61/106)	53.5 (48/90)	1.972
Hypertension	47.1 (66/140)	41.8 (41/98)	1.018	50.9 (54/106)	38.5 (35/91)	1.294
Low-HDL-C	37.5 (57/152)	19.4 (19/98)	2.414**	22.1 (23/104)	21.1 (19/90)	1.586
MetS[b]	36.6 (52/142)	24.4 (21/86)	1.511	29.8 (31/104)	16.3 (14/86)	1.873
Type 2 diabetes	1.9 (3/161)	1.8 (2/109)	1.117	4.6 (5/109)	2.1 (2/96)	2.006
BMI[a]	26.1 (25.3, 27.0)	26.7 (25.6, 27.8)	-0.124	26.2 (25.3, 27.1)	25.9 (24.8, 27.0)	0.074
Waist, cm	93.1 (87.7, 98.5)	92.1 (88.7, 95.5)	0.067	94.4 (87.1, 101.8)	86.8 (83.5, 90.0)	0.452
Systolic BP, mm HG	121.5 (119.0, 124.0)	119.5 (116.1, 122.8)	0.127	126.8 (123.7, 129.9)	116.6 (112.5, 120.7)	0.542*
Diastolic BP, mm HG	79.4 (77.6, 81.2)	78.5 (75.7, 81.2)	0.071	81.8 (79.5,84.1)	77.3 (74.4, 80.3)	0.342*
Cholesterol, mmol/L	5.3 (5.1, 5.4)	5.2 (4.9, 5.4)	0.094	5.4 (5.2, 5.6)	4.8 (4.6, 5.1)	0.531**
HDL-C, mmol/L	1.3 (1.2, 1.3)	1.4 (1.3, 1.5)	-0.181	1.5 (1.4, 1.5)	1.5 (1.4, 1.6)	-0.075
LDL-C, mmol/L	3.2 (3.1, 3.4)	3.3 (3.1, 3.5)	-0.111	3.3 (3.1, 3.5)	3.0 (2.8, 3.2)	0.313
Glucose, mmol/L	5.1 (4.9, 5.2)	5.3 (5.1, 5.5)	-0.271	5.3 (5.1, 5.5)	5.1 (4.8, 5.3)	0.245
Triglycerides, mmol/L	1.8 (1.6, 2.0)	1.5 (1.3, 1.8)	0.091	1.5 (1.3, 1.7)	1.2 (1.0, 1.5)	0.234

Mean (95% CI) levels and percentages (N) of cardiovascular risk factors for the two patient samples. Effect sizes are reported in Cohen's d for continuous variables and odds ratio for categorical variables. All values except from percentages (N) are adjusted for age, duration of treatment and duration of illness with ANCOVA and logistic regression.

[a]Weight in kg/height in m^2.

[b]In the comparison of MetS between samples, BMI ≥ 30 was used an alternative measure of central obesity due to waist measurements for a limited number of patients in 2005 sample.

*p value < 0.05. ** < 0.01.

Abbreviations: BMI = body mass index, BP = blood pressure, HDL-C = high density lipoprotein cholesterol, LDL-C = low high density lipoprotein cholesterol, MetS = Metabolic syndrome

Supplementary table 6. Cardiovascular Risk Factors in 2014-2017 sample versus controls

CVD variable	Healthy controls (N=227)	Schizophrenia (N=109)		Bipolar disorder (N=96)	
		Statistic	Effect size	Statistic	Effect size
Obesity (BMI≥30)[a]	10.9 (20/183)	$\chi^2 = 12.523$	3.259***	$\chi^2 = 2.978$	1.467
Overweight (BMI≥25)[a]	39.9 (73/183)	$\chi^2 = 9.035$	2.042**	$\chi^2 = 21.482$	2.088**
Central obesity[b]	17.2 (39/227)	$\chi^2 = 20.990$	2.953***	$\chi^2 = 12.458$	1.761
Hypertension[c]	28.9 (43/149)	$\chi^2 = 8.183$	1.965*	$\chi^2 = 8.991$	1.702
Low-HDL[d]	16.6 (36/217)	$\chi^2 = 3.571$	1.309	$\chi^2 = 3.625$	1.402
MetS	8.0 (8/100)	$\chi^2 = 11.821$	3.411**	$\chi^2 = 7.090$	1.606
BMI[a]	24.7 (24.1, 25.4)	F = 11.169	0.398**	F = 5.814	0.291*
Waist, cm	85.6 (83.8, 87.5)	F = 14.787	0.439***	F = 2.531	0.193
Systolic BP, mm HG	118.5 (116.3, 120.8)	F = 0.000	0.002	F = 1.869	-0.173
Diastolic BP, mm HG	76.9 (75.1, 78.8)	F = 0.090	0.037	F = 0.001	-0.005
Cholesterol, mmol/L	4.7 (4.6, 4.9)	F = 9.937	0.371**	F = 0.053	0.027
HDL-C, mmol/L	1.5 (1.4, 1.5)	F = 6.221	-0.292*	F = 0.023	-0.017
LDL-C, mmol/L	2.9 (2.8, 3.0)	F = 11.365	0.401**	F = 0.411	0.077
Glucose, mmol/L	5.1 (4.9, 5.2)	F = 5.646	0.307*	F = 0.699	0.094
Triglycerides, mmol/L	1.0 (0.9, 1.2)	F = 21.257	0.669***	F = 4.678	0.311*

Percentages (N) and mean (95% CI) values of metabolic risk variables for healthy controls. Logistic regression was used to adjust for age differences between controls and patients when comparing categorical CVD variables. ANCOVA was used to adjust for age differences when comparing continuous CVD variables. Reported effects sizes are Cohen's d computed from ANCOVA, and odds ratio from logistic regression. Statistical significant difference in the prevalence of smokers and diabetes are not computed as these data are available from only a limited number of controls from 2014-2017 and none of these were registered as smokers or having diabetes.

[a]Weight in kg/height in m^2.

[b]Waist > 102 cm (males), < 88 cm (females).

[c]Systolic blood pressure ≥ 130 mm HG and/or diastolic blood pressure ≥ 85 mm HG or taking antihypertensive.

[d]Low-HDL < 1.0 mmol/L (males), < 1.3 mmol/L (females).

*p value < 0.05. ** < 0.01. *** <.001.

Abbreviations: BMI = body mass index, HDL-C = high density lipoprotein cholesterol, LDL-C = low high density lipoprotein cholesterol, BP = blood pressure, MetS = Metabolic syndrome

CVD risk factors in the 2014-2017 sample compared with the Statistics Norway sample

Statistics Norway has obtained self-reported data on BMI (N = 1387) and daily smoking (N = 675) in the general population of Oslo between 2014 and 2017. Analyses show a considerably higher prevalence of daily smokers and overweight/obesity among both patients with SCZ and BD from 2014 to 2017 compared with the Statistics Norway sample from the same period (SCZ: smoking: χ^2 (1, 781) = 95.63 phi = 0.35, $p < 0.001$; overweight/obesity: χ^2 (1, 1483) = 15.54, phi = 0.19, $p < 0.001$; BD: smoking: χ^2 (1, 771) = 25.99, phi = 0.18, $p < 0.001$; overweight/obesity: χ^2 (1, 1477) = 12.04, phi = 0.09, $p < 0.001$). There is also a decline in the prevalence of daily smokers in the Statistics Norway sample from 2014-2017 compared to the Statistics Norway 2005 sample (χ^2 (1, 1215) = 37.59, phi = 0.18, $p < 0.001$).

Study II

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Polygenic overlap and shared genetic loci between loneliness, severe mental disorders, and cardiovascular disease risk factors suggest shared molecular mechanisms

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Abstract

Clinical and epidemiological evidence suggest that loneliness is associated with severe mental disorders (SMDs) and increases the risk of cardiovascular disease (CVD). However, the mechanisms underlying the relationship between loneliness, SMDs, and CVD risk factors remain unknown. Here we explored overlapping genetic architecture and genetic loci shared between SMDs, loneliness, and CVD risk factors. We analyzed large independent genome-wide association study data on schizophrenia (SCZ), bipolar disorder (BD), major depression (MD), loneliness and CVD risk factors using bivariate causal mixture mode (MiXeR), which estimates the total amount of shared variants, and conditional false discovery rate to evaluate overlap in specific loci. We observed substantial genetic overlap between SMDs, loneliness and CVD risk factors, beyond genetic correlation. We identified 149 loci jointly associated with loneliness and SMDs (MD $n = 67$, SCZ $n = 54$, and BD $n = 28$), and 55 distinct loci jointly associated with loneliness and CVD risk factors. A total of 153 novel loneliness loci were found. Most of the shared loci possessed concordant effect directions, suggesting that genetic risk for loneliness may increase the risk of both SMDs and CVD. Functional analyses of the shared loci implicated biological processes related to the brain, metabolic processes, chromatin and immune system. Altogether, the study revealed polygenic overlap between loneliness, SMDs and CVD risk factors, providing new insights into their shared genetic architecture and common genetic mechanisms.

Introduction

Patients with severe mental disorders (SMDs), including schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD), have 15–20 years reduced life span compared to the general population[1]. A major cause of the increased mortality is a high cardiovascular disease (CVD) risk[2,3], and some of this CVD risk seems to be related to an unhealthy lifestyle, medication side-effects, and genetic susceptibility to CVD[4–6]. More recently, evidence has emerged implicating loneliness as a factor that may contribute to CVD comorbidity[7,8]. Loneliness is defined as a subjective discrepancy between the desired and achieved level of social relationships[9]. Loneliness is a considerable concern in Western societies, reportedly affecting more than a fifth of adults in the United States

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and the United Kingdom[10]. Feeling lonely has increasingly been recognized as an important health issue, as people who feel alone have increased risk for premature death and CVD morbidity, even after controlling for factors such as health-related behavior, age, gender, marital status, and depressive symptoms[11–15]. The influence of deficient social relationships on mortality is shown to be comparable with well-established risk factors such as smoking and exceeds the risk associated with obesity and hypertension[12]. Notably, during the coronavirus pandemic, social isolation is increasing across the globe, and the expected mental and physical health effects are large[16–18].

Loneliness is a particular challenge for people with SMDs[19]. The annual rate of loneliness is ~2.3 times higher in SMDs than in the general population[20,21], and loneliness is related to poorer quality of life, functioning and recovery[22–24]. Despite the high prevalence and adverse effects of loneliness in SMDs with vulnerability to CVD, little is known about the mechanisms underlying this association. Furthermore, development of interventions that reduce loneliness and comorbid CVD in SMDs is precluded by this limited understanding. Several factors might contribute to the co-occurrence of loneliness and CVD risk in SMDs, including unhealthy lifestyle, stigma, and stress activation[7,25–27]. Moreover, the phenotypic overlap raises an intriguing question: to what extent does a shared genetic architecture between SMDs, loneliness, and CVD risk factors drive the observed association?

SMDs are complex disorders, with heritability estimates of 0.6–0.8 for SCZ and BD[28], and ~0.4 for MDD[29]. Despite their different clinical characteristics, there is a substantial genetic overlap between the disorders[30,31]. Recent genome-wide association studies (GWASs) have identified several genetic variants associated with the disorders[32–34]. GWASs have also reported loci associated with CVD risk factors, including body mass index (BMI)[35,36], type 2 diabetes mellitus (T2D)[37], total cholesterol (TC)[38], high-density lipoprotein (HDL) cholesterol[38], systolic blood pressure (SBP)[39], diastolic blood pressure (DBP)[39], along with coronary artery disease (CAD)[40]. While loneliness is influenced by social network, support, and poverty[41,42], its estimated heritability is 0.4–0.5[43]. Specific genetic determinants of loneliness were also recently identified[44], and loneliness showed genetic correlation with MDD, SCZ, and body size[44]. However, the genetic correlations with SCZ and body size were low ($r_g = 0.17$) and insignificant with BD. A limitation with measures of genetic correlation is that the method requires consistent effect directions among the shared variants[45]. Thus, insignificant or low genetic correlations do not necessary imply no genetic overlap, but may rather be due to a mixture of positive and negative effect directions of the overlapping variants. Therefore, to obtain a comprehensive understanding of the genetic relationship between loneliness, SMDs and CVD risk, measures of genetic correlations should be complemented by tools that allow for the discovery of shared variants regardless of their effect directions[46].

In the current study, we aimed to identify the shared genetic architecture of loneliness, SMDs and CVD risk factors beyond genetic correlations by applying the recently developed bivariate causal mixture model (MiXeR), which evaluates overlap at the architecture level, estimating the total number of shared and trait-specific genetic variants[47]. The results are presented with Venn diagrams visualizing the estimated shared and unique polygenic variants[47]. Further, we applied the conditional false discovery rate (condFDR) approach, which can uncover overlapping genetic variants irrespective of direction of effects. This method builds on an empirical Bayesian statistical framework, and increases the power to detect shared loci by leveraging the combined power of several large independent GWASs[48–50]. We have used this approach to identify the shared genetic underpinnings of several complex human traits and disorders in recent years[5,6,51]. This method fits well to disentangle any complex genetic relationship with loneliness, SMDs and CVD risk factors.

Here we investigated the genetic relationship between SMDs, loneliness, and CVD risk by analyzing summary data from recent large-scale GWASs using MiXeR[47] and condFDR[50]. We hypothesize that genetic determinants contributing to SMDs and comorbid CVD, overlap with the genetic risk for loneliness, with different levels of overlap across SCZ, BD, and MDD given their different clinical characteristics. Investigating overlap in genetic variants can elucidate important shared pathobiology and have implications for the understanding of CVD comorbidity in SMDs.

Methods

Participant samples

We obtained GWAS summary data on SCZ ($n =$ 82,315), BD ($n = 51{,}710$), and major depression (MD) ($n = 450{,}619$) from Psychiatric Genomics Consortium[32–34]. We use MD instead of the diagnostic term "major depressive disorder", since many of the MD cases were identified by self-report[33]. Data on loneliness ($n = 452{,}302$) were obtained from the UK Biobank study based on self-reported responses to three questions regarding perceived loneliness, frequency of social contact, and the ability to confide in someone close[44]. The vast majority of participants in the UK Biobank are healthy individuals. A small fraction of participants has a psychiatric diagnosis, including 2483 with SCZ, 2123 with BD and 8276 with MD (UK Biobank data field 41270, Supplementary Methods and Supplementary Table 1). While the number of participants

with self-reported depression is higher (Supplementary Table 2)[52], Day et al.[44] performed a sensitivity analysis by repeating the loneliness GWAS excluding individuals with self-reported depression ($N = 26{,}801$), which did not result in any appreciable change in results[44]. Consequently, it seems unlikely that psychiatric diagnoses that are far less prevalent than self-reported depression in the UK Biobank (see Supplementary Tables 1, 2), have confounded the results significantly. Therefore, similar to Day et al.[44] we did not exclude participants with self-reported depression or other psychiatric diagnoses from the loneliness GWAS data set. Further, we used GWAS data on the CVD risk factors BMI, TC, SBP, DBL, HDL-C, and T2D, ($n =$ 159,208–795,640 depending on CVD risk factor)[35–39]. We also included CAD ($n = 185{,}000$) as this is a major CVD[40], and smoking for supplementary analysis[53]. For cond/conjFDR analyses, overlapping cohorts between GWAS samples were excluded. For details, see Supplementary Methods and original publications[32–40,44,53]. All GWASs investigated in the current study were approved by local ethics committees, and all participants provided informed consent[32–40,44,53]. The Regional Committee for Medical Research Ethics—South-East Norway has evaluated the current protocol and found that no additional institutional review board approval was necessary because no individual data were used.

Statistical analysis

For further information about the statistical approaches described below, see Supplementary Methods. We explored pleotropic enrichment by constructing conditional quantile–quantile (Q–Q) plots. Enrichment is visualized in conditional Q–Q plots as successive leftward deflections from the null distribution[48,49,54].

We used the statistical tool, MiXeR, which quantifies polygenic overlap irrespective of genetic correlation using GWAS summary statistics[47]. This method estimates the total number of shared and trait-specific causal variants (i.e., variants with nonzero additive genetic effects on a trait). We applied MiXeR for phenotypes that demonstrated most significant genetic overlap in conditional Q–Q plots (i.e., loneliness and SMDs and BMI). To evaluate model fit, i.e., the ability of the MiXeR model to predict the actual GWAS data, we constructed modeled vs. actual conditional Q–Q plots, log-likelihood plot, and Akaike information criterion (AIC). For further information about MiXeR, see Supplementary Methods and Frei et al.[47].

To improve the discovery of specific genetic variants shared between phenotypes, we applied the condFDR statistical framework[48,49]. This approach is an extension of the standard FDR method, and re-ranks the test statistics of a primary phenotypes (e.g., SCZ) based on the strength of the association with a secondary phenotype (e.g., loneliness)[48,49,54]. After repeating the condFDR analysis for both phenotypes, we identified *shared* genetic loci at conjunctional FDR (conjFDR) <0.05[48,54]. The conjFDR is defined as the maximum of two condFDR values, which provides a conservative estimate of the FDR for association with both phenotypes[48,54]. Unlike MiXeR, conjFDR identifies the localization of specific shared variants[48,54]. Thus, MiXeR and conjFDR are complementary methods that offer information about genetic overlap on different levels (i.e., *total amount* of overlap and *specific* shared variants, respectively). These methods do not build on one another; rather, conjFDR is an extension of condFDR. Thus, we applied conjFDR for phenotypes that demonstrate polygenic overlap based on condFDR analysis, and applied condFDR for phenotypes that showed polygenic overlap in conditional Q–Q plots.

Genomic loci definition and effect direction

We defined independent genomic loci using FUMA (http://fuma.ctglab.nl/ and Supplementary Methods)[55]. Further, we evaluated the directional effects of the loci shared between loneliness and SMDs and CVD risk factors by comparing their *z*-scores or odds ratios. Effect direction could not be computed for blood pressure because effect scores were not available from the original GWAS[39]. Genetic correlations were estimated using MiXeR and LD score regression[47,56].

Functional annotation

We used FUMA[55] to functionally annotate candidate SNPs within the genomic loci with a condFDR or conjFDR value of <0.10 and an LD $r^2 \geqq 0.6$ with one of the independent significant SNPs. We further annotated SNPs using three tools: *Combined Annotation Dependent Depletion*[57], which predicts the deleteriousness of SNPs on protein structure/function; *RegulomeDB*[58], which predicts regulatory functions; and *chromatin states* that indicates the transcription/regulation effects of chromatin states at the SNP locus[59,60]. We also used FUMA[55] to map lead and candidate SNPs to genes and investigate whether these genes were overrepresented in gene-sets associated with particular biological functions (Supplementary Methods).

Results

Genetic overlap between SMDs and loneliness

In conditional Q–Q plots, we observed SNP enrichment for loneliness as a function of the significance of SNP associations with MD, SCZ, and BD (Supplementary Fig. 1). This indicates polygenic overlap between the phenotypes. The reverse conditional Q–Q plots also demonstrate consistent enrichment in MD, SCZ, and BD given associations with loneliness (Supplementary Fig. 2).

We performed MiXeR analysis with loneliness and the three SMDS after observing their polygenic overlap in

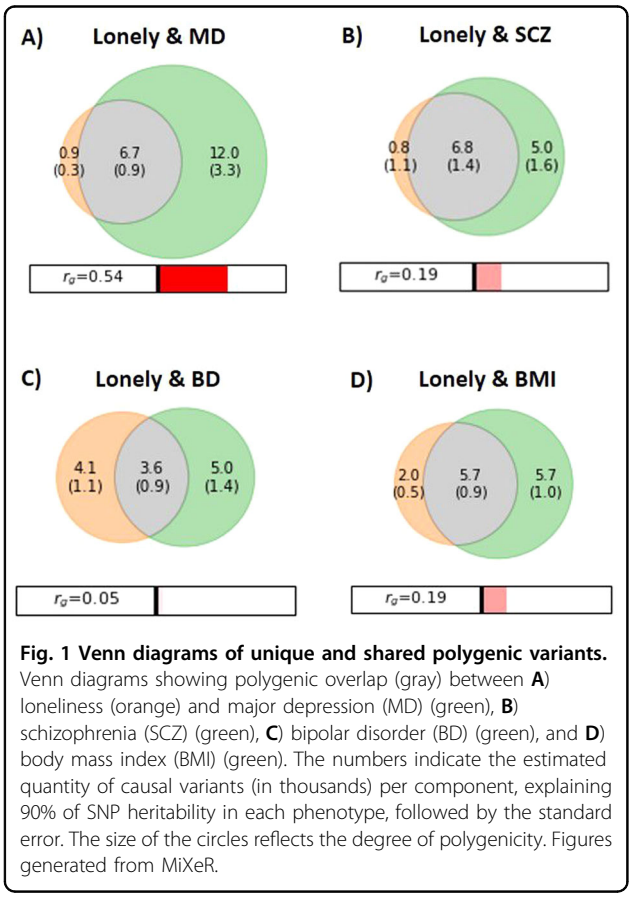

Fig. 1 Venn diagrams of unique and shared polygenic variants. Venn diagrams showing polygenic overlap (gray) between **A**) loneliness (orange) and major depression (MD) (green), **B**) schizophrenia (SCZ) (green), **C**) bipolar disorder (BD) (green), and **D**) body mass index (BMI) (green). The numbers indicate the estimated quantity of causal variants (in thousands) per component, explaining 90% of SNP heritability in each phenotype, followed by the standard error. The size of the circles reflects the degree of polygenicity. Figures generated from MiXeR.

Q–Q plots. Using MiXeR we found further evidence of polygenic overlap between loneliness and SMDs (Fig. 1; Supplementary Figs. 3,5). The Venn diagram for loneliness and MD demonstrates substantial polygenic overlap, sharing 6.7K out of 19.6K causal variants (Fig. 1A). Further, loneliness and SCZ also show polygenic overlap, sharing 6.8K out of 12.6K causal variants (Fig. 1B). In addition, loneliness and BD exhibit polygenic overlap, sharing 3.6K out of 12.7K causal variants (Fig. 1C). The MiXeR estimates adequately model the GWAS data (Supplementary Figs. 3–5; Supplementary Results), while the results of loneliness vs. MD analysis are more uncertain. Negative AIC values indicate that the MiXeR model cannot be adequately differentiated from a scenario of maximum possible overlap and a scenario of minimum overlap (Supplementary Table 3). A larger MD GWAS is needed to obtain more certain MiXeR estimates.

MiXeR estimates of genetic correlation (Fig. 1A–C) were consistent with those of LD score regression (Table 1). Loneliness exhibited a significant positive genetic correlation with MD and weaker, yet significant, correlation with SCZ, but not with BD (Table 1).

Further, using condFDR analysis, we discovered several SNPs significantly associated with loneliness conditional on their association with MD, SCZ and BD (Supplementary Tables 4–6), and vice versa (Supplementary Table 7) at condFDR <0.01.

Genetic overlap between CVD risk factors and loneliness

We uncovered polygenic overlap between loneliness and CVD risk factors. In the conditional Q–Q plots, we observed SNP enrichment for loneliness as a function of the significance of the association with CVD risk factors (Supplementary Fig. 6), and vice versa (Supplementary Fig. 7), suggesting polygenic overlap between loneliness and CVD risk factors, especially BMI.

MiXeR was performed with loneliness and BMI given their substantial polygenic overlap demonstrated by conditional Q–Q plot. MiXeR revealed considerable polygenic overlap between loneliness and BMI, sharing 5.7K out of 13.4K causal variants (Fig. 1D). MiXeR results for BMI should be interpreted with caution due to more uncertain estimates (Supplementary Fig. 8; Supplementary Table 3).

MiXeR estimates of genetic correlation (Fig. 1D) were consistent with those of LD score regression (Table 1). Loneliness showed significant positive genetic correlations with BMI, smoking, CAD and T2D, and negative genetic correlation with HDL-C (Table 1).

Further, using condFDR, we identified several loneliness SNPs conditional on their association with CVD risk factors (Supplementary Tables 8–15), and vice versa (Supplementary Table 16) at condFDR <0.01.

Genetic loci shared between SMDs, loneliness, and CVD risk factors

At conjFDR <0.05, loneliness shared 67 loci with MD, 54 loci with SCZ, and 28 loci with BD (Fig. 2A–C, Table 1; Supplementary Tables 17–19). Some of these were overlapping between the SMDs (27), yielding a total of 122 distinct loci associated with both loneliness and SMDs. Among these shared loci, 115 loci were not identified in the original loneliness GWAS[44]. We evaluated the directionality of allelic effects in the loci shared between the phenotypes by investigating their *z*-scores. As denoted by the sign of the effect sizes, effect directions were mostly consistent (Table 1; Supplementary Tables 17–19). The majority of MD risk alleles (95.5%), SCZ risk alleles (74.1%), and BD risk alleles (61.7%) showed same effect direction in loneliness (Supplementary Tables 17–19).

In addition, loneliness shared multiple loci with CVD risk factors, including BMI (36 loci; Fig. 2D), TC (6 loci), HDL-C (5 loci), SBP (9 loci), DBP (4 loci), CAD (12 loci), and T2D (1 locus) (Table 1; Supplementary Tables 20–26; Supplementary Fig. 9), but no loci shared with smoking. Some of these were overlapping across CVD risk factors, yielding a total of 55 distinct loci shared between loneliness and CVD risk factors. Among these shared loci, 49

Table 1 Shared loci between loneliness and SMDs and CVD risk factors.

Associated phenotype	Shared conjFDR	Loci (*n*) concordant effect (%)	Genetic correlation
SMD			
MD	67	95.5%	**0.570** ($p = 2.74E{-}116$)
SCZ	54	74.1%	**0.167** ($p = 5.08E{-}12$)
BD	28	61.7%	0.018 ($p = 0.60$)
CVD risk factor			
BMI	36	69.4%	**0.182** ($p = 3.73E{-}17$)
TC	6	83.3%	0.039 ($p = 0.26$)
HDL-C	5	60.0%	**−0.101** ($p = 6.62E{-}5$)
SBP	9	na	na
DBP	4	na	na
T2D	1	na	**0.119** ($p = 0.0003$)
CAD	12	58.3%	**0.129** ($p = 4.60E{-}5$)
Smoking	0	na	**0.252** ($p = 0.0002$)

Number of shared loci at conjFDR <0.05, concordant effect directions in percentage, and genetic correlation estimated by LD score regression. Bold values in the genetic correlation column are significant after Bonferroni correction ($p < 0.05/11$).
SMD severe mental disorder, *MD* major depression, *SCZ* schizophrenia, *BD* bipolar disorder, *CVD* cardiovascular disease, *BMI* body mass index, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *T2D* type 2 diabetes mellitus, *CAD* coronary heart disease, *na* not available, *conjFDR* conjunctional FDR, *Na* effect directions not available from the SBP/DBP GWAS. As there were no shared loci between loneliness and smoking, percentage of concordant effects were not computed. As only one shared locus was found between T2D and loneliness, percentage with concordant effect is not given.

were not identified in the original loneliness GWAS[44]. For the loci shared between loneliness and CVD risk factors, we discovered same effect directions of 69.4% of loci shared with BMI, 83.3% of loci shared with TC, 60% of loci shared with HDL-C, and 58.3% of loci shared with CAD (Supplementary Tables 20–26).

Further, the trio conjFDR analyses identified loci shared between loneliness, BMI and MD (4), SCZ (5), and BD (1) (Fig. 3; Supplementary Tables 27–29). 60% of the loci shared between both loneliness, SMDs, and BMI possessed same effect directions (Supplementary Tables 27–29). Further, genetic correlations were in line with the consistent effect directions (Table 1).

Altogether, we identified a total number of 163 distinct loci shared between loneliness, SMDs, and CVD risk factors. Of these shared loci, 153 were not identified in the original loneliness GWAS[44]. To visualize the shared loci, we constructed conjFDR Manhattan plots (Figs. 2, 3; Supplementary Fig. 9) where all SNPs without pruning are shown, and the independent lead SNPs are encircled in black.

Functional annotation

Functional annotation of all SNPs with a conjFDR value <0.1 within loci shared between loneliness and either SMDs or CVD risk factors demonstrated that these were mostly intronic and intergenic (Supplementary Tables 30–39). Gene-mapping of shared variants between loneliness and SMDs and CVD risk factors implicated brain-expressed genes (Supplementary Tables 30–39; Supplementary Results). For gene-set analyses, we focused on genes mapped to the loci shared between loneliness and SMDs and BMI, as these phenotypes showed most genetic overlap in the above results. Gene-set analyses for loneliness and SMDs discovered several biological processes, including "chromatin assembly", "negative regulation of biosynthetic process", "immune system development", "synapse", and "dentritic tree" (Supplementary Tables 40–42; Supplementary Results). Gene-set analyses for loneliness and BMI implicated "positive regulation of biosynthetic process" and "regulation of response to cytokine stimulus" (Supplementary Table 43; Supplementary Results). Further information about FUMA results are provided in Supplementary Results and Supplementary Tables 17–43.

Discussion

Here, we discovered polygenic overlap between loneliness, SMDs and CVD risk factors and quantified their shared genetic architecture. We identified shared loci between loneliness and MD (67 loci), SCZ (54 loci) and BD (28 loci), and loneliness and CVD risk factors (55 loci). In addition, 10 loci were found to jointly influence SMDs, loneliness and BMI. Among the shared loci identified, 153 were novel to loneliness. While there was distinct differences between MD, SCZ, and BD, the majority of the

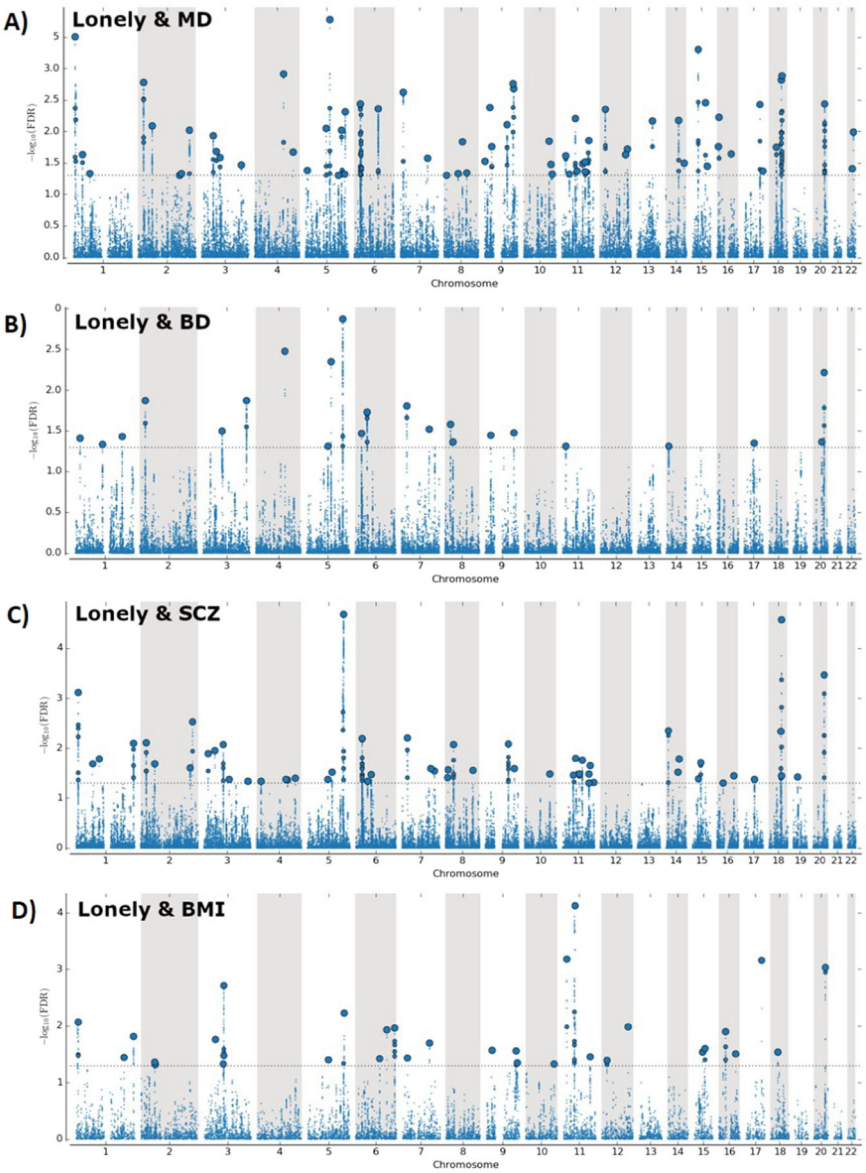

Fig. 2 Common genetic variants jointly associated with loneliness and MD, BD, SCZ, and BMI at conjFDR <0.05. Manhattan plots for loneliness and **A**) major depression, **B**) bipolar disorder, **C**) schizophrenia and **D**) body mass index. Manhattan plots showing the −log10 transformed conjFDR values for each SNP on the *y* axis and chromosomal positions along the *x* axis. SNPs with conjunction FDR < 0.05 (i.e., −log10 FDR > 1.3) are shown with enlarged data points. A black circle around the enlarged data points indicates the most significant SNP in each LD block. The figure shows the localization of the "conjunctional loci", and further details are provided in Supplementary Tables 17–20. MD major depression, SCZ schizophrenia, BD bipolar disorder, BMI body mass index, conjFDR conjunctional FDR.

shared variants (~80%) showed consistent effect directions, suggesting that genetic susceptibility to loneliness may also increase the risk of SMDs and CVD. The present results, together with prior evidence of genetic overlap between SMDs and CVD risk factors[5,6], demonstrate shared genetic loci between loneliness, SMDs, and CVD risk factors, which may underlie some of the clinical relationship between loneliness, SMDs, and CVD comorbidity.

We used MiXeR[47] to reveal polygenic overlap between loneliness, SMDs and BMI irrespective of genetic correlation. We applied conjFDR to leverage the boost in power from cross-trait enrichment, and uncovered multiple shared genetic variants between loneliness, SMDs and CVD risk factors. The conjFDR approach extends measures of genetic correlation by allowing discovery of shared loci regardless of their effect directionality[48,54]. Most of the loci shared between loneliness and MD

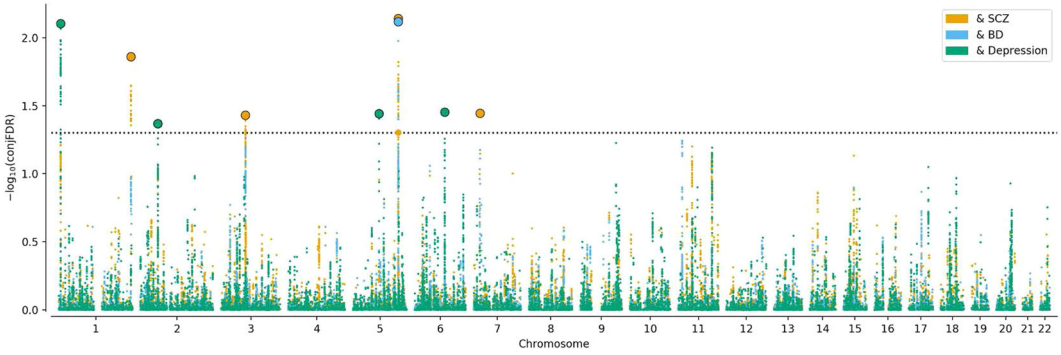

Fig. 3 Common genetic variants jointly associated with SMDs, BMI and loneliness at conjFDR <0.05. Manhattan plot showing the −log10 transformed conjFDR values for each SNP on the *y* axis and chromosomal positions along the *x* axis. SNPs with conjunction FDR < 0.05 (i.e., −log10 FDR > 1.3) are shown with enlarged data points. A black circle around the enlarged data points indicates the most significant SNP in each LD block. The figure shows the localization of the "conjunctional loci". SMDs severe mental disorders, MD major depression, SCZ schizophrenia, BD bipolar disorder, BMI body mass index, conjFDR conjunctional FDR.

(95.5%) and SCZ (74.1%) had the same effect direction, confirming the positive genetic correlation[44]. However, many of the shared loci between BD and loneliness had mixed effect directions, in line with the non-significant genetic correlation[44]. This demonstrates the usefulness of the condFDR approach to discover polygenic overlap between complex phenotypes despite the lack of genetic correlation. The results indicate that large fractions of the genomic risk architectures underlying MD, SCZ, and BD also influence loneliness, albeit in a different manner, providing new insights into their genetic nature.

Genetic risk factors of loneliness involve a propensity to experience psychological pain in response to social disconnection[26]. The perception of being socially disconnected introduces a hypervigilance to social threats, which can cause cognitive biases:[26] lonely individuals appear to perceive the social world as more threatening, and expect and remember more negative social experiences (e.g., rejection)[25,26]. Although speculative, negative social expectations may increase the risk of paranoia, and thereby, the risk of developing a psychotic disorder[61,62]. Therefore, a genetic overlap between loneliness and SCZ may reflect shared genetics influencing a tendency to view the world as unsafe, contributing to poor social interactions and, thereby, increase the risk of loneliness and psychotic disorders. Also, loneliness is likely to be associated with social withdrawal and amotivation, which are negative symptoms in SCZ. Further, cognitive biases tend to negatively influence the behavior of lonely individuals (e.g., exhibit less interest and trust) which may discourage others from seeking contact and elicit depressive symptoms[25,26]. In addition, loneliness is associated with difficulties regulating emotions[63], including diminished ability to downregulate negative emotions, similar to what is seen in MD[64]. Accordingly, the genetic overlap between loneliness and MD may reflect a genetic disposition to cognitive biases, emotional dysregulation, and behavior patterns (e.g., social withdrawal).

Similar processes may be involved in BD, which is characterized by mood disturbances, with psychotic features in 60%[65]. We may speculate that people with BD who exhibit psychotic symptoms like paranoia, are more prone to social withdrawal, contributing to loneliness. Conversely, individuals who are more socially active in manic phases, may feel less lonely. However, uncritical social behavior related to mania may contribute to social rejection and thus induce loneliness. We need further research on loneliness across different types of mood episodes in BD, which so far has provided inconsistent results[23,66]. The phenotypic heterogeneity in BD would be in line with our findings of many loci with mixed effect directions in BD and loneliness, while no genetic correlation. Taken together, our findings suggest that genetic determinants of mental processes and behavior contributing to loneliness overlap with SMDs. However, environmental factors such as a limited social network, lack of opportunities for social interactions, poverty and stigma[27,67], remain important predictors of loneliness in SMDs.

Some of the genetic overlap discovered between loneliness and MD may be due to loneliness being an aspect of the phenomenology of MD. Still, considerable evidence suggests that depression and loneliness are distinct; while loneliness is a negative feeling signaling inadequate social contact, depression is a psychiatric diagnosis reflecting a more general dysphoric state[25,26,68]. A distinction between loneliness and depression is also supported by a loneliness GWAS that demonstrated that while loneliness and MD are genetically correlated, the loneliness loci remained significant after excluding individuals with depression from the analyses[44].

By using conjFDR we discovered 55 loci that jointly influence loneliness and CVD risk factors. Further, we found overlapping loci between both loneliness, SMDs and BMI. The majority of the shared SNPs possessed the same effect directions, in line with positive genetic correlations identified between loneliness, CAD and most CVD risk factors. These findings imply that genetic susceptibility to loneliness is related to increased CVD risk, consistent with epidemiological data of positive associations between loneliness and CVD risk[11–15,69,70]. Several potential mechanisms may link loneliness to CVD risk[25], including stress activation, lifestyle and psychological coping[25]. In particular, loneliness has been linked to activation of the hypothalamic–pituitary–adrenal axis[71], which in turn has been implicated in the development of atherosclerosis[72]. Loneliness may also have indirect effects on CVD through lifestyle[25], emotional regulation[25], and mental illness[13]. Our findings suggest that the co-occurrence of loneliness and CVD risk may partly be driven by shared genetic architecture, and may explain some of comorbid CVD in SMDs. Further, gene-set analyses of the shared loci between loneliness and SMDs indicated genes associated with biological processes involving chromatin processes and brain functions, including synapses and dendrites. This provides plausible genetic links between loneliness, SMDs, and brain function. The gene-set analyses of loneliness loci shared with SMDs and BMI also indicated genes related to metabolic mechanisms and immune system, which have been implicated in the pathophysiology of SMDs and CVD morbidity[73]. However, experimental investigations are necessary to understand how the identified variants influence brain, metabolic and immune system development and function. Further, gene-mapping of shared variants between loneliness and SMDs and CVD risk factors, implicated genes expressed in brain tissue. Although the identified genes are not necessarily the genes by which the genetic variants exert their phenotypic effect, the results support the importance of brain-expressed genes in the shared genetic etiology of SMDs, loneliness and CVD. Thus, it seems likely that the shared genetic variants, together with environmental factors, contribute to brain dysfunction that affect different mental processes (cognitive bias, emotional regulation) and behavior (e.g., lifestyle, withdrawal) and thereby associated with the development of SMDs, loneliness and CVD. Other pathways are also possible; for instance, shared variants between loneliness and BMI may affect metabolism and increase the risk of overweight, which may hamper self-esteem contributing to development of loneliness and SMDs.

Although loneliness is highly prevalent in SMDs and associated with poorer quality of life, lower functioning and higher CVD risk[7,8,22–24], interventions that effectively reduce loneliness in people with SMDs are limited[67]. Promising results suggest that correcting maladaptive social thinking offers a chance for reducing loneliness in people with mental disorders[74]. Our findings highlight the importance of an integrated approach to people with SMDs focusing on social contact. The results are also relevant for the social isolation strategies to prevent the coronavirus pandemic: While social distancing may protect against the coronavirus infection, it may increase loneliness[16–18]. Our findings suggest that people with SMDs may have a genetic susceptibility for loneliness, making them particularly vulnerable to these adverse effects of the solitude enforced in numerous countries[16–18]. Preventing and reducing loneliness may have beneficial effects both on psychosocial functioning, quality of life, and the illness course itself. Whether reducing loneliness in SMDs may also improve cardiovascular health, should be explored in future research.

Loneliness is a complex phenotype characterized by the perception that one's social needs are not being met[9,25]. A challenge in studying loneliness has been the lack of a measure suitable for large-scale studies[75]. Therefore, recommendations for loneliness assessment in large studies were recently published[76]. A direction question of loneliness is recommended at a minimum[76], such as "Do you often feel lonely?" used in the UK Biobank[44]. In addition, indirect measures of loneliness are recommended as loneliness is associated with stigma and, therefore, some people may be reluctant to admit to feeling lonely[75,76]. While the UK Biobank did not use any of the proposed indirect items[76], participants were asked about their ability to confide in someone close[44]. Lonely people perceive themselves as less able to confide and have fewer people to confide in than non-lonely individual[77,78], providing support for this item as an indirect probe of loneliness. Further, to increase power, the loneliness GWAS also included data on frequency of contact with family and friends and living alone[44]. This data concerns information about objective rather than subjective social isolation. However, lonely people tend to spend more time alone[79] and are more likely to live alone than people who are not lonely[80]. Further support for the association between loneliness and objective isolation comes from the loneliness GWAS: the genetic loci identified in the complete analysis (including perceived loneliness, ability to confide, frequency of contact and living alone) were similar to those reported from analyzing only subjective loneliness[44]. Nevertheless, loneliness and objective isolation are distinct, and the loneliness measure in the UK biobank is limited by not using the best validated loneliness items[75,76].

In conclusion, our study demonstrates shared genetic loci between loneliness, SMDs, and CVD risk factors, providing new insights into their shared genetic architecture. This suggests a potential genetic basis for the

clinical association between loneliness, SMDs, and CVD. The findings further our understanding of comorbid CVD in SMDs and, ultimately, may form the basis of prevention and treatment development. The study illustrates the utility of the condFDR approach to increase gene discovery and disentangle the complex genetic relationship between loneliness, SMDs, and CVD risk factors.

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Author contributions
Designated authors meet the criteria for authorship in line with Nature journal policies on author responsibilities (https://www.nature.com/nature-research/editorial-policies/authorship). Contributions that are more specific are listed below. L.R. and S.B. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: L.R. and O.L.A. Acquisition, analysis, or interpretation of data: L.R., S.B., A.L., K.S.O.C., O.F., G.F.L.H., A.S., and O.A.A. Drafting of the paper: L.R. and O.A.A. Statistical analysis: S.B., A.L., K.S.O.C., O.F., A.S., and O.G. Obtained funding: O.A.A. Supervision: O.A.A., T.V.L., and T.E. Critical revision of the paper for important intellectual content: L.R., O.A.A., N.E.S., O.B.S., T.V.L., G.F.L.H., T.E., M.C.F.W., D.S.Q., S.B., A.L., K.V.S.O.C., O.F., A.S., A.W., S.D., O.G., and A.M.D. (all authors). All authors approved the final version of the paper and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability
The datasets analyzed during the current study are available in repositories of GWASs: SCZ: https://www.med.unc.edu/pgc/download-results/scz/. BD: https://www.med.unc.edu/pgc/download-results/bip/. MD: https://www.med.unc.edu/pgc/download-results/mdd/. Loneliness: https://www.repository.cam.ac.uk/handle/1810/277812. BMI: https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files. TC: http://csg.sph.umich.edu/abecasis/public/lipids2013/. SBP: http://www.georgehretlab.org/. DBP: http://www.georgehretlab.org/. HDL-C: http://csg.sph.umich.edu/abecasis/public/lipids2013/. T2D: https://diagram-consortium.org/downloads.html. CAD: http://www.cardiogramplusc4d.org/data-downloads/. Smoking: https://www.med.unc.edu/pgc/download-results/tag/. All data/results generated during the current study are included in this published article [and its Supplementary Information Files]. Supplementary Information is available at the journal's website.

Code availability
Codes used for carrying out the described analyses are available here: https://github.com/precimed/pleiofdr, https://github.com/precimed/mixer, https://github.com/bulik/ldsc.

Conflict of interest
O.A.A. is a consultant for HealthLytix and has received speaker's honoraria from Lundbeck and Sunovion. T.E. has received speaker's fee from Lundbeck and Janssen Cilag. A.M.D. is a Founder of and holds equity in CorTechs Labs, Inc, and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc. and receives funding through research agreements with General Electric Healthcare and Medtronic, Inc. The terms of these arrangements have been reviewed and approved by UCSD in accordance with its conflict of interest policies. The other authors report no conflicts of interest.

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SUPPLEMENTARY INFORMATION for

Polygenic overlap and shared genetic loci between loneliness, severe mental disorders and cardiovascular disease risk factors suggest shared molecular mechanisms

SUPPLEMENTARY METHODS

Participant samples

We obtained GWAS results in the form of summary statistics. Data on schizophrenia (SCZ), bipolar disorder (BD) and major depression (MD) were retrieved from Psychiatric Genomics Consortium (PGC)[1-3]. The SCZ dataset contained 49 non-overlapping case-control samples (34 241 cases with SCZ or schizoaffective disorder and 45 604 controls) and 3 family-based association studies (1235 parent affected-offspring trios)[1]. The BD dataset consisted of 20 352 cases and 31 358 controls from 32 samples[2]. Among the cases, 14,879 individuals were diagnosed with BD type I (BD1), 3,421 with BD type II (BD2), 977 with schizoaffective disorder, bipolar type (SAB), and the remaining unspecified BD[2]. The major depression (MD) dataset involved 135 458 cases and 344 901 controls[3]. The UK biobank cohort (n = 29 740) was excluded from the MD data set to avoid sample overlap.

Data on loneliness was obtained from the general population in the UK Biobank study (n = 452 302)[5]. 487 647 people responded to three questions regarding perceived loneliness, frequency of social contact, and ability to confide in someone close[5]. Genomic and phenotypic data were available from 452 302 participants after quality control criteria. The UK Biobank primarily compromises healthy individuals, and a small proportion of participants have a psychiatric diagnosis based on the International Classification of Diseases (ICD)-10, retrieved from health records (UK Biobank data field 41270). The estimated prevalence of individuals with ICD-10 coded diagnosis are 0.6% with SCZ or another

psychotic disorder, 0.6% with BD, 5% with depression and less than 4% with anxiety disorder, as shown in Supplementary Table 1. The number of self-reported diagnoses is higher (Supplementary Table 2)[6]. However, the generalizability of these estimates is limited by the availability of self-report data from only a subset of the UK Biobank cohort. In addition, self-reported diagnoses should be considered with caution as they are less reliable than ICD-coded diagnoses. Therefore, any diagnostic classification arising from self-report should be regarded as probable, rather than a confirmed mental disorder[6]. For further information about self-reported diagnoses and symptoms in the UK Biobank, see Davis et al.[6]. In the loneliness GWAS, Day et al. performed a sensitivity analyses by repeating the GWAS without individuals with self-reported depression[5]. This sensitivity analysis did not result in any appreciable change in results, suggesting that depression did not confound the findings of loneliness loci[5]. Anxiety disorders did not seem to confound the findings either as most individuals with self-reported anxiety disorder were excluded when individuals with depression were removed from analysis, given the high comorbidity between these disorders[6].

Further, we used data from GWASs on cardiovascular disease (CVD) risk factors, including body mass index (BMI) (n = 339 224)[7], type 2 diabetes mellitus (T2D) (n = 159 208)[8], total cholesterol (TC) (n = 188 578)[9], high-density lipoprotein (HDL) cholesterol (n = 188 578)[9], systolic blood pressure (SBP) (n = 200 000)[10], diastolic blood pressure (DBP) (n = 200 000)[10], along with coronary artery disease (CAD) (n =185 000)[11]. In addition, we used GWAS data on smoking (n > 200 000) for supplementary analysis[12]. We used a larger BMI GWAS (n = 795 640)[13] including UK biobank data for MiXeR than for condFDR/conjFDR because MiXeR controls for overlapping samples and does, therefore, not require excluding overlapping participants (see below for description of MiXeR). The GWAS samples used for the present study are previously shown to be sufficiently powered to identify gene variants at

genome-wide significant level. For further details of the inclusion criteria, genotyping and phenotype characteristics, see the original publications[1-3, 5, 7-13].

MiXeR

We applied causal mixture models[14, 15] to the GWAS summary statistics, using the MiXeR tool (https://github.com/precimed/mixer). For each SNP, i, univariate MiXeR models its additive genetic effect of allele substitution, β_i, as a point-normal mixture, $\beta_i = (1-\pi_1)N(0,0) + \pi_1 N(0,\sigma_\beta^2)$, where π_1 represents the proportion of non-null SNPs (`polygenicity`) and σ_β^2 represents variance of effect sizes of non-null SNPs (`discoverability`). Then, for each SNP, j, MiXeR incorporates LD information and allele frequencies for M=9,997,231 SNPs extracted from 1000 Genomes Phase3 data by LD score regression software[16], and estimate the expected probability distribution of the signed test statistic, $z_j = \delta_j + \epsilon_j = N\sum_i \sqrt{H_i} r_{ij}\beta_i + \epsilon_j$, where N is sample size, H_i indicates heterozygosity of i-th SNP, r_{ij} indicates allelic correlation between i-th and j-th SNPs, and $\epsilon_j \sim N(0,\sigma_0^2)$ is the residual variance. Further, the three parameters, $\pi_1, \sigma_\beta^2, \sigma_0^2$, are fitted by direct maximization of the likelihood function. The number of causal variants is estimated as $M\pi_1$, where M=9,997,231 gives the number of SNPs in the reference panel.

In the cross-trait analysis, MiXeR models additive genetic effects as a mixture of four components, representing null SNPs in both traits (π_0); SNPs with a specific effect on the first and on the second trait (π_1 and π_2, respectively); and SNPs with non-zero effect on both traits (π_{12}). In the last component, MiXeR models variance-covariance matrix as $\mathbf{\Sigma_{12}} = \begin{bmatrix} \sigma_1^2 & \rho_{12}\sigma_1\sigma_2 \\ \rho_{12}\sigma_1\sigma_2 & \sigma_2^2 \end{bmatrix}$ where ρ_{12} indicates correlation of effect sizes within the shared component, and σ_1^2 and σ_2^2 correspond to the discoverability parameter estimated in the univariate analysis of the two traits. After fitting parameters of the model, the Dice coefficient

of polygenic overlap is then calculated as $\frac{2\pi_{12}}{\pi_1+2\pi_{12}+\pi_2}$, and genetic correlation is calculated as $r_g = \frac{\rho_{12}\pi_{12}}{\sqrt{(\pi_1+\pi_{12})(\pi_2+\pi_{12})}}$. Further information is available in[14].

To filter situations with insufficiently powered GWAS summary statistics, we use Akaike information criterion ($AIC = 2k - 2\ln L$), where k is the number of free parameters in the model, L is the value of the likelihood function, and n is the effective number of SNPs used in optimization procedure. We calculate the difference between *AIC* for the full bivariate model, $k = 3$, and AIC for the reduced bivariate model, $k = 2$, due to π_{12} being constrained to smallest or largest possible ($\pi_{12}^{min} = r_g\sqrt{\pi_1^u\,\pi_2^u}$ and $\pi_{12}^{max} = \min(\pi_1^u, \pi_2^u)$, respectively). A positive value of AIC indicates that GWAS summary statistics have enough information to distinguish the custom polygenic overlap, as shown on the MiXeR Venn diagrams, versus the constrained models with minimal (π_{12}^{min}) and maximum (π_{12}^{max}) polygenic overlap. MiXeR results are presented as a Venn diagram of shared and unique polygenic components across traits.

Conditional False Discovery Rate

The 'enrichment' seen in the conditional Q-Q plots can be directly interpreted in terms of true discovery rate (TDR = 1 – false discovery rate (FDR))[17]. More specifically, for a given p-value cutoff, the FDR is defined as

$$FDR(p) = \pi_0 F_0(p) / F(p), \qquad [1]$$

where π_0 is the proportion of null SNPs, F_0 is the null cumulative distribution function (cdf), and F is the cdf of all SNPs, both null and non-null[18]. Here, we assume the SNP *p* values are a priori independent and identically distributed. Under the null hypothesis, F_0 is the cdf of the uniform distribution on the unit interval [0,1], so that Eq. [1] reduces to

$$FDR(p) = \pi_0 p / F(p), \qquad [2]$$

The cdf F can be estimated by the empirical cdf $q = N_p / N$, where N_p is the number of SNPs with p-values $\leq p$, and N is the total number of SNPs. Replacing F by q in Eq. [2], we get

$$\text{Estimated FDR}(p) = \pi_0 p / q, \qquad [3]$$

which is biased upwards as an estimate of the FDR[19]. Replacing π_0 in Equation [3] with unity gives an estimated FDR that is further biased upward;

$$q^* = p / q, \qquad [4]$$

If π_0 is close to one, which is probably true for most GWASs, the increase in bias from Eq. [3] is minimal. Therefore, the quantity 1 – p/q, is biased downward and thus a conservative estimate of the TDR. Referring to the Q-Q plots, we see that q* is equivalent to the nominal p-value divided by the empirical quantile, as defined previously. We can thus read the FDR estimate directly off the Q-Q plot as

$$-\log_{10}(q^*) = \log_{10}(q) - \log_{10}(p), \qquad [5]$$

demonstrating that the estimated FDR is directly related to the horizontal shift of the curves in the Q-Q plots from the expected line x = y, i.e. a larger shift corresponds to a smaller FDR.

Conditional Q-Q plots

Q-Q plots compare a nominal probability distribution against an empirical distribution. In the presence of all null relationships, nominal p-values form a straight line on a Q-Q plot when plotted against the empirical distribution. For SCZ, BD, MD, loneliness and CVD risk factor SNPs and for each categorical subset (strata), $-\log_{10}$ nominal p-values were plotted against $-\log_{10}$ empirical p-values (conditional Q-Q plots). Leftward deflections of the observed distribution from the projected null line illustrate increased tail probabilities in the distribution of test statistics (z-scores) and consequently an over-abundance of low p-values compared to that expected by chance, also called ‘enrichment’.

Under large-scale testing paradigms, such as GWAS, we can calculate quantitative estimates of likely true associations from the distributions of summary statistics[18, 20]. Conditional Q-Q plots of nominal p-values from GWAS summary statistics visualizes this enrichment of statistical association relative to that expected under the global null hypothesis. The usual Q-Q curve has the nominal p value, denoted by "p", as the y-ordinate and the corresponding value of the empirical cdf, denoted by "q", as the x-ordinate. Under the global null hypothesis the theoretical distribution is uniform on the interval [0,1]. As is common in GWAS, we instead plot $-\log_{10}$ p against $-\log_{10}$ q to emphasize tail probabilities of the theoretical and empirical distributions. Therefore, genetic enrichment is illustrated with a leftward shift in the Q-Q curve, corresponding to a larger fraction of SNPs with nominal $-\log_{10}$ p-value greater than or equal to a given threshold. Conditional Q-Q plots are constructed by creating subsets of SNPs based on levels of an auxiliary measure for each SNP, and computing Q-Q plots separately for each level. If SNP enrichment is captured by variation in the auxiliary measure, this is expressed as successive leftward deflections in a conditional Q-Q plot as levels of the auxiliary measure increase. We constructed conditional Q-Q plots of empirical quantiles of nominal $-\log_{10}$ values for SNP association for all SNPs, and for subsets (strata) of SNPs determined by the nominal p-values of their association with the conditional phenotypes, and vice versa. In particular, we computed the empirical cumulative distribution (cdf) of nominal p-values for a given phenotype for all SNPs and for SNPs with significance levels below the indicated cut-offs for the conditional phenotypes ($-\log_{10}(p) \geq 1$, $-\log_{10}(p) \geq 2$, $-\log_{10}(p) \geq 3$ corresponding to $p < 0.1$, $p < 0.01$, $p < 0.001$ respectively). The nominal p-values ($-\log_{10}(p)$) are plotted on the y-axis, and the empirical quantiles ($-\log_{10}(q)$, where q=1-cdf(p)) are plotted on the x-axis. To assess for polygenic effects below the standard GWAS significance threshold, we focused the conditional Q-Q plots on SNPs with nominal $-\log_{10}(p) < 7.3$ (corresponding to $p > 5x10^{-8}$). We controlled for spurious enrichment by calculating all

conditional Q-Q plots after random pruning averaged over 500 iterations. At each iteration, one SNP in every LD block (defined by an r^2 >0.1) was randomly selected and the empirical cdfs were computed using the corresponding p-values.

Detection of SNPs using conditional and conjunctional FDR

The FDR can be interpreted as the probability that a SNP is null given that its p-value is as small as or smaller than its observed p-value. The conditional FDR (condFDR) is an extension of the standard FDR, which incorporates information from GWAS summary statistics of a second phenotype to adjust its significance level. The condFDR is defined as the probability that a SNP is null in the first phenotype given that the p-values in the first and second phenotypes are as small as or smaller than the observed ones. It is important to note that ranking SNPs by the standard FDR or by p-values gives the same ordering of SNPs. In contrast, ranking SNPs by condFDR will reorder SNPs when the primary and secondary phenotypes are genetically related.

To identify SNPs that are associated with *both* phenotypes, we used conjunctional FDR (conjFDR)[21, 22], employing an overall FDR threshold of 0.05 according to the standard FDR approach[4]. The conjunctional FDR (conjFDR) is defined as the posterior probability that a SNP is null for either phenotype or both simultaneously, given that its p-values for association with both phenotypes are as small as or smaller than the observed p-values[21, 23-26]. A conservative estimate of the conjFDR is obtained by the maximum condFDR for a given SNP after repeating the condFDR procedure for both traits and inverting their roles[27]. Given that complex correlations in regions with intricate LD can bias FDR estimation[28], we excluded SNPs in the extended major histocompatibility complex and chromosome 8p23.1 (genome build 19 locations 25119106–33854733 and 7242715–12483982, respectively) and SNPs in LD (r^2>0.1) with such SNPs before fitting the FDR models. To investigate loci

shared between three phenotypes, including SMDs, loneliness and BMI, we used trio conjFDR. Trio conjFDR value of an SNP is defined as the maximum of three pairwise conjFDR values of the SNP. For example, trio $conjFDR_{\{SCZ\ \&\ BMI\&\ loneliness\}c}$ = max($conjFDR_{\{SCZ\ \&\ BMI\}}$, $conjFDR_{\{SCZ\ \&\ loneliness\}}$, $conjFDR_{\{BMI\ \&\ loneliness\}}$). Effect size (z-scores) of SNPs were obtained from the original summary statistics (see original publications for how they were calculated[1-3, 5, 7-13]). P-values were corrected for inflation using a genomic inflation control procedure[21].

Genomic loci definition

We defined independent genomic loci using the FUMA, an online tool for functional mapping of genetic variants (http://fuma.ctglab.nl/)[29]. Summary statistics from the GWASs on SMDs, loneliness and CVD risk factors were used as input for FUMA. First, *independent significant SNPs* were identified as SNPs with condFDR < 0.01 and independent from each other at LD $r^2 < 0.6$. Secondly, *lead SNPs* were identified by retaining those independent significant SNPs that were independent from each other at $r^2 < 0.1$. Next, *distinct genomic loci* were identified by merging physically overlapping lead SNPs (LD blocks < 250 kb apart). Borders of the genomic loci were determined by identifying all SNPs in LD ($r^2 \geqq 0.6$) with one of the independent significant SNPs in the locus. The region containing all of these *candidate SNPs* was regarded as a single independent genomic locus. All LD information was calculated from the 1000 Genomes Project reference panel[30].

Genetic correlation

We estimated the genetic correlation using MiXeR[14] and LD score regression[31], procedures that control for overlapping samples without requiring individual genotype data. LD score regression was estimated using the Python-based package available at

https://github.com/bulik/ldsc. The procedure is described in the documentation of the package (https://github.com/bulik/ldsc/wiki/Heritability-and-Genetic-Correlation).

Functional annotation

We used FUMA[29], an online annotation platform (http://fuma.ctglab.nl/) to functionally annotate all candidate SNPs in the genomic loci with a condFDR or conjFDR value<0.10 having an $r^2 \geqq 0.6$ with one of the independent significant SNPs. SNPs were annotated with Combined Annotation Dependent Depletion (CADD) scores[32], RegulomeDB[33] scores, and chromatin states[34, 35] (see below). We conducted gene-set analysis to evaluate whether the genes mapped to the shared loci were overrepresented via FUMA[29]. We used Bonferroni-adjusted p-value threshold of 0.05 to correct for multiple comparisons.

The CADD score is a deleterious score of variants computed by integrating 63 functional annotations[32]. The higher the score, the more deleterious. A CADD score above 12.37 is the threshold to be potentially pathogenic[32]. The RegulomeDB score is a categorical score to guide interpretation of regulatory variants[33]. It is based on information from eQTLs and chromatin marks, ranging from 1a to 7 with lower scores indicating a higher likelihood of having a regulatory function. Scores are as follows: 1a=eQTL + Transcription Factor (TF) binding + matched TF motif + matched DNase Footprint + DNase peak; 1b=eQTL + TF binding + any motif + DNase Footprint + DNase peak; 1c=eQTL + TF binding + matched TF motif + DNase peak; 1d=eQTL + TF binding + any motif + DNase peak; 1e=eQTL + TF binding + matched TF motif; 1f=eQTL + TF binding / DNase peak; 2a=TF binding + matched TF motif + matched DNase Footprint + DNase peak; 2b=TF binding + any motif + DNase Footprint + DNase peak; 2c=TF binding + matched TF motif + DNase peak; 3a=TF binding + any motif + DNase peak; 3b=TF binding + matched TF motif; 4=TF binding + DNase peak; 5=TF binding or DNase peak; 6=other; 7=Not available[33].

The chromatin state represents the accessibility of genomic regions (every 200bp) with 15 categorical states predicted by a hidden Markov model based on 5 chromatin marks for 127 epigenomes in the Roadmap Epigenomics Project[35]. A lower state indicates increased accessibility, with states 1-7 referring to open chromatin states. We annotated the minimum chromatin state across tissues to SNPs. The 15-core chromatin states as suggested by Roadmap are as follows: 1=Active Transcription Start Site (TSS); 2=Flanking Active TSS; 3=Transcription at gene 5' and 3'; 4=Strong transcription; 5= Weak Transcription; 6=Genic enhancers; 7=Enhancers; 8=Zinc finger genes & repeats; 9=Heterochromatic; 10=Bivalent/Poised TSS; 11=Flanking Bivalent/Poised TSS/Enh; 12=Bivalent Enhancer; 13=Repressed PolyComb; 14=Weak Repressed PolyComb; 15=Quiescent/Low.

We also used FUMA to link candidate and lead SNPs to genes using either of three gene-mapping strategies: 1) positional mapping to link SNPs to genes based on their physical proximity (i.e., within a 10kb window), 2) expression quantitative trait locus (eQTL) mapping to match cis-eQTL SNPs to genes whose expression is associated with allelic variation at the SNP level, and 3) chromatin interaction mapping to link SNPs to genes based on three-dimensional DNA–DNA interactions between each SNP's genomic region and nearby or distant genes, as used in a recent GWAS from our group[36]. We considered eleven eQTL databases in FUMA which include eQTL information from several human tissue types including multiple brain regions (http://fuma.ctglab.nl/tutorial#eQTLs). The eQTL analyses were corrected for multiple comparisons using an FDR threshold of 0.05. FUMA includes Hi-C data of over 21 tissue/cell types including human brain tissue (https://fuma.ctglab.nl/tutorial#chromatin-interactions). We used an FDR of 1×10^{-6} to define significant chromatin interactions, in line with recommendations[37]. Analyses were corrected for multiple comparisons.

Image processing software

Matplotlib Python library (https://matplotlib.org/) and Matlab.

SUPPLEMENTARY RESULTS

MiXeR results

The MiXeR model provides adequate fit to the GWAS data of loneliness and SMDs, as indicated by AIC in Supplementary Table 3, conditional Q-Q plots and negative log-likelihood (Supplementary Figures 3-5), while the results of loneliness vs MD analysis are more uncertain, suggesting that a larger MD GWAS is needed to obtain more certain MiXeR estimates. In particular, the negative values of AIC indicate that GWAS summary statistics do not have enough power to distinguish the estimated polygenic overlap, as shown on the MiXeR Venn diagrams, versus the constrained models with minimal (π_{12}^{min}) and maximum (π_{12}^{max}) polygenic overlap (Supplementary Table 3). Nevertheless, the Venn diagram suggests that loneliness and MD share genetic architecture (Figure 1a), although the amount of shared genetic variants remains uncertain, as indicated by AIC. Further, the MiXeR results for BMI should be interpreted with some caution because the MiXeR model was less accurate in predicting the empirical data (see conditional Q–Q plot in Supplementary Figure 8) than the MiXeR model for loneliness and SMDs (Supplementary Figure 3-5). Further information about the quality of the MiXeR model for loneliness and BMI, see Supplementary Figure 8 and AIC in Supplementary Table 3.

Gene-mapping results

We performed gene-mapping of lead and candidate SNPs, which provided consistent results, implicating brain-expressed genes. Among lead SNPs shared between loneliness and MD

(67), positional mapping aligned the SNPs to 44 genes, cis-eQTL mapping implicated 20 genes, and chromatin interaction mapping implicated 5 genes (Supplementary Table 17). Of SNPs shared with SCZ (54), positional mapping aligned the SNPs to 34 genes, cis-eQTL mapping implicated 20 genes, and chromatin interaction mapping implicated 7 genes (Supplementary Table 18). Among SNPs shared with BD (28), positional mapping linked the SNPs to 14 genes, cis-eQTL mapping indicated 13 genes, and chromatin interaction mapping implicated 2 genes (Supplementary Table 19). Taken together, 69.8% (104/149) of the SNPs shared between loneliness and SMDs were mapped to genes when considering all gene-mapping strategies, of which approximately 40.3 % of them mapped to brain-expressed genes (60/149) based on eQTL and chromatin interaction mapping (Supplementary Tables 17-19). Among SNPs shared between loneliness and BMI (36), positional mapping aligned the SNPs to 25 genes, cis-eQTL mapping implicated 14 genes, and chromatin interaction mapping implicated 1 gene (Supplementary Table 20). Of the SNPs shared between loneliness and the remaining CVD risk factors and CAD, all SNPs were mapped to genes when considering all three gene-mapping strategies (Supplementary Tables 21-26). The majority of these SNPs were mapped to genes with eQTL and chromatin interaction mapping, indicating brain-expressed genes (TC: 6/6; HDL-C: 3/5, SBP: 5/9; DBP: 3/4; CAD: 8/12; and T2D: 1/1). Among lead SNPs shared between loneliness, BMI and MD, positional mapping aligned the SNPs to 2 genes, while no SNPs were gene-mapped based on the other two strategies (Supplementary Table 27). Among SNPs shared between loneliness, BMI and SCZ, positional mapping linked the SNPs to 3 genes, 2 of which were mapped using eQTL and chromatin interaction mapping (Supplementary Table 28). No SNPs shared between loneliness, BMI and BD were mapped to genes (Supplementary Table 29).

Among candidate SNPs shared between loneliness and MD (4256), positional mapping aligned the SNPs to 2895 genes, cis-eQTL mapping implicated 1737 genes, and

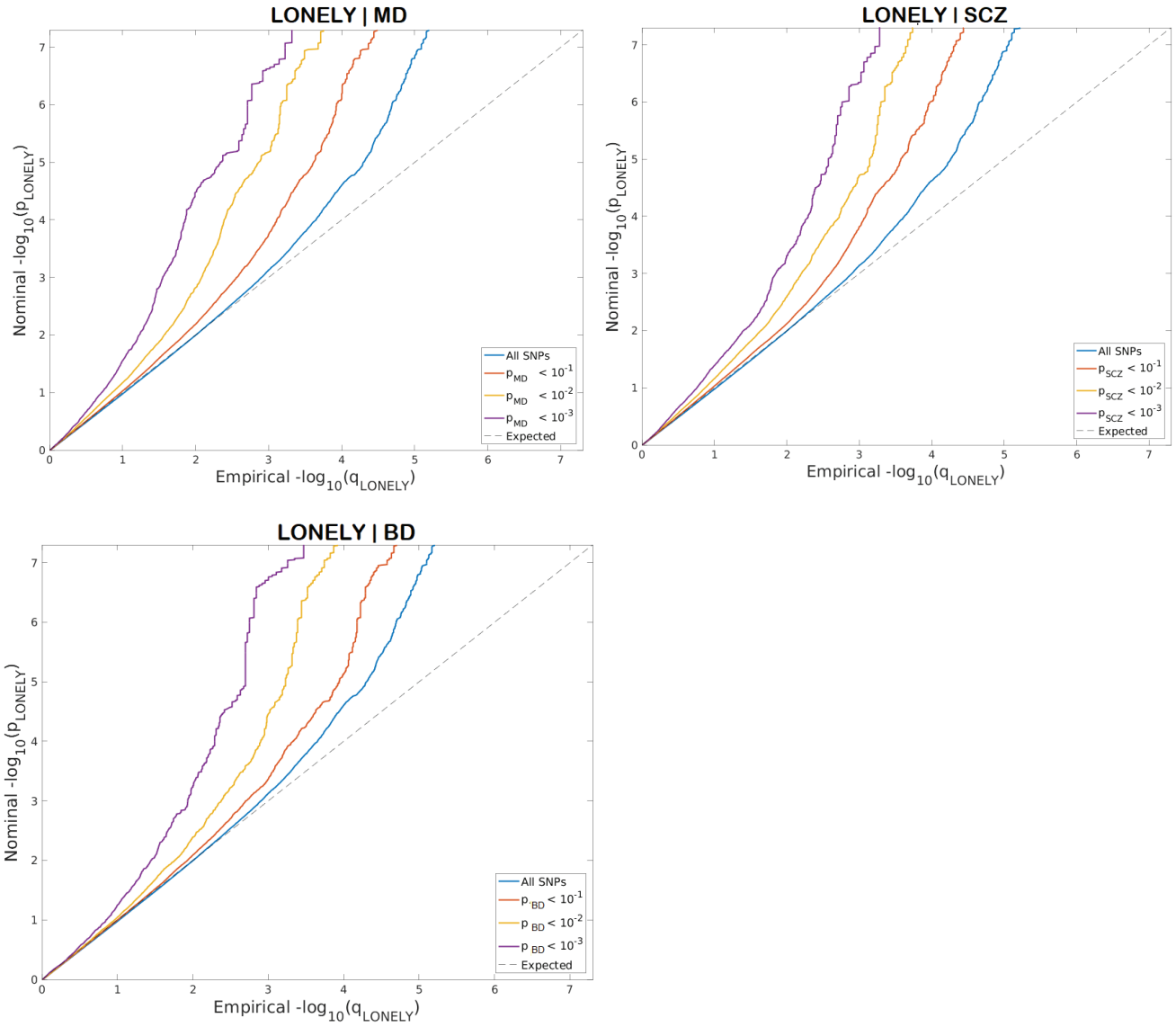
chromatin interaction mapping implicated 124 genes (Supplementary Table 30). Of candidate SNPs shared with SCZ (4021) positional mapping aligned the SNPs to 2273 genes, cis-eQTL mapping implicated 1851 genes, and chromatin interaction mapping implicated 201 genes (Supplementary Table 31). Among the candidate SNPs shared with BD (1349), positional mapping aligned the SNPs to 532 genes, cis-eQTL mapping implicated 489 genes, and chromatin interaction mapping implicated 25 genes (Supplementary Table 32). Taken together, 69.8% (6716/9626) of the SNPs shared between loneliness and SMDs were mapped to genes when considering all gene-mapping strategies, of which approximately 42.8 % of them mapped to genes (4219/9626) based on eQTL and chromatin interaction mapping (Supplementary Tables 30-32). Further, among the candidate SNPs shared with BMI (1037), positional mapping aligned the SNPs to 732 genes, cis-eQTL mapping implicated 450 genes, and chromatin interaction mapping implicated 46 genes (Supplementary Table 33). Of the SNPs shared between loneliness and the remaining CVD risk factors and CAD, all SNPs were mapped to genes (expect for 22% of CAD SNP shared with loneliness) when considering all three gene-mapping strategies (Supplementary Tables 34-39). The majority of these SNPs were mapped to genes with eQTL and chromatin interaction mapping (TC: 187/190; HDL-C: 181/194, SBP: 503/519: DBP: 120/122; CAD: 700/996; and T2D: 8/8).

Gene-set analysis results

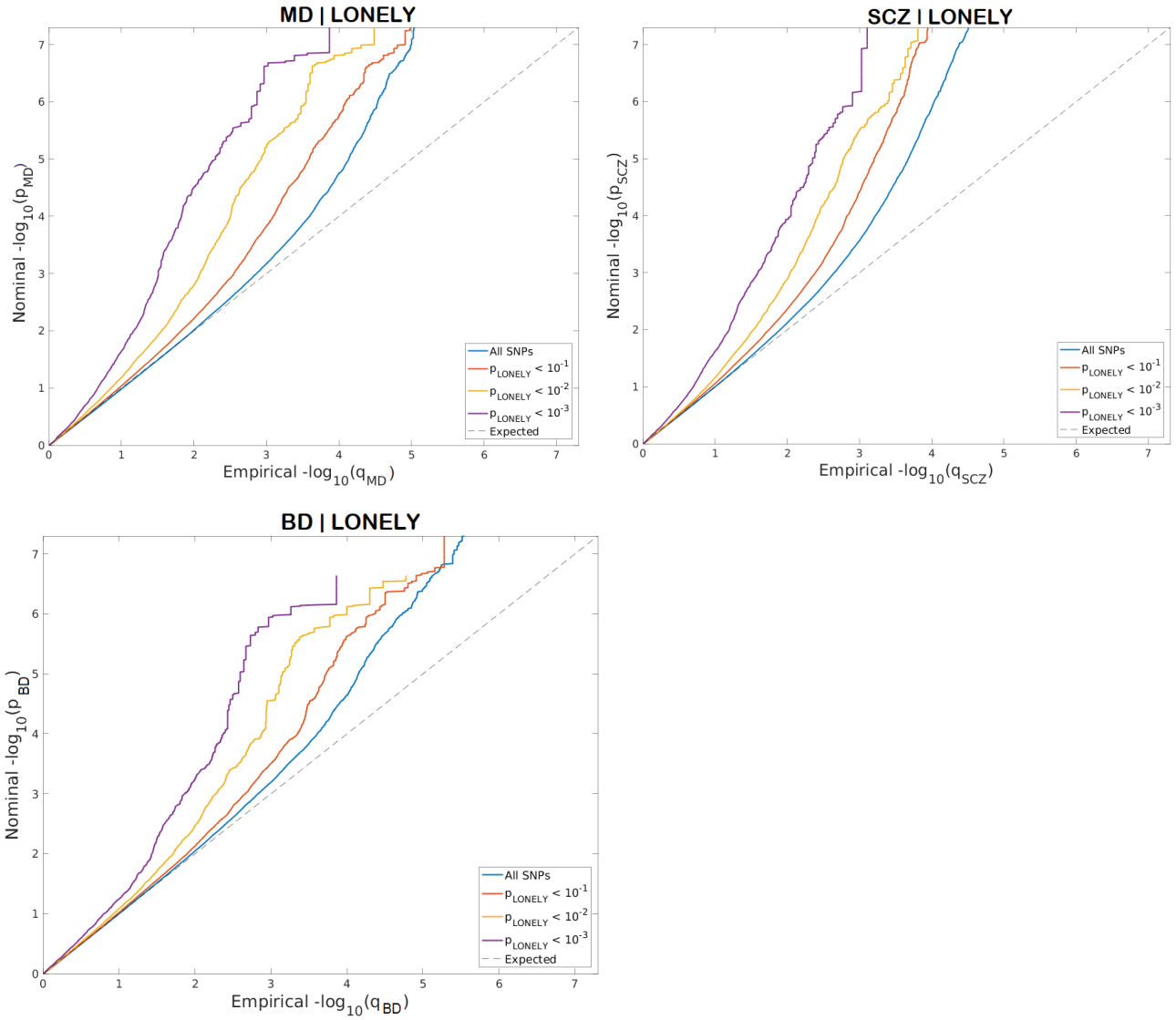
For gene-set analyses, we focused on the genes mapped to the loci shared between loneliness and SMDs and BMI, as these phenotypes showed most genetic overlap in the above results. Gene-set analyses for genes mapped to loci shared between loneliness and SMDs discovered several biological and cellular processes, including “chromatin assembly”, “nucleosome organization”, “negative regulation of biosynthetic process” and “DNA packaging complex” (Supplementary Tables 40-42). Other significant processes involved “immune system

development" and neural processes (e.g. "synapse", "postsynapse" and "dendritic tree") (Supplementary Tables 40-42). Further, genes mapped to loci shared between loneliness and BMI, were significantly associated with four biological processes, the most strongly associated being "positive regulation of RNA biosynthetic process" (Supplementary Table 43), suggesting metabolic processes.

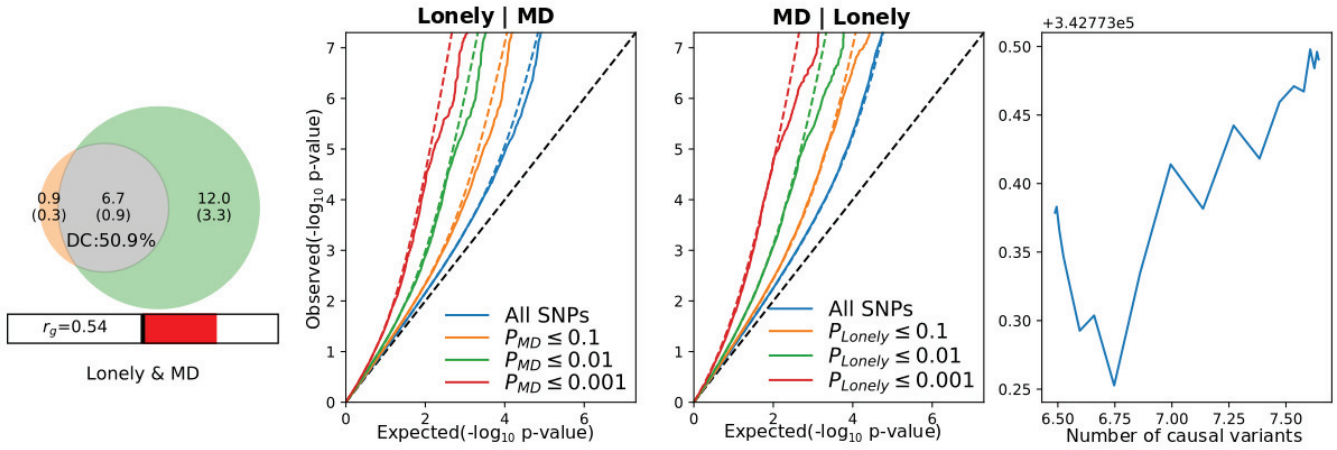
SUPPLEMENTARY FIGURES



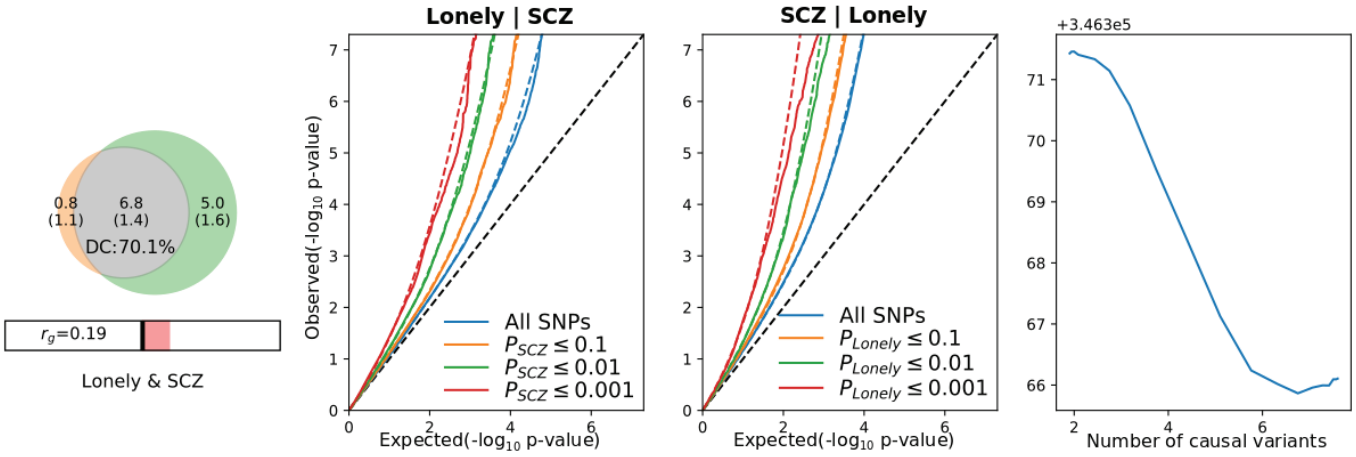
Supplementary Figure 1. Polygenic overlap between loneliness and MD, SCZ and BD. Conditional Q-Q plots of nominal versus empirical −log10p values (corrected for inflation) in loneliness below the standard GWAS threshold of $p < 5 \times 10{-}8$ as a function of significance of association with MD, SCZ and BD at the level of $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively. The blue lines indicate all SNPs. The dashed lines indicate the null hypothesis. Abbreviations: MD, major depression; SCZ, schizophrenia; BD, bipolar disorder. The conditional Q-Q plots build on the condFDR method.



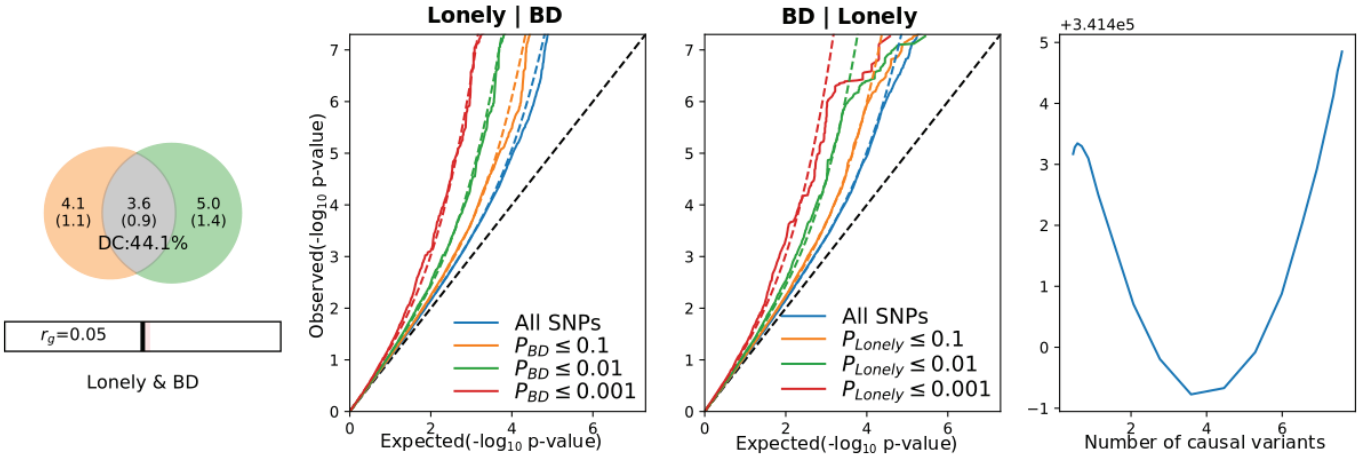
Supplementary Figure 2. Polygenic overlap between loneliness and MD, SCZ and BD. Conditional Q-Q plots of nominal versus empirical $-\log_{10}$ p-values (corrected for inflation) in MD, SCZ and BD below the standard GWAS threshold of $p < 5\times10^{-8}$ as a function of significance of association with loneliness, at the level of $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively. The blue lines indicate all SNPs. The dashed lines indicate the null hypothesis. Abbreviations: MD, major depression; SCZ, schizophrenia; BD, bipolar disorder. The conditional Q-Q plots build on the condFDR method.



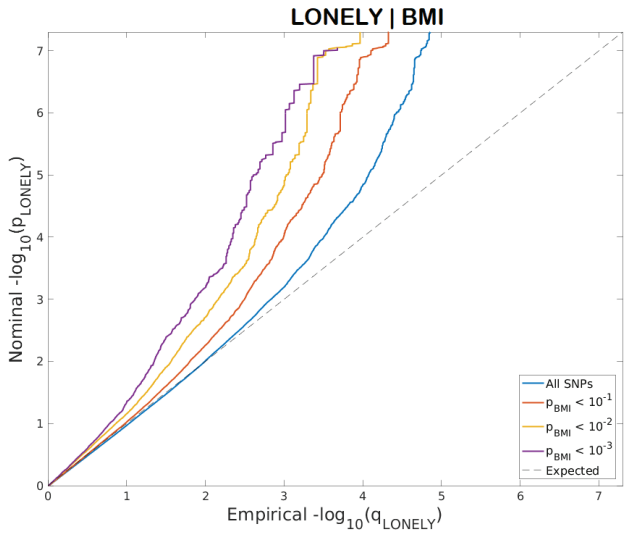
Supplementary Figure 3. Venn diagram, conditional Q-Q plots, and negative log-likelihood plot, respectively. *Venn diagram* of unique and shared polygenic components at the causal level, showing polygenic overlap (gray) between loneliness (orange) and major depression (MD) (green). The numbers in the Venn diagram indicate the estimated quantity of causal variants (in thousands) per component, explaining 90% of SNP heritability in each phenotype, followed by standard error. The size of the circles reflects the degree of polygenicity. The Dice coefficient (DC) in the Venn diagram indicates the percentage of shared causal variants between the two phenotypes. *Conditional Q–Q plots* of observed versus expected $-\log_{10}$ *p*-values in the primary trait as a function of significance of association with a secondary trait at the level of $p < 0.1$, $p < 0.01$, $p < 0.001$. Blue line indicates all SNPs. Dotted lines in blue, orange, green, and red indicate model predictions for each stratum. Black dotted line is the expected Q–Q plot under null hypothesis. *Negative log-likelihood plot*: minus log-likelihood calculated for the bivariate model as a function of π parameter. The remaining parameters of the model were constrained to their fitted values. Figures generated from MiXeR.

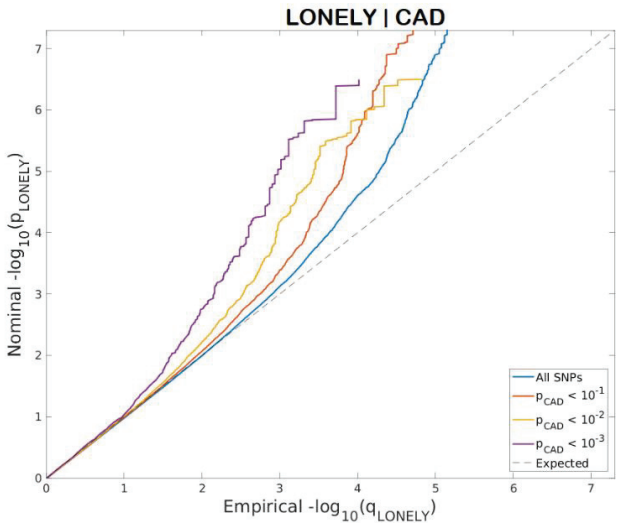


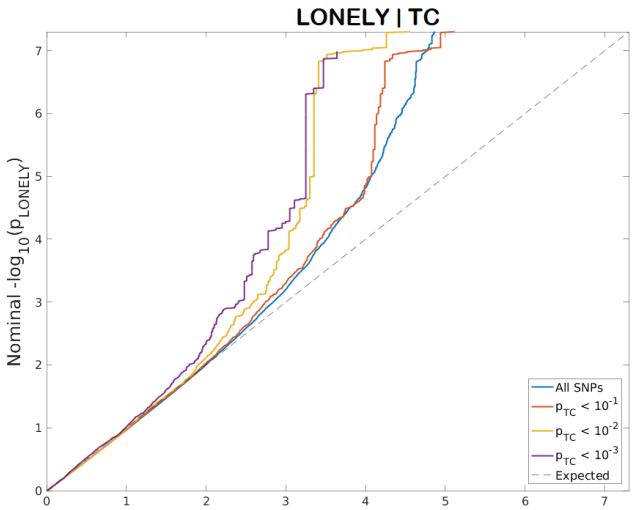
Supplementary Figure 4. Venn diagram, conditional Q-Q plots, and negative log-likelihood plot, respectively. Venn diagram of unique and shared polygenic components at the causal level, showing polygenic overlap (gray) between loneliness (orange) and schizophrenia (SCZ) (green). The numbers in the Venn diagram indicate the estimated quantity of causal variants (in thousands) per component, explaining 90% of SNP heritability in each phenotype, followed by standard error, and Dice coefficient (DC) indicates the percentage of shared causal variants between the two phenotypes. Appearance of the Q-Q plot and negative log-likelihood plot are described below the previous figure (Supplementary Figure 3). Figures generated from MiXeR.

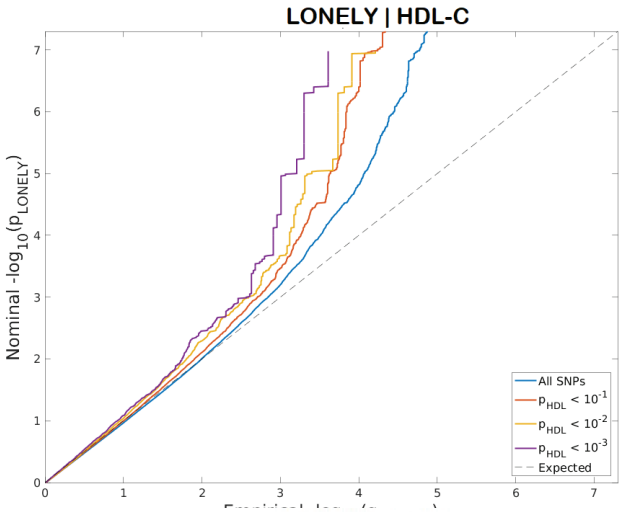


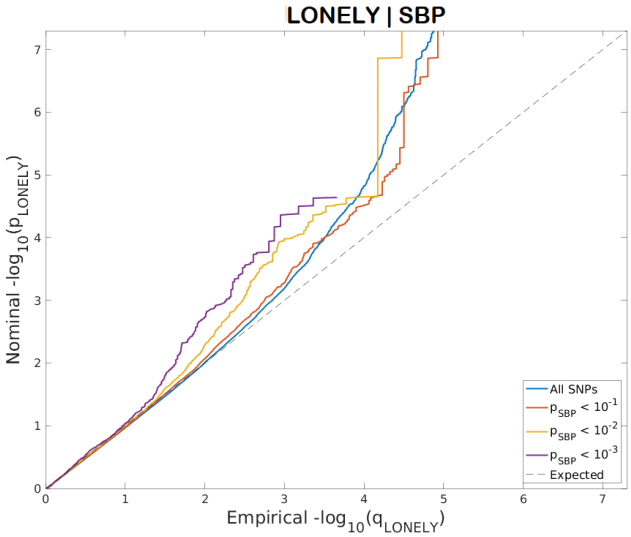
Supplementary Figure 5. Venn diagram, conditional Q-Q plots, and negative log-likelihood plot, respectively. Venn diagram of unique and shared polygenic components at the causal level, showing polygenic overlap (gray) between loneliness (orange) and bipolar disorder (BD) (green). The numbers indicate the estimated quantity of causal variants (in thousands) per component, explaining 90% of SNP heritability in each phenotype, followed by standard error, and Dice coefficient (DC) indicates the percentage of shared causal variants between the two phenotypes. Appearance of the Q-Q plot and negative log-likelihood plot are described below Supplementary Figure 3. Figures generated from MiXeR.

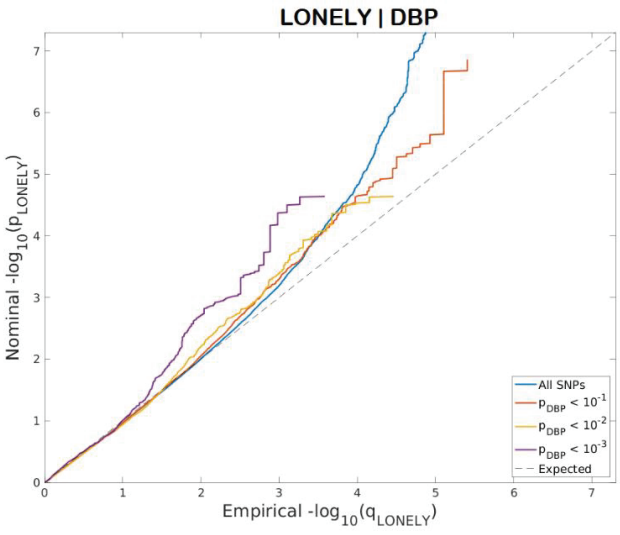

LONELY | BMI
Nominal -log10(pLONELY)
Empirical -log10(qLONELY)
All SNPs
pBMI < 10-1
pBMI < 10-2
pBMI < 10-3
Expected

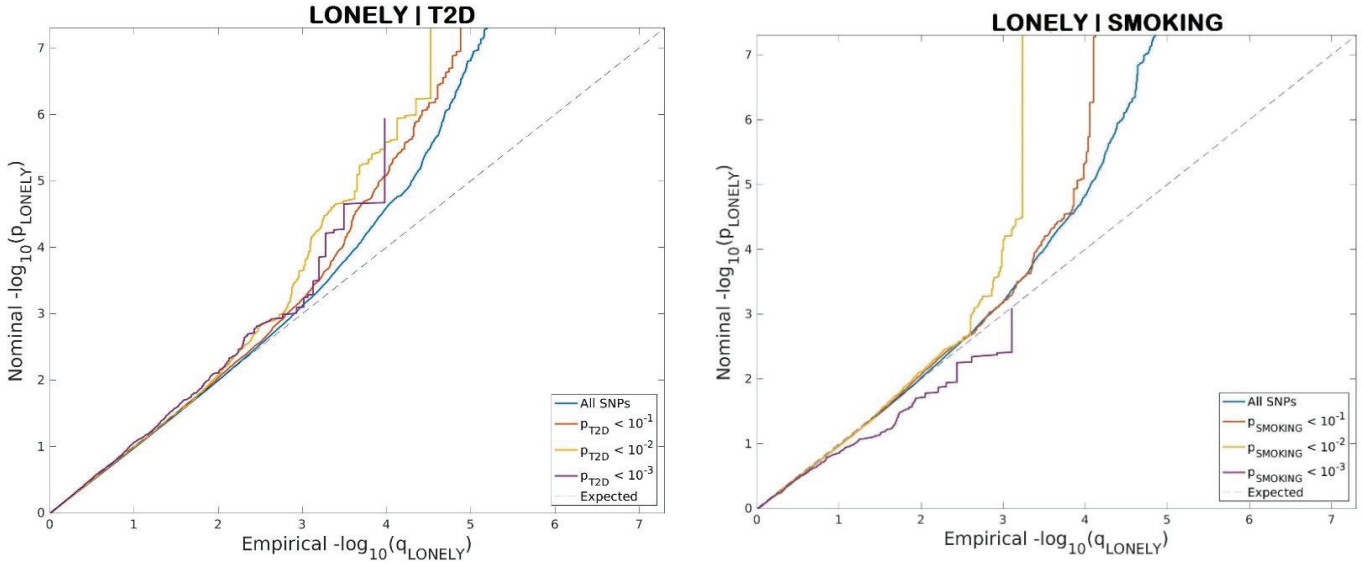

LONELY | CAD
Nominal -log10(pLONELY)
Empirical -log10(qLONELY)
All SNPs
pCAD < 10-1
pCAD < 10-2
pCAD < 10-3
Expected


LONELY | TC
Nominal -log10(pLONELY)
All SNPs
pTC < 10-1
pTC < 10-2
pTC < 10-3
Expected

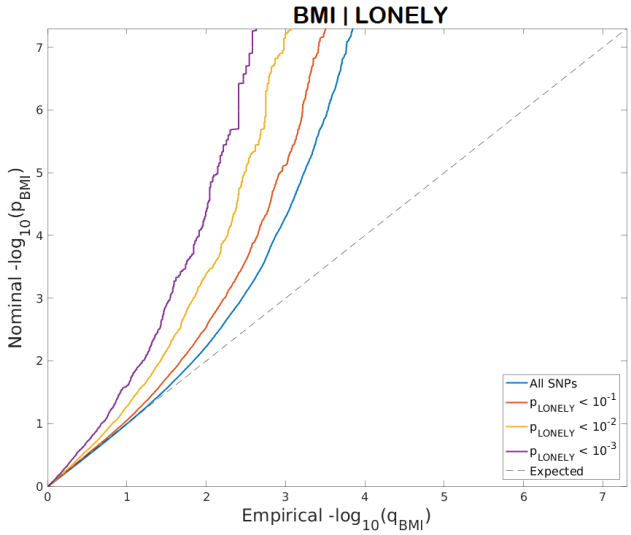

LONELY | HDL-C
Nominal -log10(pLONELY)
All SNPs
pHDL < 10-1
pHDL < 10-2
pHDL < 10-3
Expected

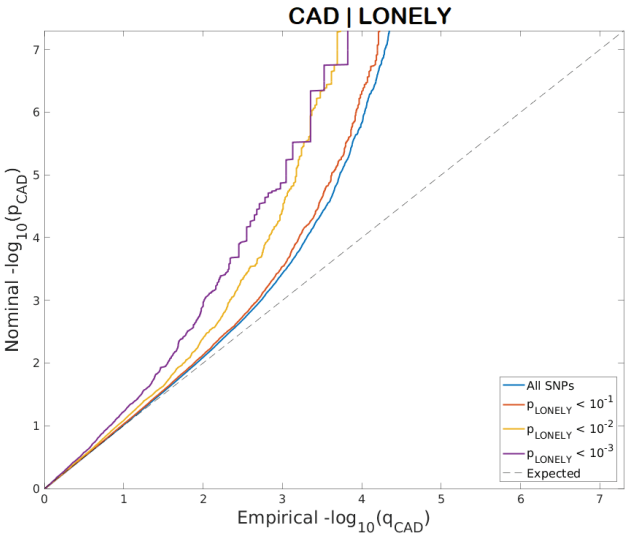

LONELY | SBP
Nominal -log10(pLONELY)
Empirical -log10(qLONELY)
All SNPs
pSBP < 10-1
pSBP < 10-2
pSBP < 10-3
Expected

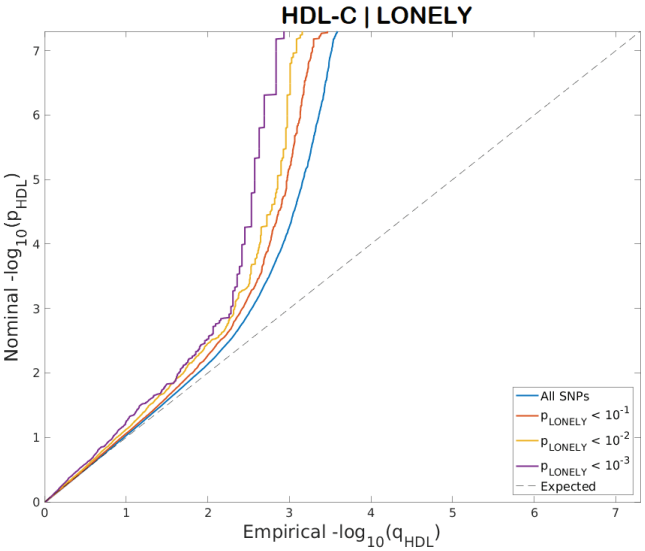

LONELY | DBP
Nominal -log10(pLONELY)
Empirical -log10(qLONELY)
All SNPs
pDBP < 10-1
pDBP < 10-2
pDBP < 10-3
Expected

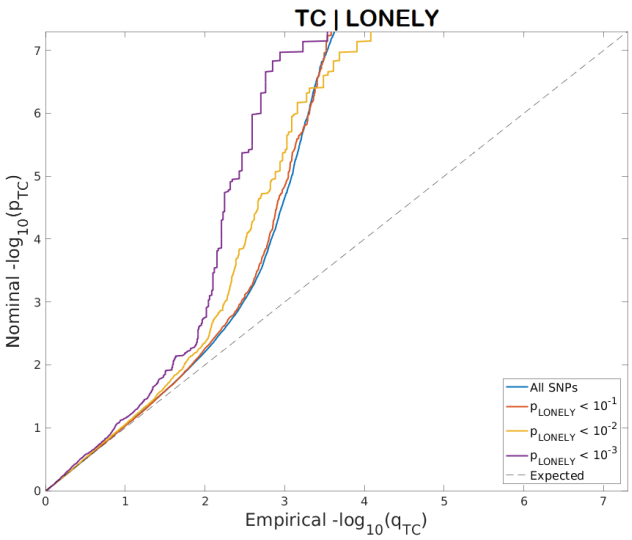


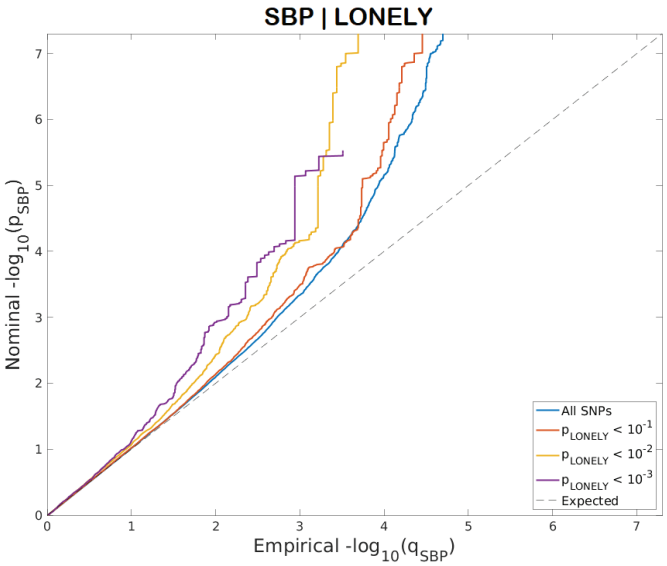
Supplementary Figure 6. Polygenic overlap between loneliness and CVD risk factors. Conditional Q-Q plots of nominal versus empirical $-\log_{10}$ p-values (corrected for inflation) in loneliness below the standard GWAS threshold of $p < 5\times10^{-8}$ as a function of significance of association with CVD risk factors at the level of $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively. The blue lines indicate all SNPs. The dashed lines indicate the null hypothesis. Abbreviations: CVD, cardiovascular disease; BMI, body mass index; CAD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; T2D, type 2 diabetes mellitus. The conditional Q-Q plots build on the condFDR method.

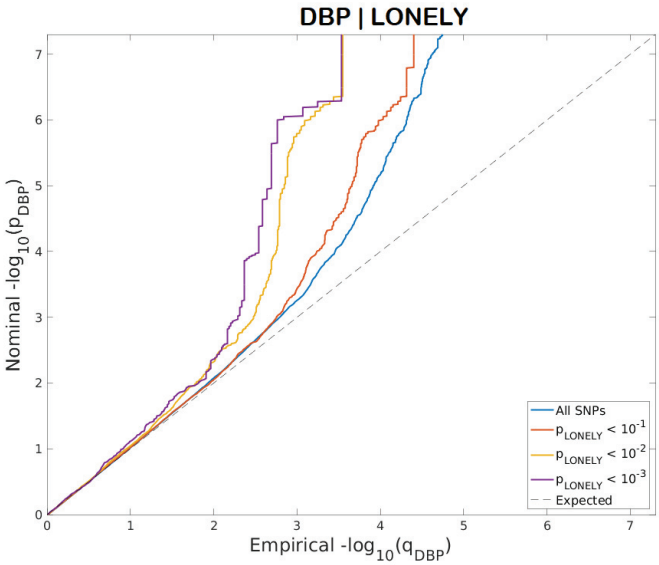

BMI | LONELY
Nominal -log10(pBMI)
Empirical -log10(qBMI)
All SNPs
pLONELY < 10-1
pLONELY < 10-2
pLONELY < 10-3
Expected

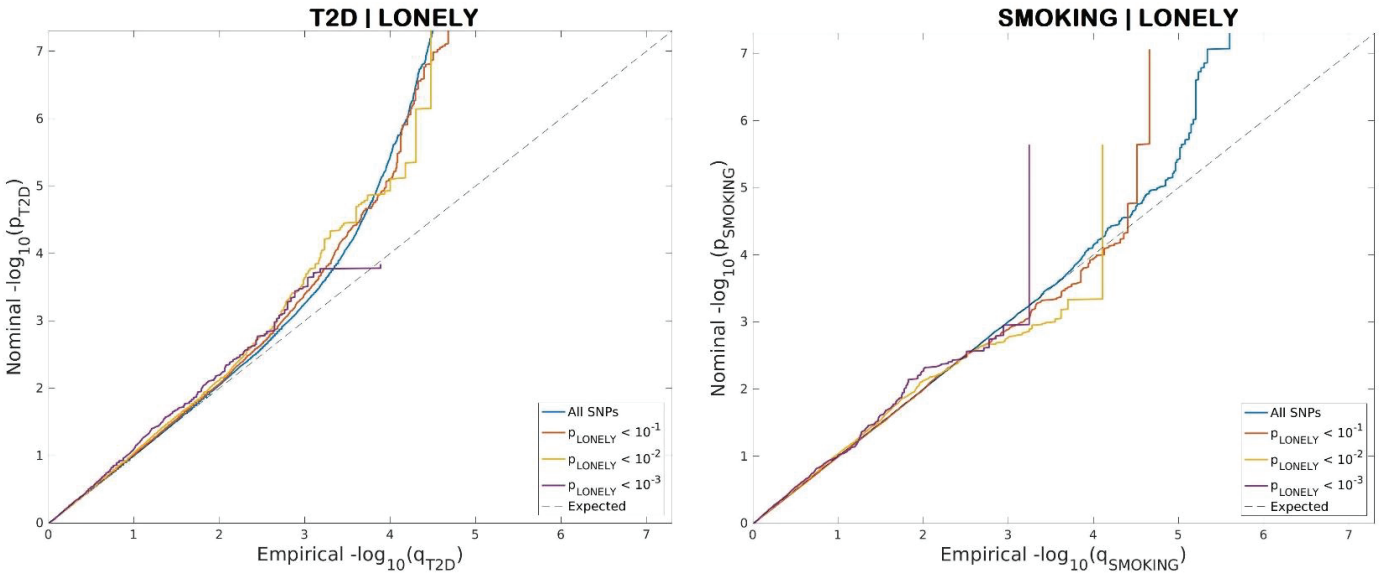

CAD | LONELY
Nominal -log10(pCAD)
Empirical -log10(qCAD)
All SNPs
pLONELY < 10-1
pLONELY < 10-2
pLONELY < 10-3
Expected


HDL-C | LONELY
Nominal -log10(pHDL)
Empirical -log10(qHDL)
All SNPs
pLONELY < 10-1
pLONELY < 10-2
pLONELY < 10-3
Expected

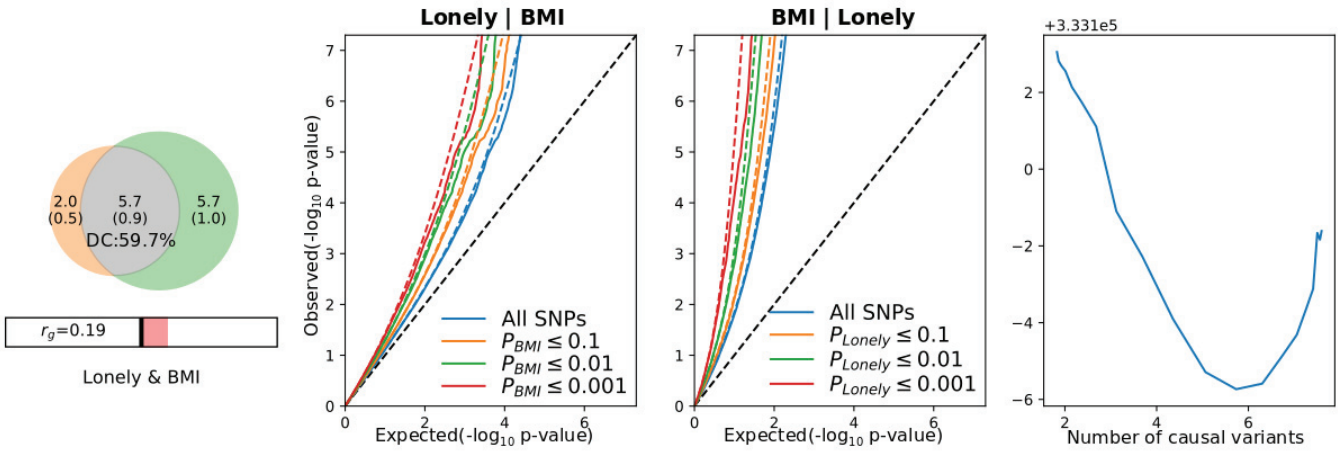

TC | LONELY
Nominal -log10(pTC)
Empirical -log10(qTC)
All SNPs
pLONELY < 10-1
pLONELY < 10-2
pLONELY < 10-3
Expected


SBP | LONELY
Nominal -log10(pSBP)
Empirical -log10(qSBP)
All SNPs
pLONELY < 10-1
pLONELY < 10-2
pLONELY < 10-3
Expected

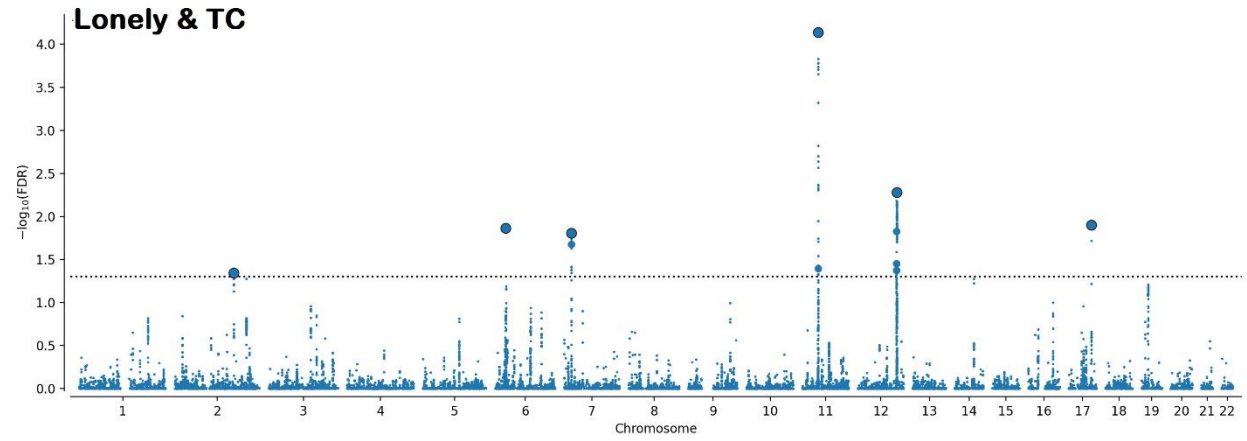

DBP | LONELY
Nominal -log10(pDBP)
Empirical -log10(qDBP)
All SNPs
pLONELY < 10-1
pLONELY < 10-2
pLONELY < 10-3
Expected

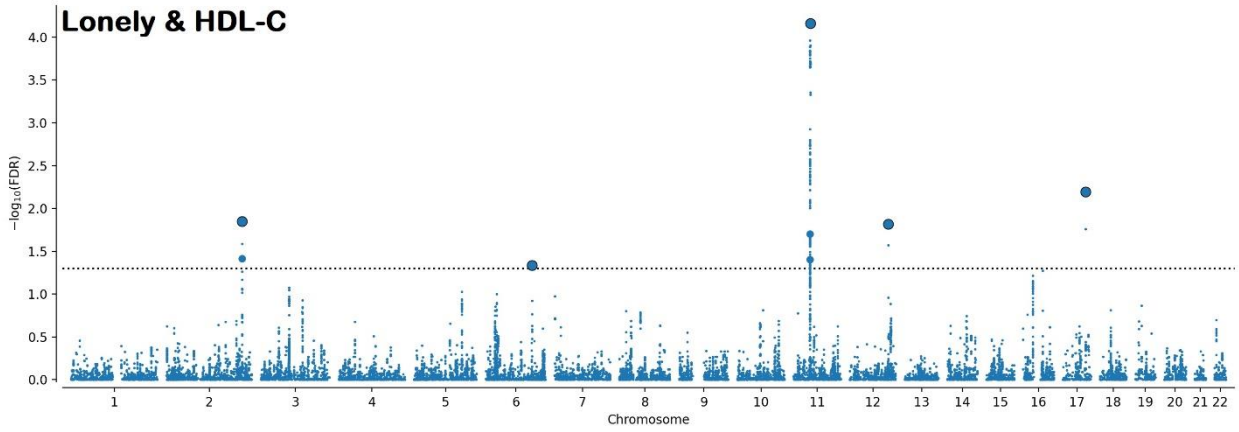


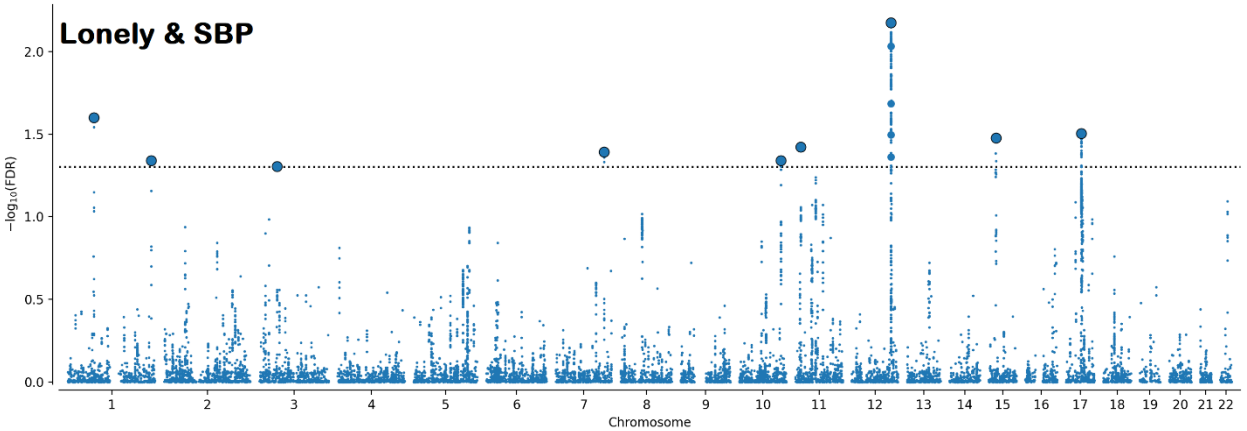
Supplementary Figure 7. Polygenic overlap between loneliness and CVD risk factors. Conditional Q-Q plots of nominal versus empirical $-\log_{10}$ p-values (corrected for inflation) in CVD risk factors below the standard GWAS threshold of $p < 5\times10^{-8}$ as a function of significance of association with the loneliness at the level of $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively. The blue lines indicate all SNPs. The dashed lines indicate the null hypothesis. Abbreviations: CVD, cardiovascular disease; BMI, body mass index; CAD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; T2D, type 2 diabetes mellitus. The conditional Q-Q plots build on the condFDR method.

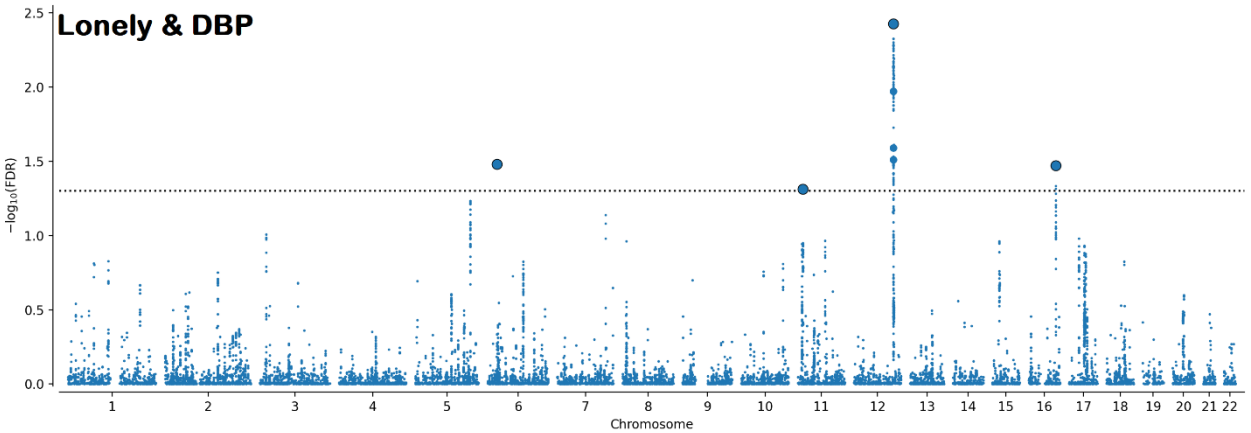


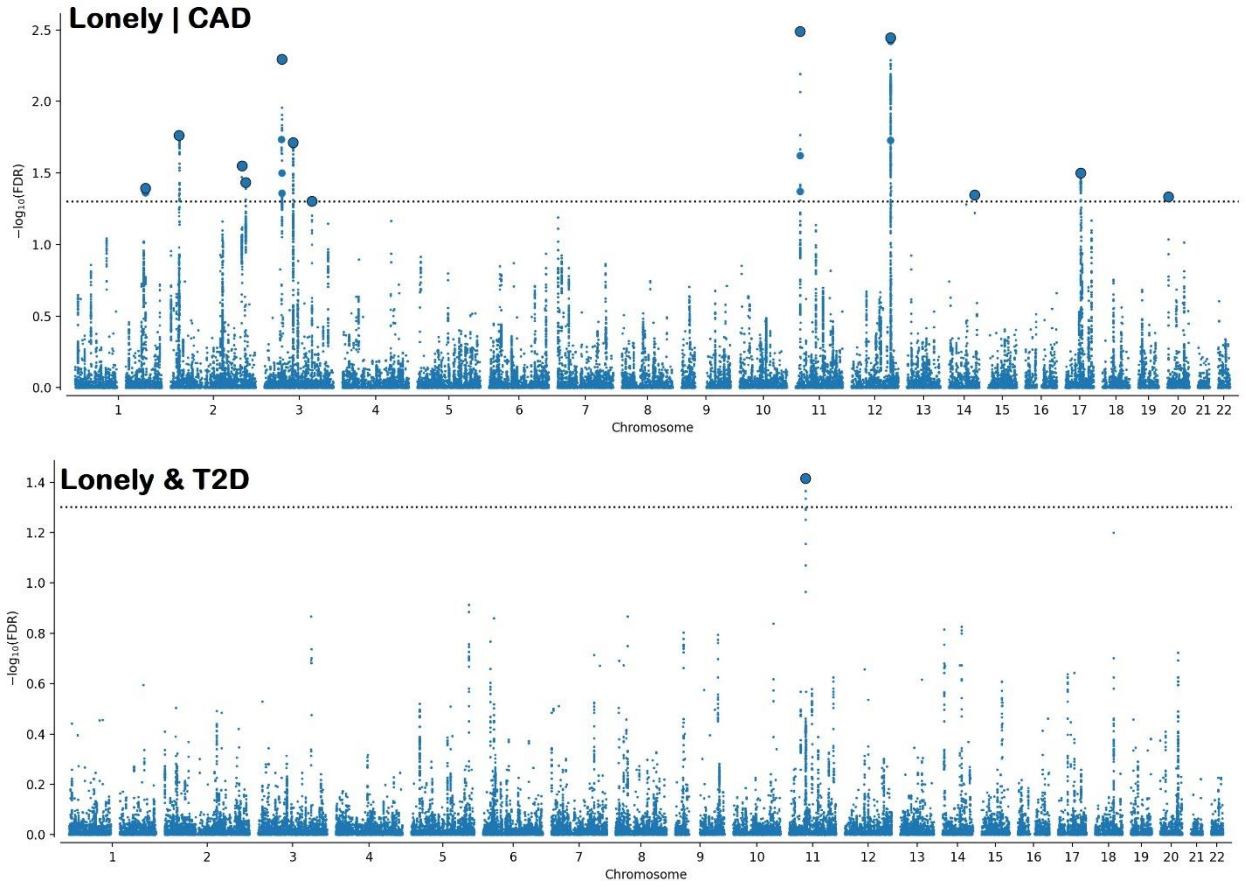
Supplementary Figure 8. Venn diagram, conditional Q-Q plots, and negative log-likelihood plot, respectively. Venn diagram of unique and shared polygenic components at the causal level, showing polygenic overlap (gray) between loneliness (orange) and body mass index (BMI) (green). The numbers indicate the estimated quantity of causal variants (in thousands) per component, explaining 90% of SNP heritability in each phenotype, followed by standard error, and Dice coefficient (DC) indicates the percentage of shared causal variants between the two phenotypes. Appearance of the Q-Q plot and negative log-likelihood plot are described below Supplementary Figure 3. Figures generated from MiXeR.


Lonely & TC
−log10(FDR)
Chromosome


Lonely & HDL-C
−log10(FDR)
Chromosome


Lonely & SBP
−log10(FDR)
Chromosome


Lonely & DBP
−log10(FDR)
Chromosome



Supplementary Figure 9. Common genetic variants jointly associated with loneliness and CVD risk factors at conjFDR < 0.05. Manhattan plot showing the –log10 transformed conjFDR values for each SNP on the y axis and chromosomal positions along the x axis[4]. SNPs with conjFDR < 0.05 (i.e., −log10 FDR > 1.3) are shown with enlarged data points. A black circle around the enlarged data points indicates the most significant SNP in each LD block. The figure shows the localization of the 'conjunctional loci', and further details are provided in Supplementary Tables 21-26. Abbreviations: CVD: cardiovascular disease; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; DBP, diastolic blood pressure; SBP, systolic blood pressure; CAD, coronary heart disease; T2D, type 2 diabetes mellitus: conjFDR, conjunctional FDR.

Supplementary Table 1. ICD-coded diagnosis in the UK Biobank		
ICD-10 diagnosis	**Count**	**Percentage of the UK Biobank sample**
F20-29 Schizophrenia/schizotypal and delusional disorder	2483	0.6%
F30 Manic episode; F31 Bipolar disorder	245; 2123	0.6%[a]
F32 Depressive episode; F33 Recurrent depressive disorder; F34 Persistent mood disorders; F38/39 Other/Unspecified mood disorders Major depressive disorder[c]	19542; 1156; 95; 93 8276	5.1%[b]
F40-48 Neurotic, stress-related and somatoform disorders	14914	3.6%
F50-59 Behavioural syndrome associated with physiological disturbances/physical factors	729	<0.2%
F60-69 Disorder of adult personality and behaviour	800	<0.2%
F70-99 Other behavioural and mental disorders	1018	0.2%
Numbers of ICD-10 coded psychiatric diagnoses from the UK Biobank data field 41270. Data was available from 410 320 individuals. [a]This percentage includes manic episode and bipolar disorder. [b]This percentage includes depressive episode and depressive disorder. [c]The diagnostic term "major depressive disorder " (MDD) is used in Diagnostic and Statistical Manual of Mental Disorders (DSM), not in ICD-10. The number of individuals meeting the criteria of MDD is estimated by Howard et al. 2018[38]. ICD: International Classification of Diseases.		

Supplementary Table 2. Self-reported diagnosis in the UK Biobank sample		
Self-reported diagnosis	**Count**	**Percentage of the UK Biobank sample**
Depression	33 424	21.1%
Schizophrenia	157	0.1%
Any other type of psychotic disorder	604	0.4
Bipolar disorder	837	0.5
Anxiety, nerves or generalized anxiety	22 036	14.0%
The numbers are retrieved from the 157 366 participants that completed the Mental Health Questionnaire and published in Davis et al. 2020[6].		

Supplementary Table 3. Results of cross-trait analysis with the MiXeR model for loneliness, MD, SCZ, BD and BMI

Trait1	Trait2	AIC	
		best vs min. overlap	best vs max. overlap
Loneliness	MD	-1.739	-1.515
Loneliness	SCZ	9.231	-1.413
Loneliness	BD	5.955	9.315
Loneliness	BMI	16.180	6.852

AIC - results from Akaike information criterion, showing AIC calculated for the full versus reduced bivariate MiXeR model[14], constrained to minimal feasible polygenic overlap ("best vs min.") or to the complete polygenic overlap ("best vs max."). A negative value indicates that AIC chooses reduced model, while a positive value provides an evidence for the polygenic overlap, shown in the MiXeR Venn diagram. MD: Major depression; SCZ, schizophrenia; BD, bipolar disorder; BMI, body mass index.

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Study III

Extensive bidirectional genetic overlap between bipolar disorder and cardiovascular disease phenotypes

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Abstract

Patients with bipolar disorder (BIP) have a high risk of cardiovascular disease (CVD), despite considerable individual variation. The mechanisms underlying comorbid CVD in BIP remain largely unknown. We investigated polygenic overlap between BIP and CVD phenotypes, including CVD risk factors and coronary artery disease (CAD). We analyzed large genome-wide association studies of BIP (n=51 710) and CVD phenotypes (n=159 208–795 640), using bivariate causal mixture model (MiXeR), which estimates the total amount of shared genetic variants, and conjunctional false discovery rate (FDR), which identifies specific overlapping loci. MiXeR revealed polygenic overlap between BIP and body mass index BMI (82%), diastolic and systolic blood pressure (20-22%) and CAD (11%) despite insignificant genetic correlations. Using conjunctional FDR<0.05, we identified 129 shared loci between BIP and CVD phenotypes, mainly BMI (n=69), systolic (n=53) and diastolic (n=53) blood pressure, of which 22 are novel BIP loci. There was a pattern of mixed effect directions of the shared loci between BIP and CVD phenotypes. Functional analyses indicated that the shared loci are linked to brain-expressed genes and involved in neurodevelopment, lipid metabolism, chromatin assembly/disassembly and intracellular processes. Altogether, the study revealed extensive polygenic overlap between BIP and comorbid CVD, implicating shared molecular genetic mechanisms. The mixed effect directions of the shared loci suggest variation in genetic susceptibility to CVD across BIP subgroups, which may underlie the heterogeneity of CVD comorbidity in BIP patients. The findings suggest more focus on targeted lifestyle interventions and personalized pharmacological treatment to reduce CVD comorbidity in BIP.

Introduction

People with bipolar disorder (BIP) have on average twice as high risk of cardiovascular disease (CVD) compared to the general population, contributing to a reduction in life expectancy[1-3]. CVD comorbidity and mortality have remained high during the past decades, indicating that most patients with BIP have not benefited from recent advances in medicine[4-7]. The etiology the CVD comorbidity remains largely unknown, but it is likely to be associated with medication side-effects and lifestyle factors, such as poor diet, physical inactivity and smoking[1, 8]. A genetic susceptibility to CVD may also play a role, similar to what has been indicated in schizophrenia[9, 10], including overlapping genetic loci[11, 12]. This is supported by the considerable genetic overlap between schizophrenia and BIP[13]. However, there is a large individual variation in CVD comorbidity[2-4], which suggests increased genetic risk for CVD in subgroups of BIP.

BIP is a complex disorder with heritability estimates of 70-80% [14]. The polygenic nature of BIP is becoming increasingly apparent as recent genome-wide association studies (GWASs) have identified 64 risk loci for BIP[15]. GWASs have also discovered many genetic loci associated with CVD risk factors, including body mass index (BMI)[16, 17], type 2 diabetes (T2D)[18], total cholesterol (TC)[19], low-density lipoprotein (LDL) cholesterol[19], high-density lipoprotein (HDL) cholesterol[19], systolic blood pressure (SBP)[20], diastolic blood pressure (DBP)[20], along with coronary artery disease (CAD)[21].

Few studies have investigated the genetic relationship between BIP and CVD risk factors and CAD[22-24]. A recent study suggested an inverse genetic relationship between BIP and CVD risk factors (BMI, TC, LDL, HDL)[23], indicating that BIP may be related to reduced genetic risk of CVD. However, the results varied depending on using polygenic risk scores (PRS) or linkage disequilibrium score regression (LDSR)[23]; the latter did not provide significant results. Importantly, a significant genetic correlation estimated with LDSR

requires consistent effect directions of the shared variants between the phenotypes[25]. Thus, genetic correlation fails to capture polygenic overlap in the presence of a mixture of effect directions across shared variants[26]. The bivariate causal mixture model (MiXeR), which estimates the *total number* of shared genetic variants[27], can identify polygenic overlap (i.e. shared genetic architecture among common variants), beyond genetic correlations. Further, the conditional/conjunctional false discovery rate (cond/conjFDR) methodology can identify the *specific* overlapping loci[28]. These methods have the advantage of identifying shared variants regardless of their effect directions[27, 28]. In addition, the cond/conjFDR tools increase the power for genetic discovery due to joint analysis of two GWAS, leading to the identification of loci that do not reach significance threshold in traditional GWAS analyses[28], as illustrated with several complex human traits[24, 29-31].

We recently discovered 69 shared loci between BIP and BMI, of which 52 % possessed concordant effect directions, while genetic correlation was insignificant[24]. These results demonstrate polygenic overlap between BIP and BMI and the mixed effect directions may suggest subgroups of BIP with higher susceptibility for weight gain. Further, the findings highlight the importance of analysis of genetic correlation with analytical methods that allow for identification of shared genetic variants irrespective of their effect directions[26].

In the present study, we investigated the polygenic overlap between BIP, CVD risk factors and CAD beyond genetic correlations with the MiXeR method[27], and applied the cond/conjFDR approach to identify shared loci[28]. We expect to unravel more of the shared genetic architecture between BIP, CVD risk factors and CAD, and enhance the discovery of specific overlapping genetic loci to inform the underlying molecular mechanisms.

Methods

Participant samples

We obtained GWAS results in the form of summary statistics (p-values and z-scores). BIP data were retrieved from Psychiatric Genomics Consortium (PGC) and consisted of 20 352 cases and 31 358 controls from 32 samples[32]. Among the cases, 14,879 individuals were diagnosed with BIP type I (BIP1), 3,421 with BIP type II (BIP2), 977 with schizoaffective disorder, bipolar type (SAB), and the BIP not otherwise specified (NOS)[32]. Further we used data from large GWASs on CVD phenotypes, including BMI, TC, HDL, LDL, SBP, DBP and T2D and CAD (n=159 208 – 795 640)[17-21, 33]. We repeated the previously published analysis of genetic overlap between BIP and BMI[24] using cond/conjFDR. While MiXeR corrects for overlapping samples[27], cond/conjFDR do not[28]. Thus, we screened for overlapping samples between the BIP GWAS and the CVD GWASs by checking the substudies included in the GWASs, and found no overlapping samples. However, we did not have access to individual genotype data and were thus prevented from determining whether any individuals participated in both the BIP GWAS and any of the CVD GWASs. For further information about the GWASs, see Supplementary Methods and original publications[17-21, 32]. The local ethics committees approved all GWASs used in the current study, and all participants provided informed consent. Regional Committees for Medical Research Ethics - South East Norway has evaluated the current protocol and found that no additional institutional review board approval was necessary because no individual data were used.

Statistical analysis

We constructed conditional quantile-quantile (Q-Q) plots to visualize the putative overlap in SNPs associations, i.e. cross-trait enrichment. Enrichment exists when the proportion of SNPs associated with a phenotype (e.g. BIP) increases as a function of the strength of the association with a secondary phenotype (e.g. BMI)[28]. In the conditional Q-Q plots, this cross-

trait enrichment is visualized as successive leftward shifts from the null line[12, 28]. Details about this method are available in Supplementary Methods.

Next, we used the statistical tool MiXeR to estimate the total number of shared and unique trait-influencing variants (i.e. variants with pure genetic effects not induced by LD) using GWAS summary data[27]. This method evaluates polygenic overlap independent of genetic correlation between phenotypes. The MiXeR results are illustrated with Venn diagrams of shared and unique variants. Estimates of uncertainty are provided, including standard error in parenthesis in the Venn diagrams. We evaluated the model fit, i.e. the ability of the MiXeR model to predict the actual GWAS data, based on modelled vs. actual conditional Q-Q plots, negative log-likelihood plots and Akaike information criterion (AIC). For details about MiXeR, see Supplementary Methods and Frei et al.[27].

The condFDR approach was used to increase discovery of specific genetic variants associated with BIP and CVD phenotypes[28]. The condFDR method builds on Bayesian statistics and increases the power to identify loci associated with a primary phenotype (e.g., BIP) by leveraging associations with a secondary phenotype (e.g., BMI). Thus, this method re-ranks the test-statistics of a primary phenotype (e.g. BIP) based on a conditional variable, i.e. the strength of the association with a secondary phenotype (e.g. BMI)[28]. Inverting the roles of primary and secondary phenotypes yields the inverse condFDR value[28]. ConjFDR is an extension of condFDR and can detect loci *jointly* associated with two phenotypes (e.g. both BIP and BMI)[28]. ConjFDR is defined as the maximum of the two condFDR values, providing a conservative estimate of the FDR for a SNP association with *both* phenotypes[12, 28]. P-values are corrected for inflation using a genomic inflation control procedure [12, 28]. Consistent with previous publications[24, 29, 34, 35], we used the thresholds condFDR<0.01 and conjFDR<0.05. For further information, see Supplementary Methods and method reviews[28, 36].

Genomic loci definition

To define the independent genomic loci, we applied FUMA, an online tool for functional mapping of genetic variants (http://fuma.ctglab.nl/)[37]. Independent significant SNPs were defined as SNPs with condFDR<0.01 or conjFDR<0.05 and independent from each other at LD r^2<0.6. Lead SNPs were identified by retaining those independent significant SNPs that were independent from each other at r^2< 0.1. To define distinct genomic loci, we merged any physically overlapping lead SNPs (LD blocks <250 kb apart) selecting a SNP with the lowest p-value as a lead SNP of the merged locus. The borders of the genomic loci were defined by identifying all SNPs (candidate SNPs) in LD (r^2≧0.6) with one of the independent significant SNPs in the locus[37] (see Supplementary Methods).

Effect directions and genetic correlations

We evaluated the directional effects of the shared lead SNPs between BIP and CVD phenotypes by comparing their *z*-scores and odds ratios from the original publications[16, 18-21, 32]. Genetic correlations were estimated using LDSR and corrected for multiple testing (0.05/8)[38].

Functional annotation

We used FUMA[37] to functionally annotate candidate SNPs in the genomic loci with a condFDR/conjFDR value<0.10 and an LD r^2≧0.6 with one of the independent significant SNPs. SNPs were annotated using three different tools, including Combined Annotation Dependent Depletion (CADD)[39], a method that predicts the deleteriousness of SNPs on protein structure/function; RegulomeDB[40], which predicts regulatory functions; and chromatin states that indicate the transcription/regulation effects at the SNP locus[41, 42]. We also identified previously reported GWAS associations in the GWAS catalog[43] overlapping

with the identified loci. We proceeded with further functional analyses provided that we identified at least one shared locus at conjFDR<0.05. Thus, the prerequisite for performing functional analysis was the presence of ≥ one locus jointly associated with BIP and a given CVD phenotype. The functional analyses included gene-mapping, gene-set analysis and pathway analysis. In particular, FUMA was used to map lead and candidate SNPs to genes based on either of three properties of the SNPs: 1) their physical position (i.e. proximity to a gene), 2) expression quantitative trait locus (eQTL) functionality and 3) chromatin interaction[37]. Next, we investigated whether genes mapped to all SNPs in shared loci were overrepresented in gene-sets using FUMA[37] and in pathways using ConsensusPathDB[44]. For details, see Supplementary Methods.

Results

Genetic overlap between BIP and CVD phenotypes

In the conditional Q-Q plots, we observed enrichment in BIP SNPs as a function of the significance of associations with CVD phenotypes (Supplementary Figure 1), indicating polygenic overlap. The reverse conditional Q-Q plots also demonstrated enrichment in CVD phenotypes given associations with BIP (Supplementary Figure 2).

After observing cross-trait enrichment, we applied MiXeR which discovered different polygenicity of BIP (8.1k), BMI (11k), SBP (4.4k), DBP (3.9k) and CAD (1.4k). Parameter estimates of the MiXeR model and corresponding standard error are provided in Table 1 and Figure 1. MiXeR revealed polygenic overlap between BIP and BMI, sharing 6.6k of 12.5k variants, as illustrated by the Venn diagram (Figure 1a). The shared variants constitute 81.5% and 60% of variants influencing BIP and BMI, respectively. MiXeR also revealed polygenic overlap between BIP and SBP, sharing 1.8k of 10.7k variants (Figure 1b), representing 22.2% and 40.9% of variant influencing BIP and SBP, respectively. Similarly, MiXeR identified polygenic overlap with DBP, sharing 1.6k of 10.4K variants (Figure 1c),

constituting 19.8% and 41.0% of the genetic variants underlying BIP and DBP, respectively. In addition, BIP shared 0.9k of 8.6k variants with CAD (Figure 1d), representing 11.1% and 64.3% of the genetic basis of BIP and CAD, respectively. Model fit was considered adequate as indicated by model-based Q-Q plots following the actual Q-Q plots (Supplementary Figures 3-6), although some caution in interpreting the MiXeR model for BIP and CAD is needed as the predicted Q-Q plots follow the observed Q-Q plots less closely at smaller p-values. The log-likelihood plots illustrated adequate model fit (Supplementary Figures 3-6) and AIC demonstrated sufficiently powered model (Supplementary MiXeR Table). The MiXeR model was not used for the other CVD phenotypes due to inadequate model fit (Supplementary Figures 7a-d).

Loci shared between BIP and CVD phenotypes

At condFDR<0.01, we identified multiple loci associated with BIP conditional on their association with each CVD phenotype (Supplementary Tables 1-8), and vice versa (Supplementary Tables 9-16, and Supplementary Results). At conjFDR<0.05, we discovered several loci jointly associated with BIP and CVD phenotypes, including 69 loci shared with BMI as previously reported[24], and 53 loci with SBP, 53 loci with DBP, 15 with TC, 13 loci with LDL, 10 loci with HDL, 4 loci with T2D and 10 loci with CAD (Figure 2a-h; Supplementary Tables 17-24). We observed small SNP p-values for both phenotypes, which indicate true associations with both BIP and CVD phenotypes. Several loci were jointly associated with BIP and more than one CVD phenotype, resulting in 129 distinct loci associated with both BIP and CVD phenotypes at conjFDR<0.05. Twenty two of the shared loci are novel BIP loci (Supplementary Table 25). See Supplementary Methods for all the studies reviewed to determine the number of novel BIP loci.

We evaluated the directionality of allelic effects of the shared lead SNPs between the phenotypes by investigating their z-scores. There was a pattern of mixed effect directions of the shared SNPs between BIP and CVD risk factors (Table 2). We discovered the same effect direction of 52.2% of SNPs shared with BMI (as previously reported[24]), 49.1% SNPs shared with SBP, 47.2% SNPs shared with DBP, 26.7 % SNPs shared with TC, 46.2% SNPs shared with LDL, 40% SNPs shared with HDL, 25% SNPs shared with T2D, and 70% SNPs shared with CAD (Supplementary tables 17-24). The genetic correlations were insignificant (rg=-0.06-0.04) (Table 2).

Functional annotation

Functional annotation of all SNPs having a conjFDR value<0.1 in the loci shared between BIP and CVD phenotypes demonstrated that these were mostly intronic and intergenic (Supplementary Tables 26-33). *Gene-mapping* of shared loci between BIP and CVD phenotypes largely implicated brain-expressed genes (Supplementary Tables 34-41; Supplementary Results). Further, *gene-set analyses* revealed several significantly associated biological and cellular processes with the genes mapped to the shared loci between BIP and BMI, including “chromatin organization”, “chromatin assembly/disassembly” and “DNA packaging complex” (Supplementary Table 42). The genes mapped to the shared loci between BIP and SBP were most significantly associated with “neurogenesis”, “neuronal differentiation” and “mitochondrion” (Supplementary Tables 43). Gene-set analyses also identified several significantly associated processes with the genes mapped to the shared loci between BIP and DBP, including “chromatin assembly”, “nucleosome organization” and “DNA backpacking complex” (Supplementary Tables 44). Here, the three most significant biological processes and the most significant cellular process seem to be driven by associations from the histone gene cluster (Supplementary Tables 44). Since many of the

genes in these gene sets are localized in a single cluster, a single association in this cluster can drive the apparent enrichment of the entire gene set. Therefore, we also performed gene-set analysis of the genes *nearest* the lead SNPs in the shared loci between BIP and DBP (Supplementary Table 45). This analysis identified a different set of genes and associated biological processes (including "positive regulation of gene expression" and "maintenance of protein localization") (Supplementary Table 45) compared to the results in Supplementary Table 44. The genes mapped to the shared loci between BIP and lipids (TC, HDL and LDL) were significantly associated with "chromatin assembly/disassembly", "hyaluronan metabolic process" and "lipid biosynthetic process" (Supplementary Tables 46-48). The genes mapped to loci shared between BIP and T2D and CAD were most significantly associated with "unsaturated fatty acid biosynthesis" (Supplementary Tables 49-50).

We identified several *pathways* overrepresented among the genes mapped to loci shared between BIP and CVD phenotypes. We found neural cell adhesion molecule (NCAM) signaling for neurite out-growth pathway to be significantly overrepresented among the genes mapped to the shared loci between BIP and BMI (Supplementary Table 51). Other pathways (e.g. Organelle biogenesis and maintenance, Oxytocin signaling pathway and Cushing syndrome) were also overrepresented among these genes, but they did not reach significance after correcting for multiple testing (see q-values in Supplementary Table 51). We also identified several pathways overrepresented among the genes mapped to loci shared between BIP and SBP/DBP, including signaling by plasma membrane FGR1 fusions, beta-agonist/beta-blocker pathway, sympathetic nerve pathway, cortisol synthesis and secretion and several hormonal and metabolic pathways (Supplementary Tables 52-53). We found omega-3 fatty acid metabolism pathway and other pathways to be overrepresented among the genes mapped to the shared loci between BIP and lipids, T2D and CAD **(**Supplementary Tables 54-58).

Discussion

In the present study, we demonstrated extensive polygenic overlap between BIP and CVD phenotypes. We revealed 129 shared loci of which 22 were novel BIP loci. The shared loci possessed mixed effect directions in BIP and CVD risk factors and CAD, consistent with insignificant genetic correlations. The results provide new insights into the shared genetic architecture of BIP and CVD morbidity, implicating novel molecular genetic mechanisms, and may suggest variation in CVD risk across subgroups of patients with BIP.

The present study goes beyond standard methods to assess genetic overlap as the MiXeR can estimate polygenic overlap with mixed effect directions, and the conjFDR method can detect shared genetic variants between phenotypes regardless of the overall genetic correlation[26-28]. Using MiXeR we discovered that ~82% the genetic variants influencing BIP also influence BMI. In addition, ~20% of variants influencing BIP also influence SBP/DBP, yet a larger proportion (~40%) of genetic variants underlying SBP/DBP affect BIP. MiXeR also suggested polygenic overlap between BIP and CAD, although the degree of overlap is uncertain, suggesting that a larger CAD GWAS is needed to obtain more reliable MiXeR estimates. The differences in overlap partly reflect variation in polygenicity of these phenotypes, with BIP and BMI being more polygenic than SBP/DBP and CAD, as illustrated in the Venn diagrams.

Further, conjFDR revealed several shared loci between BIP and CVD phenotypes. More specifically, we identified a total of 227 overlapping loci between BIP and CVD risk factors at conjFDR<0.05, of which 129 were unique (Table 2). Most of the loci were shared with BMI[24] and SBP/DBP, while a smaller number of loci were shared with lipids, CAD and T2D based on conjFDR. While the GWAS sample sizes do not influence the nature of the joint association between BIP and the CVD phenotypes, they are likely to influence the

magnitude of genetic overlap across the CVD phenotypes[28]. Accordingly, while the finding of most shared loci with BMI and SBP/DBP suggests greater overlap, this finding may also be related to the larger GWAS samples used for BMI[17] and SBP/DBP[20] than for the other CVD phenotypes[18, 19, 21]. In addition, the highly polygenic nature of BMI likely contributed to the finding of more shared loci with BMI. Interestingly, there was a general pattern of bidirectional effects of the shared loci. Genetic variants with mixed effect directions "cancel each other out", resulting in insignificant genetic correlations between BIP and CVD risk factors, as well as CAD. Thus, while our results suggest shared molecular mechanisms implicating pleiotropy, there is no clear pattern of increased or decreased genetic liability to CVD in BIP.

The mixed effect directions among the loci shared between BIP and CVD phenotypes underscore the complexity of the genetic relationship. While there was a general trend of opposite effect direction (~52%), there was a majority of concordant effect directions in CAD. However, due to the small number of SNPs involved, these individual loci explain a little proportion of the overall risk. Thus, the findings indicate that common genetic variants do not explain the higher CVD risk in BIP. It is possible that genetic factors not captured by currently GWASs, such as rare variants, may contribute. However, it is likely that environmental risk factors play a central role in comorbid CVD in BIP. In particular, medication, poor nutrition, physical inactivity and smoking are important contributors to CVD in BIP[8, 45]. The mixed effect directions of the shared loci comply with previous findings of bidirectional effects among overlapping loci ~~b~~between SCZ and multiple CVD risk factors[12]. Similar to the current study, other studies also indicate genetic overlap between BIP and CVD in spite of non-significant genetic correlations[23, 46]. Further, the bidirectional effects of the shared variants between BIP and BMI are in line with the large clinical variation in weight changes during mood episodes of BIP. Some patients experience weight loss while others

gain weight during a depressive episode, and most patients lose weight during a manic episode[47]. Similarly, studies suggest variation in lipid levels and SBP/DBP related to affective episodes, with higher levels of dyslipidemia and SBP/DBP in depressive than in manic episodes[48-50].

Further, the mixed effect directions of shared variants may reflect variation in genetic liability to CVD across BIP subgroups. BIP is a heterogeneous disorder involving different subtypes, illness courses and severity[51] that may be differentially related to CVD comorbidity. Notably, while the average level of CVD risk is higher in BIP compared to the general population, the CVD comorbidity seems to be restricted to BIP subgroups, illustrated by overweight (~50-75%), dyslipidemia (~25-40%), T2D (~5-20%) and hypertension (~35-60%)[2-4], which suggest subsets of patients with different susceptibility to CVD. For instance, patients with more depressive symptoms may represent such a subgroup, as increased depressive symptoms rather than mania are associated with higher rates of obesity, dyslipidemia and T2D[48-50, 52-55]. Moreover, recent findings indicate a genetic susceptibility to weight gain in major depression[24]. Since BIP type 2 is genetically more related to major depression [32], this subtype of BIP may also involve increased genetic risk of weight gain. BIP type 1, on the other hand, is more genetically correlated with SCZ[32] and may thus have reduced genetic risk of weight gain[24]. Larger and well-characterized GWAS samples are needed to identify subgroups with varied genetic susceptibility to weight gain and other CVD phenotypes in BIP. The identification of potential subgroups with different genetic liability to CVD can increase the understanding of CVD comorbidity in BIP and help improve risk prediction and prevention.

Functional annotation indicated that the shared variants between BIP and CVD are mostly intronic and intergenic, which is in line with other GWAS findings[24, 34]. The results indicate the shared SNPs influence gene expression via regulatory effects[56]. Further functional

analyses indicated that the shared variants between BIP and CVD phenotypes are involved in several biological processes and pathways associated with neurodevelopment, lipid metabolism, intracellular processes and chromatin assembly/disassembly (i.e. formation or destruction of chromatin structures, which play an important role in regulating transcription and gene expression[57]). Further, the shared loci were largely linked to genes expressed in the brain. In line with current findings, brain dysfunction is implicated in the pathophysiology of BIP[58] and more recently linked to the shared variants between BIP and BMI[22, 24]. Moreover, lipid biology may be involved in the pathophysiology of BIP, as proposed for SCZ[29], consistent with evidence of white-matter abnormalities and myelin dysfunction in both disorders[59, 60]. Furthermore, functional analyses of the shared loci between BIP and SBP implicated genes involved in stress-related pathways, including cortisol synthesis and secretion. Similarly, recent findings indicate overlapping genetic variants between BIP and CVD risk factors associated with hypothalamic-pituitary-adrenal (HPA) axis regulation[22, 24]. Shared genetic variants associated with the HPA axis appears plausible given evidence of HPA axis dysregulation in BIP[61], obesity and hypertension[62]. However, the results from functional analyses should be considered with caution given the limitations of ConsensusPathDB and FUMA, including vulnerability to bias from clusters of genes in the genome. This bias was evident in the results from gene-set analysis of the shared loci between BIP and DBP (Supplementary Table 44), indicating that the most significant biological processes are driven by associations from the histone gene cluster.

Altogether, the current findings are in line with the hypothesis that brain-related mechanisms play a role in CVD comorbidity in BIP. It is possible that shared genetic variants, interacting with environmental risk factors, affect brain function that influences behavior (e.g. lifestyle choices) and mental processes (e.g. affective symptoms) and, thereby, the development of BIP and comorbid CVD. It is also possible that shared variants between BIP

and CVD morbidity affect metabolic mechanisms[22, 24], influencing CVD risk and brain function, contributing to development of BIP. In addition, separate pathways underlying BIP and CVD are likely given the bidirectional effects of the shared loci. However, the proposed pathways are preliminary and require further experimental investigation due to limitations of current methods used to functionally annotate SNPs[37] and the complexity of the pathophysiology of BIP and CVD.

The current results of mixed effect directions of shared loci between BIP and CVD phenotypes have important clinical implications. The results indicate that the genetic susceptibility for CVD may vary across BIP subgroups, calling for more diverse and targeted clinical interventions. Future investigations of subgroups with different genetic liability to CVD can form the basis for improved prediction tools, which can pave the way for early risk identification and prevention of CVD in BIP. Improved prevention should involve better tailored pharmacological treatment according to individuals' genetic risk and personalized lifestyle interventions with focus on the barriers for maintaining a healthy lifestyle, such as motivational and other affective symptoms, adverse effects of medication and socioeconomic issues[63, 64].

In conclusion, the current study revealed polygenic overlap between BIP and CVD phenotypes and identified 129 shared loci with mixed effect directions. Future experimental studies of the identified shared loci may provide new insights into molecular mechanisms, which can ultimately facilitate development of drugs with less cardiometabolic adverse effects by identifying potential therapeutic targets. The current results underline the importance of environmental factors in development of CVD comorbidity in BIP and may indicate variation in genetic susceptibility to CVD across BIP subgroups. Future studies with larger GWAS samples should focus on identifying patients at higher genetic risk of comorbid CVD. This

can form the basis for risk stratification and more targeted interventions for better prevention of CVD in BIP.

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Conflict of interest

Ole A. Andreassen is a consultant for HealthLytix and has received speaker's honoraria from Lundbeck and Sunovion. Torbjørn Elvsåshagen has received speaker's fee from Lundbeck and Janssen Cilag. Ander M. Dale is a Founder of and holds equity in CorTechs Labs, Inc, and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc. and receives funding through research agreements with General Electric Healthcare and Medtronic, Inc. The terms of these arrangements have been reviewed and approved by UCSD in accordance with its conflict of interest policies. The other authors report no conflicts of interest.

Author contributions

The authors meet the criteria for authorship in line with the International Committee on Medical Journal Ethics (ICMJE). Rødevand and Andreassen conceived the study, Bahrami, Frei and Chu performed statistical analyses, and Rødevand, Andreassen, Steen, Smeland and

Hindley interpreted the results. Rødevand wrote the first draft of the paper and all authors contributed to and approved the final paper.

Data availability

The datasets analyzed during the current study are available in repositories of GWASs:

BIP: https://www.med.unc.edu/pgc/download-results/bip/

BMI:

https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files

TC, LDL and HDL: http://csg.sph.umich.edu/abecasis/public/lipids2013/

T2D: https://diagram-consortium.org/downloads.html

SBP and DBP: http://ldsc.broadinstitute.org/ldhub/

CAD: http://www.cardiogramplusc4d.org/data-downloads/

Smoking: https://www.med.unc.edu/pgc/download-results/tag/

Code availability

Codes used for carrying out the described analyses are available here:

https://github.com/precimed/pleiofdr

https://github.com/precimed/mixer

https://github.com/bulik/ldsc

All data/results generated during the current study are included in this published article [and its supplementary information files]. Supplementary information is available at the journal's website.

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Tables

Table 1. The results of MiXeR analysis for bipolar disorder and cardiovascular disease phenotypes

Trait 1	Trait 2	Shared variants (se)	Unique variants trait 1 (se)	Unique variants trait 2 (se)
BIP	BMI	6.6 (0.5)	1.5 (0.4)	4.4 (0.5)
BIP	SBP	1.8 (0.3)	6.3 (0.3)	2.6 (0.3)
BIP	DBP	1.6 (0.3)	6.5 (0.4)	2.3 (0.3)
BIP	CAD	0.9 (0.3)	7.2 (0.4)	0.5 (0.3)

Number of shared and unique trait-influencing variants (in thousands), followed by standard error, estimated by MiXeR. Abbreviations: BIP; bipolar disorder; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary heart disease; se, standard error.

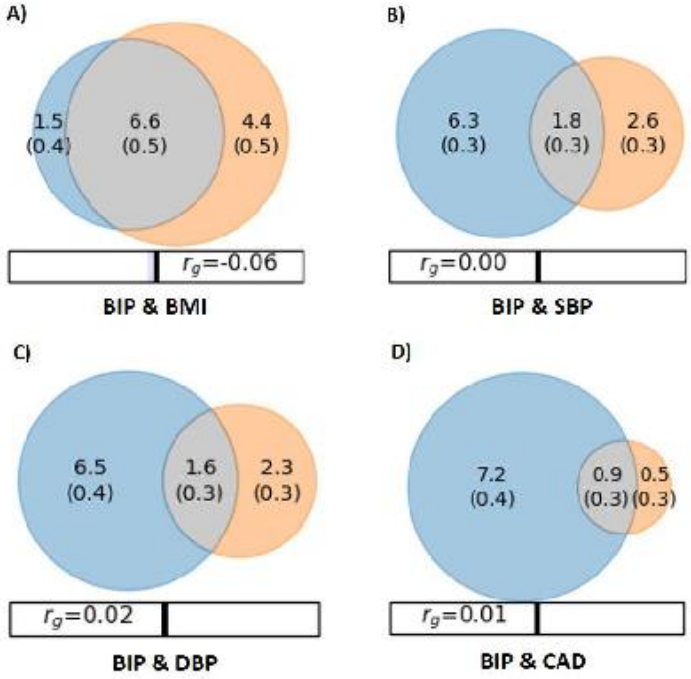
Table 2. Shared loci between BIP and CVD phenotypes

Associated phenotype	Shared loci (n) conjFDR	Concordant effect (%)	Genetic correlation
CVD phenotypes			
BMI*	69	52.2%	-0.06 (p=0.010)
SBP	53	49.1%	0.02 (p=0.396)
DBP	53	47.2%	0.04 (p=0.155)
TC	15	26.7 %	0.02 (p=0.463)
LDL	13	46.2 %	0.03 (p=0.346)
HDL	10	40.0 %	-0.02 (p=0.471)
T2D	4	25.0 %	-0.04 (p=0.422)
CAD	10	70.0 %	-0.02 (p=0.539)

Number of shared loci at conjFDR <0.05, concordant effect directions in percentage, and genetic correlation estimated by LD score regression. Abbreviations: BIP; bipolar disorder; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low- density lipoprotein cholesterol; T2D, type 2 diabetes mellitus; CAD, coronary heart disease; conjFDR, conjunctional FDR. *The results for BMI & BIP are retrieved from Bahrami et al. 2020[24].

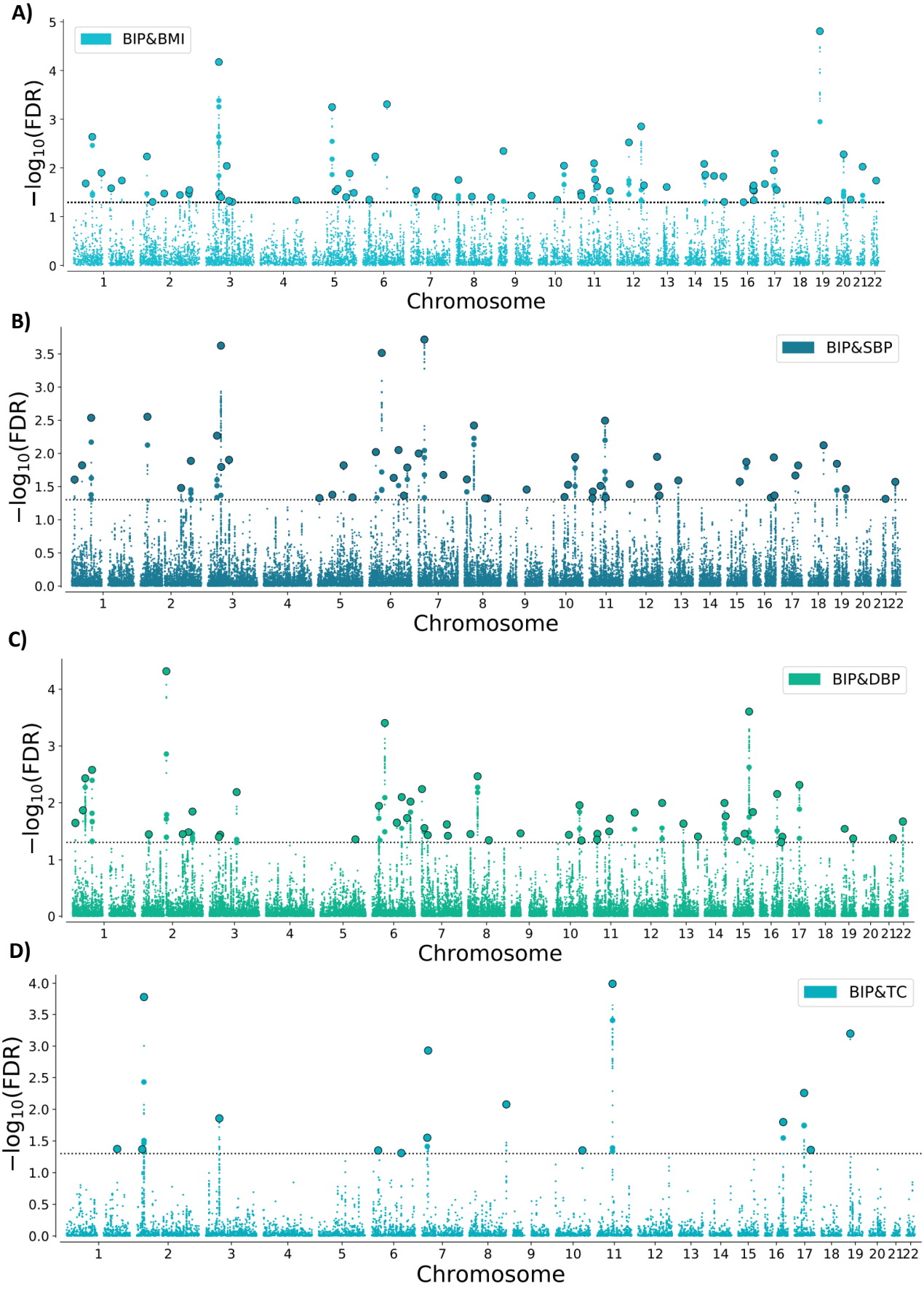
Figures

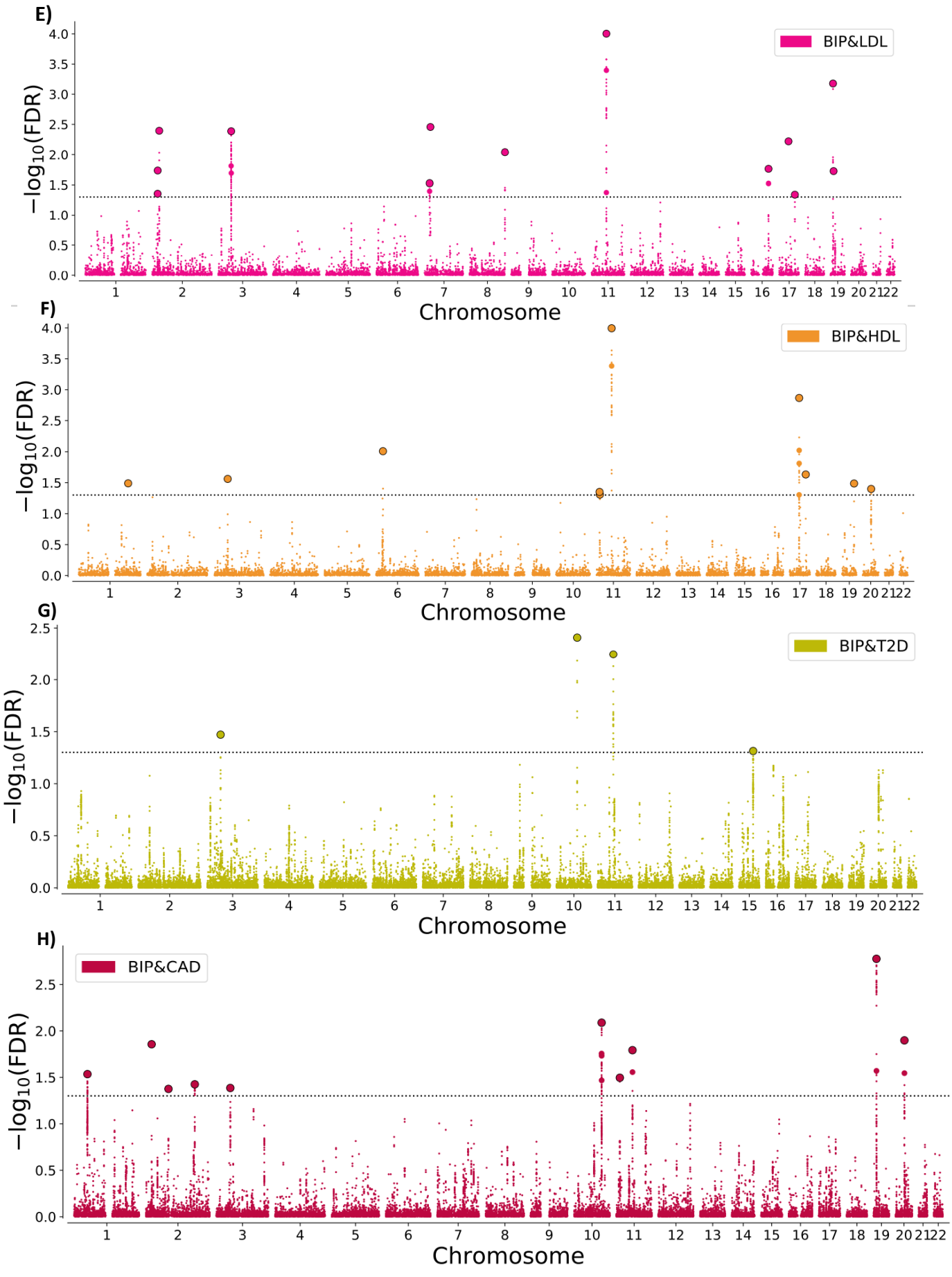
Figure 1. Venn diagrams of shared and unique polygenic variants



Venn diagrams of shared and unique trait-influencing variants, showing polygenic overlap (gray) between bipolar disorder (BIP) (blue) and body mass index (BMI) (orange), coronary artery disease (CAD) (orange), systolic blood pressure (SBP) (orange) and diastolic blood pressure (DBP (orange). The numbers in the Venn diagram indicate the estimated quantity of shared and unique trait-influencing variants (in thousands), explaining 90% of SNP heritability in each phenotype, followed by standard error. The size of the circles reflects the degree of polygenicity. The figure is based on MiXeR results.

Figure 2. Common genetic variants jointly associated with BIP and CVD phenotypes at conjFDR < 0.05




E)
BIP&LDL
F)
BIP&HDL
G)
BIP&T2D
H)
BIP&CAD
−log10(FDR)
Chromosome

Shared genetic loci between bipolar disorder and cardiovascular factors

Manhattan plot showing the –log10 transformed conjFDR values for each SNP on the y axis and chromosomal positions along the x axis. SNPs with conjunction FDR < 0.05 (i.e., −log10 FDR > 1.3) are shown with enlarged data points. A black circle around the enlarged data points indicates the most significant SNP in each LD block. The figure shows the localization of the 'conjunctional loci', and further details are provided in Supplementary Tables. Abbreviations: BIP, bipolar disorder; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; T2D, type 2 diabetes; CAD, coronary artery disease; conjFDR, conjunctional FDR. The results at conjFDR<0.01 are previously presented in Bahrami et al. 2020[24].

SUPPLEMENTARY INFORMATION for

Extensive bidirectional genetic overlap between bipolar disorder and cardiovascular disease phenotypes

SUPPLEMENTARY METHODS

Participants

We obtained GWAS results in the form of summary statistics (p-values and z-scores). Data on bipolar disorder (BIP) were retrieved from Psychiatric Genomics Consortium (PGC)[1]. The BIP dataset consisted of 20 352 cases and 31 358 controls from 32 samples[1]. Among the cases, 14,879 individuals were diagnosed with BIP type I (BIP1), 3,421 with BIP type II (BIP2), 977 with schizoaffective disorder, bipolar type (SAB), and the remaining BIP not otherwise specified (NOS)[1]. Further, we used data from GWASs on cardiovascular disease (CVD) phenotypes, including the CVD risk factors body mass index[2] (n=795 640), type 2 diabetes mellitus (T2D)[3] (n=159 208), total cholesterol (TC)[4] (n=188 578), low-density lipoprotein (LDL) cholesterol[4] (n=188 578), high-density lipoprotein (HDL) cholesterol[4] (n=188 578), systolic and diastolic blood pressure (n=745 820-757 601)[5], along with coronary artery disease (CAD, n=332 477, including 71 602 CAD cases and 260 875 controls)[6]. We repeated the previously published cond/conjFDR analysis of genetic overlap between BIP and BMI[7]. Details about the inclusion criteria, genotyping and phenotype characteristics, see the original publications[1-6]. There was no sample overlap between the BIP GWAS[1] and the CVD phenotype GWASs.

MiXeR

We applied causal mixture models[8, 9] to the GWAS summary statistics, using the MiXeR tool (https://github.com/precimed/mixer). For each SNP, i, univariate MiXeR models its additive genetic effect of allele substitution, β_i, as a point-normal mixture, $\beta_i = (1-\pi_1)N(0,0) +$

$\pi_1 N(0, \sigma_\beta^2)$, where π_1 represents the proportion of non-null SNPs (`polygenicity`) and σ_β^2 represents variance of effect sizes of non-null SNPs (`discoverability`). Then, for each SNP, j, MiXeR incorporates LD information and allele frequencies for M=9,997,231 SNPs extracted from 1000 Genomes Phase3 data by LD score regression software[9, 10], and estimate the expected probability distribution of the signed test statistic, $z_j = \delta_j + \epsilon_j = N \sum_i \sqrt{H_i} r_{ij} \beta_i + \epsilon_j$, where N is sample size, H_i indicates heterozygosity of i-th SNP, r_{ij} indicates allelic correlation between i-th and j-th SNPs, and $\epsilon_j \sim N(0, \sigma_0^2)$ is the residual variance. Further, the three parameters, $\pi_1, \sigma_\beta^2, \sigma_0^2$, are fitted by direct maximization of the likelihood function. The number of trait-influencing variants (i.e. variants with pure genetic effects not induced by LD) is estimated as $M\pi_1$, where M=9,997,231 gives the number of SNPs in the reference panel.

In the cross-trait analysis, MiXeR models additive genetic effects as a mixture of four components, representing null SNPs in both traits (π_0); SNPs with a specific effect on the first and on the second trait (π_1 and π_2, respectively); and SNPs with non-zero effect on both traits (π_{12}). In the last component, MiXeR models variance-covariance matrix as $\boldsymbol{\Sigma_{12}} = \begin{bmatrix} \sigma_1^2 & \rho_{12}\sigma_1\sigma_2 \\ \rho_{12}\sigma_1\sigma_2 & \sigma_2^2 \end{bmatrix}$ where ρ_{12} indicates correlation of effect sizes within the shared component, and σ_1^2 and σ_2^2 correspond to the discoverability parameter estimated in the univariate analysis of the two traits. After fitting parameters of the model, genetic correlation is calculated as $r_g = \frac{\rho_{12}\pi_{12}}{\sqrt{(\pi_1+\pi_{12})(\pi_2+\pi_{12})}}$. Further information is available in[8].

To evaluate model fit, i.e. the ability of the MiXeR to predict the actual GWAS data, we constructed modelled vs. actual conditional Q-Q plots (Supplementary Figures 3-6). Optimal model fit is indicated in the conditional Q-Q plots by the model-based curves closely following the actual Q-Q curves[8]. Model fit was also assessed using negative log-likelihood plots[8], which visualizes the performance of the best model versus models with minimum and

maximum polygenic overlap (Supplementary Figures 3-6). The best model represents the MiXeR model of polygenic overlap between phenotypes. The minimum model represents a scenario of least possible overlap, and the maximum model represents a scenario of largest possible overlap. In the negative log-likelihood plot (Supplementary Figures 3-6), the minimum model is represented by the point furthest to the left, the maximum model is represented by the point furthest to the right, and the best model is represented by the lower point of the curve. The lowest point on the curve (y-axis) indicates better model fit[8].

To filter situations with insufficiently powered GWAS summary statistics, we use Akaike information criterion ($AIC = 2k - 2\ln L$), where k is the number of free parameters in the model, L is the value of the likelihood function, and n is the effective number of SNPs used in optimization procedure. We calculate the difference between *AIC* for the full bivariate model, $k = 3$, and AIC for the reduced bivariate model, $k = 2$, due to π_{12} being constrained to smallest or largest possible ($\pi_{12}^{min} = r_g\sqrt{\pi_1^u\,\pi_2^u}$ and $\pi_{12}^{max} = \min(\pi_1^u, \pi_2^u)$, respectively). A positive value of AIC indicates that GWAS summary statistics have enough information to distinguish the custom polygenic overlap, as shown on the MiXeR Venn diagrams, from the constrained models with minimal (π_{12}^{min}) and maximum (π_{12}^{max}) polygenic overlap.

Conditional False Discovery Rate

The 'enrichment' seen in the conditional Q-Q plots can be directly interpreted in terms of true discovery rate (TDR = 1 – false discovery rate (FDR))[11]. More specifically, for a given p-value cutoff, the FDR is defined as

$$FDR(p) = \pi_0 F_0(p) / F(p), \qquad [1]$$

where π_0 is the proportion of null SNPs, F_0 is the null cumulative distribution function (cdf), and F is the cdf of all SNPs, both null and non-null[12]. Under the null hypothesis, F_0 is the cdf of the uniform distribution on the unit interval [0,1], so that Eq. [1] reduces to

$$FDR(p) = \pi_0 p / F(p), \qquad [2]$$

The cdf F can be estimated by the empirical cdf $q = N_p / N$, where N_p is the number of SNPs with p-values $\leq$ p, and N is the total number of SNPs. Replacing F by q in Eq. [2], we get

$$\text{Estimated } FDR(p) = \pi_0 p / q, \qquad [3]$$

which is biased upwards as an estimate of the FDR[13]. Replacing π_0 in Equation [3] with unity gives an estimated FDR that is further biased upward;

$$q^* = p / q, \qquad [4]$$

If π_0 is close to one, which is probably true for most GWASs, the increase in bias from Eq. [3] is minimal. Therefore, the quantity 1 – p/q, is biased downward and thus a conservative estimate of the TDR. Referring to the Q-Q plots, we see that q* is equivalent to the nominal p-value divided by the empirical quantile, as defined previously. We can thus read the FDR estimate directly off the Q-Q plot as

$$-\log_{10}(q^*) = \log_{10}(q) - \log_{10}(p), \qquad [5]$$

demonstrating that the estimated FDR is directly related to the horizontal shift of the curves in the Q-Q plots from the expected line x = y, i.e. a larger shift corresponds to a smaller FDR.

Conditional Q-Q plots

Q-Q plots compare a nominal probability distribution against an empirical distribution. In the presence of all null relationships, nominal p-values form a straight line on a Q-Q plot when plotted against the empirical distribution. For BIP and CVD phenotype SNPs and for each categorical subset (strata), $-\log_{10}$ nominal p-values were plotted against $-\log_{10}$ empirical p-values (conditional Q-Q plots). Leftward deflections of the observed distribution from the projected null line illustrate increased tail probabilities in the distribution of test statistics (z-scores) and consequently an over-abundance of low p-values compared to that expected by chance, also called ‘enrichment’. This is illustrated in Supplementary Figures 1-2.

Under large-scale testing paradigms, such as GWAS, we can calculate quantitative estimates of likely true associations from the distributions of summary statistics[12, 14]. Conditional Q-Q plots of nominal p-values from GWAS summary statistics visualizes this enrichment of statistical association relative to that expected under the global null hypothesis. The usual Q-Q curve has the nominal p value, denoted by "p", as the y-ordinate and the corresponding value of the empirical cdf, denoted by "q", as the x-ordinate. Under the global null hypothesis the theoretical distribution is uniform on the interval [0,1]. As is common in GWAS, we instead plot $-\log_{10}$ p against $-\log_{10}$ q to emphasize tail probabilities of the theoretical and empirical distributions. Therefore, genetic enrichment is illustrated with a leftward shift in the Q-Q curve, corresponding to a larger fraction of SNPs with nominal $-\log_{10}$ p-value greater than or equal to a given threshold. Conditional Q-Q plots are constructed by creating subsets of SNPs based on levels of an auxiliary measure for each SNP, and computing Q-Q plots separately for each level. If SNP enrichment is captured by variation in the auxiliary measure, which is expressed as successive leftward deflections in a conditional Q-Q plot as levels of the auxiliary measure increase. We constructed conditional Q-Q plots of empirical quantiles of nominal $-\log_{10}$ values for SNP association for all SNPs, and for subsets (strata) of SNPs determined by the nominal p-values of their association with the conditional phenotypes, and vice versa. In particular, we computed the empirical cumulative distribution (cdf) of nominal p-values for a given phenotype for all SNPs and for SNPs with significance levels below the indicated cut-offs for the conditional phenotypes ($-\log_{10}(p) \geq 1$, $-\log_{10}(p) \geq 2$, $-\log_{10}(p) \geq 3$ corresponding to $p < 0.1$, $p < 0.01$, $p < 0.001$ respectively). The nominal p-values ($-\log_{10}(p)$) are plotted on the y-axis, and the empirical quantiles ($-\log_{10}(q)$, where q=1-cdf(p)) are plotted on the x-axis. To assess for polygenic effects below the standard GWAS significance threshold, we focused the conditional Q-Q plots on SNPs with nominal $-\log_{10}(p) < 7.3$ (corresponding to $p > 5x10^{-8}$). We controlled for spurious enrichment by calculating all

conditional Q-Q plots after random pruning averaged over 500 iterations. At each iteration, one SNP in every LD block (defined by an r^2 >0.1) was randomly selected and the empirical cdfs were computed using the corresponding p-values.

Detection of SNPs using conditional and conjunctional FDR

The FDR can be interpreted as the probability that a SNP is null given that its p-value is as small as or smaller than its observed p-value. The conditional FDR (condFDR) is an extension of the standard FDR, which incorporates information from GWAS summary statistics of a second phenotype to adjust its significance level. The condFDR is defined as the probability that a SNP is null in the first phenotype given that the p-values in the first and second phenotypes are as small as or smaller than the observed ones. It is important to note that ranking SNPs by the standard FDR or by p-values gives the same ordering of SNPs. In contrast, ranking SNPs by condFDR will reorder SNPs when the primary and secondary phenotypes are genetically related. The conjunctional FDR (conjFDR) is defined as the posterior probability that a SNP is null for either phenotype or both simultaneously, given that its p-values for association with both phenotypes are as small as or smaller than the observed p-values[15-19]. A conservative estimate of the conjFDR is obtained by the maximum condFDR for a given SNP after repeating the condFDR procedure for both traits and inverting their roles.[20]. Given that complex correlations in regions with intricate LD can bias FDR estimation[21], we excluded SNPs in the extended major histocompatibility complex and chromosome 8p23.1 (genome build 19 locations 25119106–33854733 and 7242715–12483982, respectively) and SNPs in LD (r^2>0.1) with such SNPs before fitting the FDR models. P-values were corrected for inflation using a genomic inflation control procedure[15].

Genomic loci definition

We defined independent genomic loci using the FUMA, an online tool for functional mapping of genetic variants (http://fuma.ctglab.nl/)[22]. Summary statistics from the GWASs on BIP and CVD phenotypes were used as input for FUMA. First, *independent significant SNPs* were identified as SNPs with condFDR < 0.01 and independent from each other at LD $r^2 < 0.6$. Secondly, *lead SNPs* were identified by retaining those independent significant SNPs that were independent from each other at $r^2 < 0.1$. Next, *distinct genomic loci* were identified by merging physically overlapping lead SNPs (LD blocks < 250 kb apart) selecting a SNPO with the most significant p-value as a lead SNP if the merged locus. Borders of the genomic loci were determined by identifying all SNPs in LD ($r^2 \geqq 0.6$) with one of the independent significant SNPs in the locus. The region containing all of these *candidate SNPs* was regarded as a single independent genomic locus. All LD information was calculated from the 1000 Genomes Project reference panel[23].

Effect sizes and genetic correlation

Effect size (z-scores) of the shared SNPs were obtained from the original summary statistics (see original publications[1, 3, 4, 6, 24]). We estimated the genetic correlation using LD score regression[25]. LD score regression was estimated using the Python-based package available at https://github.com/bulik/ldsc. The procedure is described in the documentation of the package (https://github.com/bulik/ldsc/wiki/Heritability-and-Genetic-Correlation).

Identification of novel BIP loci

We identified novel BIP loci by comparing the identified loci at conjFDR <0.05 with the loci reported in the original BIP GWAS[1], the most recent BIP GWAS[26] (available through personal communication), the NHGRI-EBI catalog[27], previous cond/conjFDR analyses and other studies reporting genome-wide significant BIP loci[1, 7, 28-45].

Functional annotation

We used FUMA[22], an online annotation platform (http://fuma.ctglab.nl/) to functionally annotated all candidate SNPs in the genomic loci with a condFDR or conjFDR value<0.10 having an $r^2 \geqq 0.6$ with one of the independent significant SNPs. SNPs were annotated with Combined Annotation Dependent Depletion (CADD) scores[46], RegulomeDB[47] scores, and chromatin states[48, 49]. The CADD score is a deleterious score of variants computed by integrating 63 functional annotations[46]. The higher the score, the more deleterious. A CADD score above 12.37 is the threshold to be potentially pathogenic[46]. The RegulomeDB score is a categorical score to guide interpretation of regulatory variants[47]. It is based on information from eQTLs and chromatin marks, ranging from 1a to 7 with lower scores indicating a higher likelihood of having a regulatory function. Scores are as follows: 1a=eQTL + Transcription Factor (TF) binding + matched TF motif + matched DNase Footprint + DNase peak; 1b=eQTL + TF binding + any motif + DNase Footprint + DNase peak; 1c=eQTL + TF binding + matched TF motif + DNase peak; 1d=eQTL + TF binding + any motif + DNase peak; 1e=eQTL + TF binding + matched TF motif; 1f=eQTL + TF binding / DNase peak; 2a=TF binding + matched TF motif + matched DNase Footprint + DNase peak; 2b=TF binding + any motif + DNase Footprint + DNase peak; 2c=TF binding + matched TF motif + DNase peak; 3a=TF binding + any motif + DNase peak; 3b=TF binding + matched TF motif; 4=TF binding + DNase peak; 5=TF binding or DNase peak; 6=other; 7=Not available[47].

The chromatin state represents the accessibility of genomic regions (every 200bp) with 15 categorical states predicted by a hidden Markov model based on 5 chromatin marks for 127 epigenomes in the Roadmap Epigenomics Project[48]. A lower state indicates increased accessibility, with states 1-7 referring to open chromatin states. We annotated the minimum chromatin state across tissues to SNPs. The 15-core chromatin states as suggested by

Roadmap are as follows: 1=Active Transcription Start Site (TSS); 2=Flanking Active TSS; 3=Transcription at gene 5' and 3'; 4=Strong transcription; 5= Weak Transcription; 6=Genic enhancers; 7=Enhancers; 8=Zinc finger genes & repeats; 9=Heterochromatic; 10=Bivalent/Poised TSS; 11=Flanking Bivalent/Poised TSS/Enh; 12=Bivalent Enhancer; 13=Repressed PolyComb; 14=Weak Repressed PolyComb; 15=Quiescent/Low. Standardized SNP effect sizes were calculated for the most impactful SNPs by transforming the sample size-weighted meta-analysis *Z* score, in line with Zhu et al.[49].

Furthermore, using FUMA[22], we linked lead and candidate SNPs to genes applying either of three gene mapping strategies: 1) positional mapping to align SNPs to genes based on their physical proximity (i.e., within a 10kb window), 2) expression quantitative trait locus (eQTL) mapping to match cis-eQTL SNPs to genes whose expression is associated with allelic variation at the SNP level, and 3) chromatin interaction mapping to link SNPs to genes based on three-dimensional DNA–DNA interactions between each SNP's genomic region and nearby or distant genes. We evaluated eleven eQTL databases in FUMA which contains eQTL information from multiple human tissue types including several brain regions (http://fuma.ctglab.nl/tutorial#eQTLs). The eQTL analyses were corrected for multiple comparisons using an FDR threshold of 0.05. FUMA contains Hi-C data of over 21 tissue/cell types including human brain tissue (https://fuma.ctglab.nl/tutorial#chromatin-interactions). We used an FDR of 1×10^{-6} to define significant chromatin interactions based on the suggestion by Schmitt et al.[50]. FUMA was also used to identify previously reported GWAS associations in the NHGRI-EBI catalog[27] and to evaluate gene ontology (GO)[51] gene-set enrichment for the genes mapped to all (candidate and lead) SNPs in the identified shared loci. Finally, we performed pathway over-represented analyses of genes mapped to all (candidate and lead) SNPs in the shared loci using ConsensusPathDB[52]. ConsensusPathDB integrates interaction networks involving binary and complex protein-protein, genetic,

metabolic, signaling, gene regulatory and drug-target interactions, along with biochemical pathways[52]. ConsensusPathDB integrates 30 public interaction/pathway resources and has regular content updates, ensuring that this database stays up-to-date and comprehensive[52]. Other GWASs of overlapping loci between complex traits have also applied ConsensusPathDB for pathway analysis[7, 53]. Analyses were corrected for multiple comparisons.

SUPPLEMENTARY RESULTS

MiXeR results

MiXeR results, including number of shared and unique trait-influencing variants and corresponding standard error, are presented in Figure 1 and Table 1. Using MiXeR we discovered extensive polygenic overlap between BIP and BMI, sharing 6.6k out of 12.5k variants involved, as illustrated by the Venn diagram (Figure 1a). The shared variants represent 81.5% of the genetic variants influencing BIP (8.1k) and 60% of the variants underlying BMI (11.0k). MiXeR also revealed polygenetic overlap between BIP and SBP, sharing 1.8k out of 10.7k variants, as visualized in the Venn diagram (Figure 1b). The shared variants with SBP represent 22.2% of the genetic variants influencing BIP (8.1k), and 40.9% of variants influencing SBP (4.4k). Likewise, MiXeR identified polygenic overlap with DBP, sharing 1.6k out of 10.4K variants, as seen in the Venn diagram (Figure 1c). The shared variants with DBP represent 19.8% of the variants influencing BIP (8.1k) and 41.0% of the variants influencing DBP (3.9k). Finally, using MiXeR we discovered genetic overlap between BIP and CAD, sharing 0.9k out of 8.6k variants, as shown in the Venn diagram (Figure 1d). The overlapping variants constitute 11.1% of the genetic variants influencing BIP (8.1k) and 64.3% of the variants influencing CAD (1.4k).

The MiXeR estimates adequately model the GWAS data, as indicated by the model-

based Q-Q plots following the actual Q-Q plots (Supplementary Figures 3-6). However, the model for BIP and CAD followed the actual Q-Q plots less closely at higher p-values (Supplementary Figure 6), suggesting caution in interpreting the data. A larger CAD GWAS is necessary to obtain more reliable MiXeR estimates. The negative log-likelihood plots also illustrated adequate model fit, as indicated by the lowest point on the curve at n=the estimated number of shared variants (Supplementary Figures 3-6). Further, AIC demonstrated sufficient power of the model (Supplementary MiXeR Table). The positive AIC values indicate that the MiXeR model is adequately powered to differentiate the estimated polygenic overlap from minimum possible overlap (best vs. min. overlap) and maximum possible overlap (best vs max. overlap) (Supplementary MiXeR Table).

MiXeR was not applied for the other CVD phenotypes due to inadequate model fit, as demonstrated in the negative log-likelihood plots not showing a clear minimum on the curve (Supplementary Figures 7a-d).

Conditional FDR results

We observed consistent enrichment in BIP conditional on associations with CVD phenotypes (Supplementary Figure 1), and enrichment in CVD phenotypes given associations with BIP (Supplementary Figure 2). This indicates polygenic overlap between BIP and CVD phenotypes. To increase statistical power, we leveraged the pleiotropic enrichment using condFDR analysis and re-ranked BIP SNPs conditional on their association with CVD phenotypes, and vice versa. At condFDR<0.01, we identified 52 loci associated with BIP conditional on their association with BMI (as previously reported[7]); 45 loci conditional on SBP; 42 loci conditional on DBP, 22 conditional on TC, 21 conditional on LDL, 22 conditional on HDL, 32 loci conditional on T2D and 36 loci conditional on CAD (Supplementary Tables 1-8). Next, we identified multiple loci associated with CVD

phenotypes conditional on associations with BIP, including 679 loci associated with BMI (as previously reported[7]), 920 loci associated with SBP, 937 loci associated with DBP and 196 loci associated with TC (Supplementary Tables 9-12). Several loci were also associated with LDL (n=147), HDL (n=191), T2D (n=71) and CAD (n=130) conditional on BIP (Supplementary Tables 13-16).

Effect directions of shared lead SNPs between BIP and CVD phenotypes

We evaluated the directionality of allelic effects of the shared lead SNPs between the phenotypes by investigating their z-scores. As denoted by the sign of the effect sizes, there was a pattern of mixed effect directions of the shared SNPs between BIP and CVD risk factors (Table 2). We discovered the same effect direction in 36/69 loci (52%) in BMI and BIP as previously reported[7], 26/53 loci (49.1%) in SBP and BIP, 25/53 loci (47.2%) in DBP and BIP, 4/15 loci (26.7 %) in TC and BIP, 6/13 loci (46.2%) in LDL and BIP, 4/10 loci (40%) in HDL and BIP, 1/4 loci (25%) in T2D and BIP, and 7/10 loci (70%) in CAD and BIP (Supplementary tables 17-24).

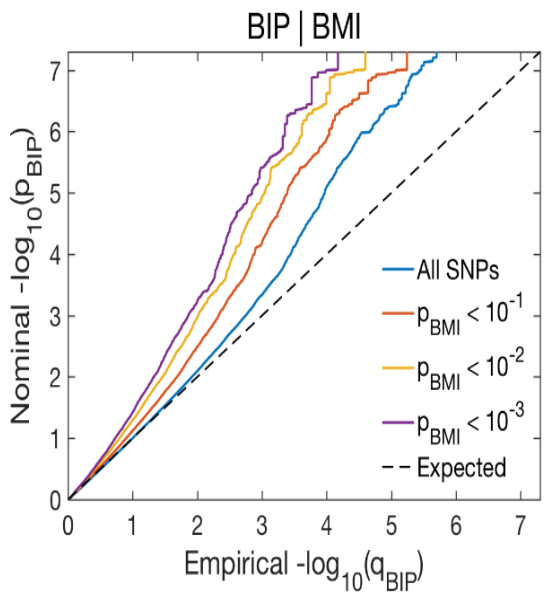
Gene-mapping results

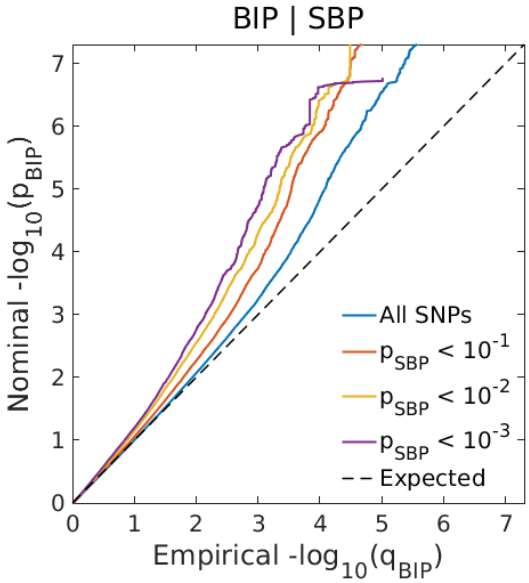
Gene-mapping of *lead* SNPs: Among SNPs shared between BIP and BMI (69), positional mapping aligned the SNPs to 48 genes, cis-eQTL mapping implicated 22 genes, and chromatin interaction mapping implicated no genes (Supplementary Table 17). Among lead SNPs shared with SBP (53), positional mapping linked the SNPs to 42 genes, cis-eQTL mapping indicated 28 genes, and chromatin interaction mapping implicated 4 genes (Supplementary Table 18). Among the SNPs shared with DBP (53), positional mapping linked the SNPs to 42 genes, cis-eQTL mapping linked the SNP to 30 genes, and chromatin interaction mapping implicated 5 genes (Supplementary Table 19). Of SNPs shared with TC

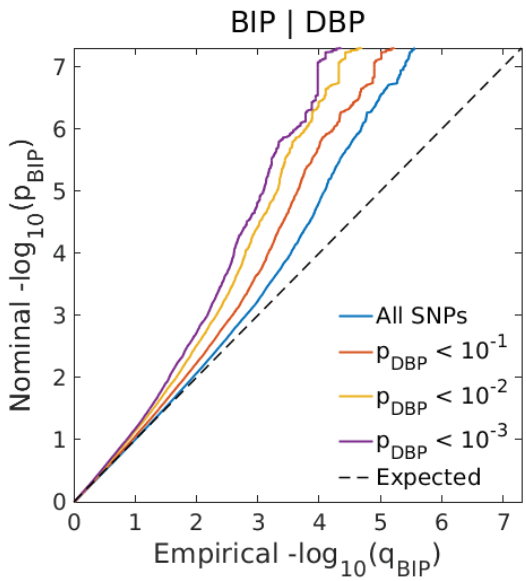
(15), positional mapping aligned the SNPs to 13 genes, cis-eQTL mapping implicated 10 genes, and chromatin interaction mapping implicated 2 genes (Supplementary Table 20). Among SNPs shared with LDL (13), positional mapping linked the SNPs to 10 genes, cis-eQTL mapping indicated 8 genes, and chromatin interaction mapping implicated no genes (Supplementary Table 21). Among SNPs shared with HDL (10), positional mapping linked the SNPs to 6 genes, cis-eQTL mapping indicated 8 genes, and chromatin interaction mapping implicated one gene (Supplementary Table 22). Among the SNPs shared with T2D (4), positional mapping linked the SNP to 2 genes, cis-eQTL mapping indicated 3 genes, and chromatin interaction mapping implicated no genes (Supplementary Table 23). Among the 10 SNPs shared with CAD, positional mapping linked the SNP to 6 gene, cis-eQTL mapping indicated 6 genes, and chromatin interaction mapping implicated one gene (Supplementary Table 24). Since chromatin interaction mapping and eQTL mapping were restricted to genes in the brain, the current results implicated that most of the shared loci were linked to genes expressed in the brain.

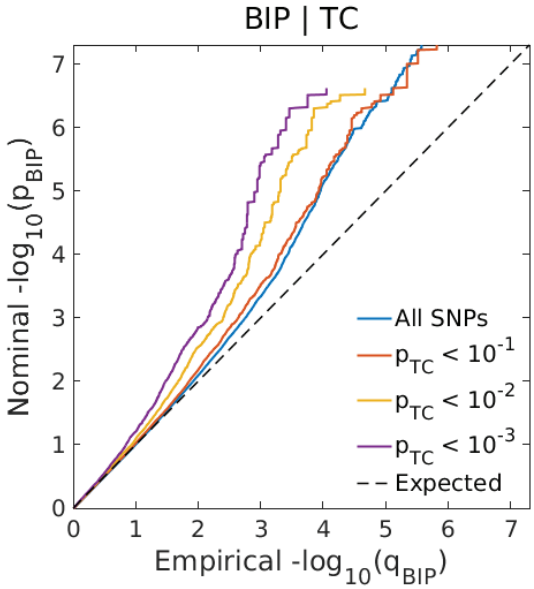
Gene-mapping of *candidate* SNPs: Using FUMA, we linked the candidate SNPs in the shared loci between BIP and BMI to 226 protein-coding genes (Supplementary Table 34). Positional mapping linked the SNPs to 159 genes, cis-eQTL mapping linked the SNP to 124 genes, and chromatin interaction mapping implicated 3 genes (Supplementary Table 34). FUMA linked the candidate SNPs in the shared loci between BIP and SBP to 226 protein-coding genes (Supplementary Table 35). Positional mapping linked the SNPs to 159 genes, cis-eQTL mapping indicated 124 genes, and chromatin interaction mapping implicated 3 genes (Supplementary Table 35). FUMA linked the candidate SNPs in the shared loci between BIP and DBP to 282 protein-coding genes (Supplementary Table 36). Positional mapping linked the SNPs to 205 genes, cis-eQTL mapping linked the SNP to 138 genes, and chromatin interaction mapping implicated 20 genes (Supplementary Table 36). FUMA linked

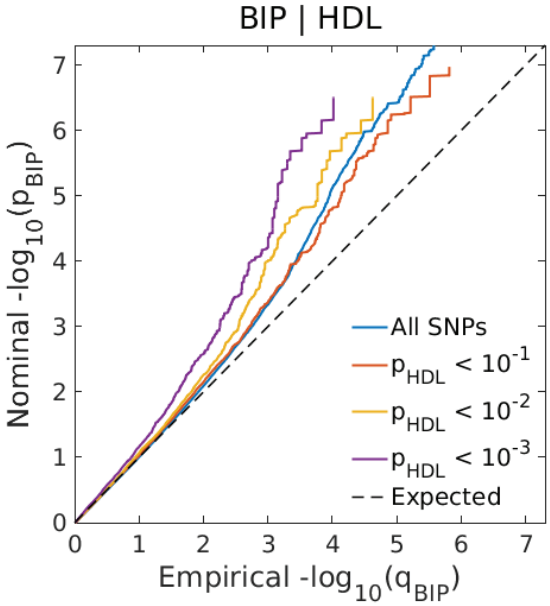
the candidate SNPs in the shared between BIP and TC to 109 protein-coding genes (Supplementary Table 37). Positional mapping linked the SNPs to 66 genes, cis-eQTL mapping linked the SNP to 69 genes, and chromatin interaction mapping implicated no genes (Supplementary Table 37). FUMA linked the candidate SNPs in the shared between BIP and LDL to 74 protein-coding genes (Supplementary Table 38). Positional mapping linked the SNPs to 40 genes, cis-eQTL mapping linked the SNP to 53 genes, and chromatin interaction mapping implicated no genes (Supplementary Table 38). FUMA linked the candidate SNPs in the shared between BIP and HDL to 68 protein-coding genes (Supplementary Table 39). Positional mapping linked the SNPs to 35 genes, cis-eQTL mapping linked the SNP to 41 genes, and chromatin interaction mapping implicated 6 genes (Supplementary Table 39). FUMA linked the candidate SNPs in the shared between BIP and T2D to 23 protein-coding genes (Supplementary Table 40). Positional mapping linked the SNPs to 14 genes, cis-eQTL mapping linked the SNP to 16 genes, and chromatin interaction mapping implicated no genes (Supplementary Table 40). FUMA linked the candidate SNPs in the shared between BIP and CAD to 63 protein-coding genes (Supplementary Table 41). Positional mapping linked the SNPs to 34 genes, cis-eQTL mapping linked the SNP to 44 genes, and chromatin interaction mapping implicated one gene (Supplementary Table 41). In line with the genes mapped to lead SNPs, the majority of the genes mapped to candidate SNPs in the shared loci between BIP and CVD phenotypes were expressed in the brain.

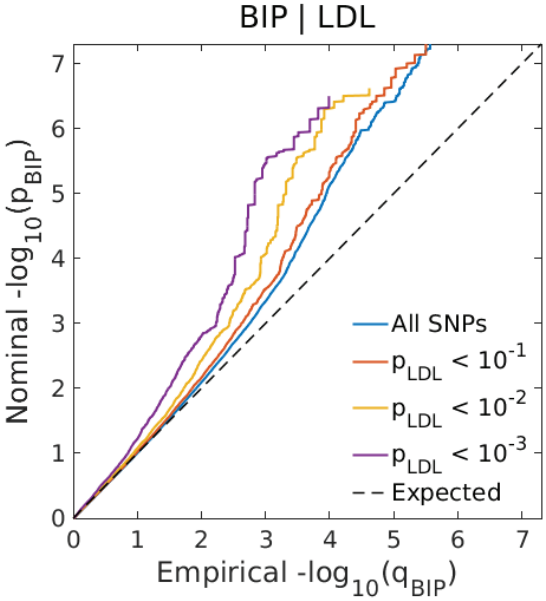

BIP | BMI
Nominal -log10(pBIP)
Empirical -log10(qBIP)
All SNPs
pBMI < 10-1
pBMI < 10-2
pBMI < 10-3
Expected

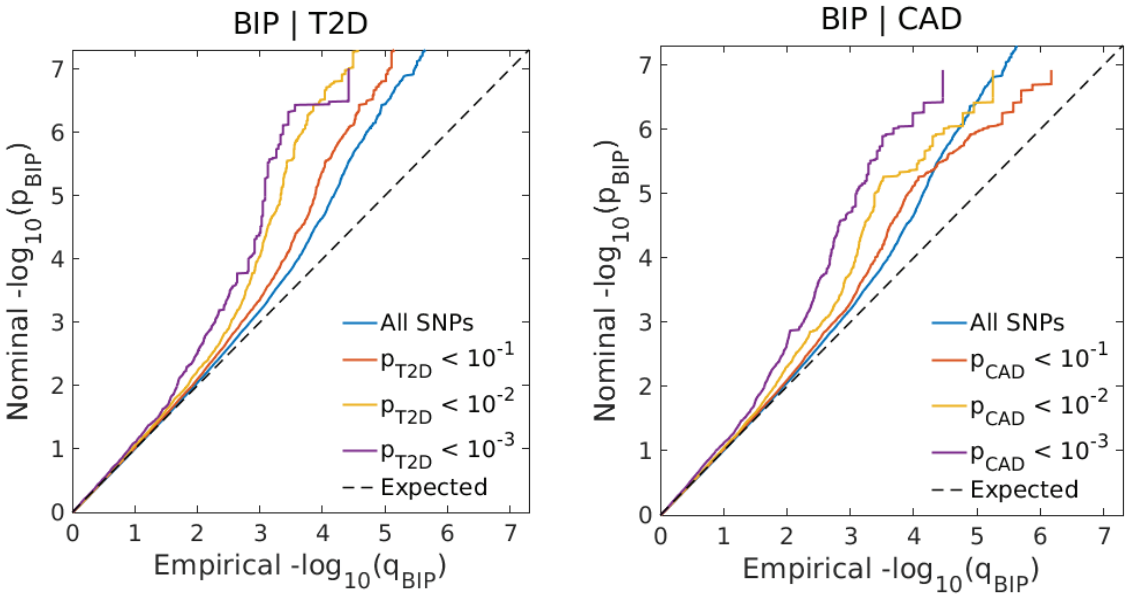

BIP | SBP
Nominal -log10(pBIP)
Empirical -log10(qBIP)
All SNPs
pSBP < 10-1
pSBP < 10-2
pSBP < 10-3
Expected


BIP | DBP
Nominal -log10(pBIP)
Empirical -log10(qBIP)
All SNPs
pDBP < 10-1
pDBP < 10-2
pDBP < 10-3
Expected

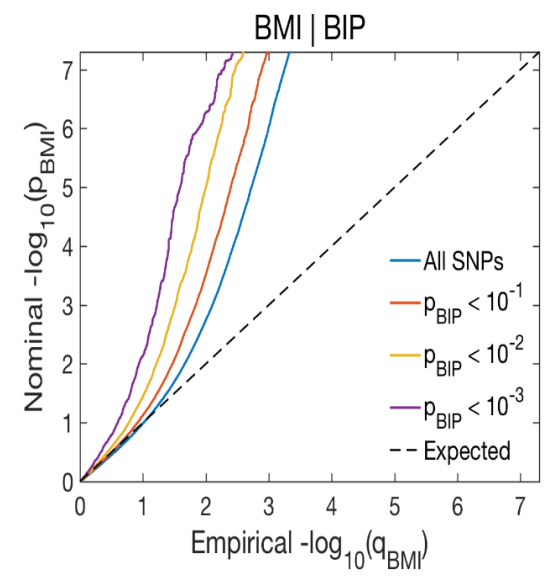

BIP | TC
Nominal -log10(pBIP)
Empirical -log10(qBIP)
All SNPs
pTC < 10-1
pTC < 10-2
pTC < 10-3
Expected

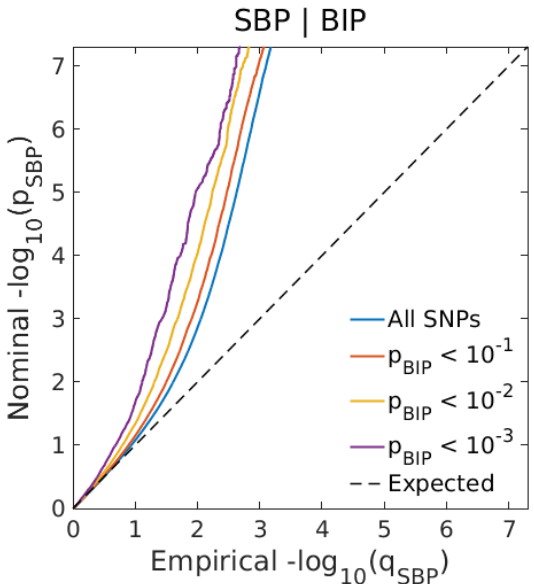

BIP | HDL
Nominal -log10(pBIP)
Empirical -log10(qBIP)
All SNPs
pHDL < 10-1
pHDL < 10-2
pHDL < 10-3
Expected

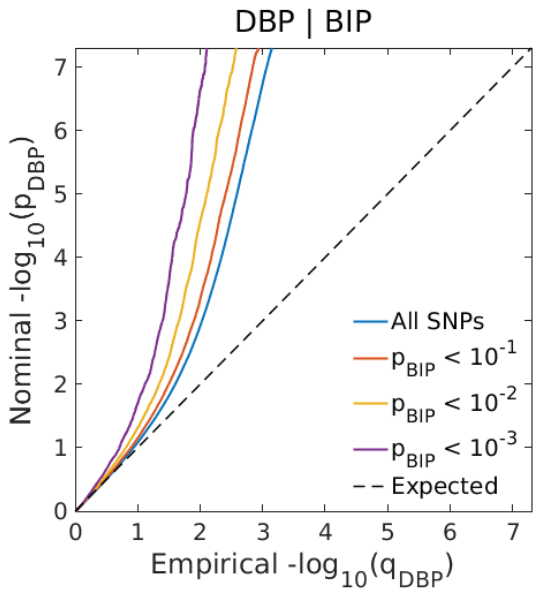

BIP | LDL
Nominal -log10(pBIP)
Empirical -log10(qBIP)
All SNPs
pLDL < 10-1
pLDL < 10-2
pLDL < 10-3
Expected

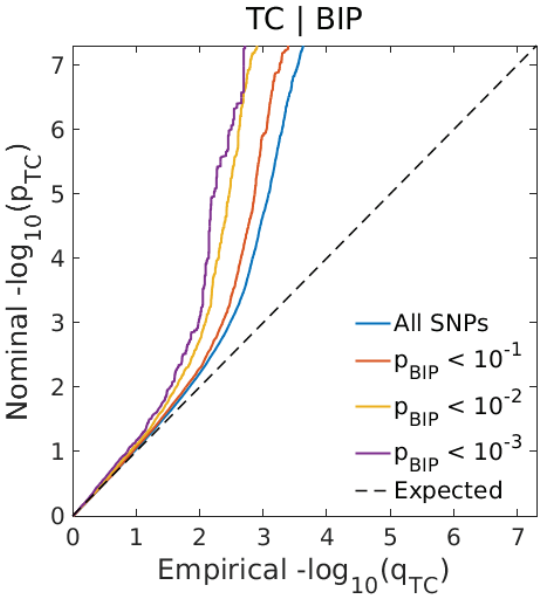


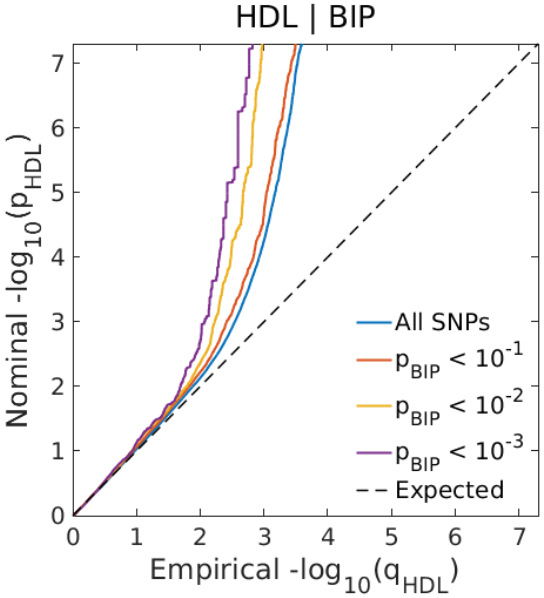
Supplementary Figure 1. Polygenic overlap between BIP and CVD phenotype. Conditional Q-Q plots of nominal versus empirical −log10p values (corrected for inflation) in BIP below the standard GWAS threshold of $p < 5 \times 10{-}8$ as a function of significance of association with CVD phenotype, at the level of $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively. The blue lines indicate all SNPs. The dashed lines indicate the null hypothesis. The Q-Q plot for BIP and BMI is previously published in Bahrami et al. 2020[7]. Abbreviations: BIP, bipolar disorder; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; T2D, type 2 diabetes; CAD, coronary artery disease. The conditional Q-Q plots build on the condFDR method.

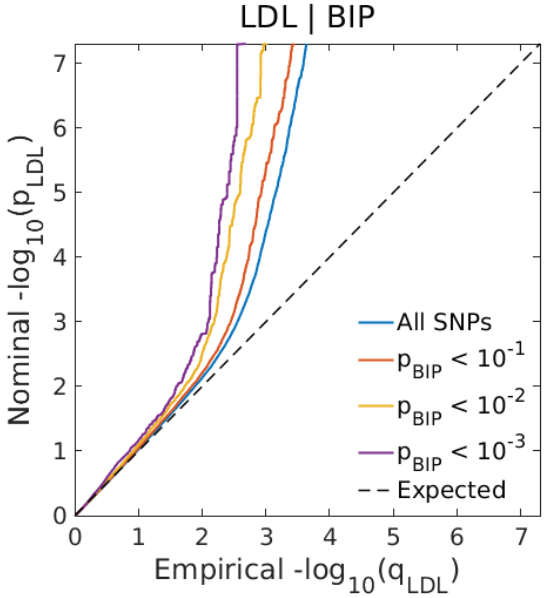

BMI | BIP
Nominal -log10(pBMI)
Empirical -log10(qBMI)
All SNPs
pBIP < 10-1
pBIP < 10-2
pBIP < 10-3
Expected

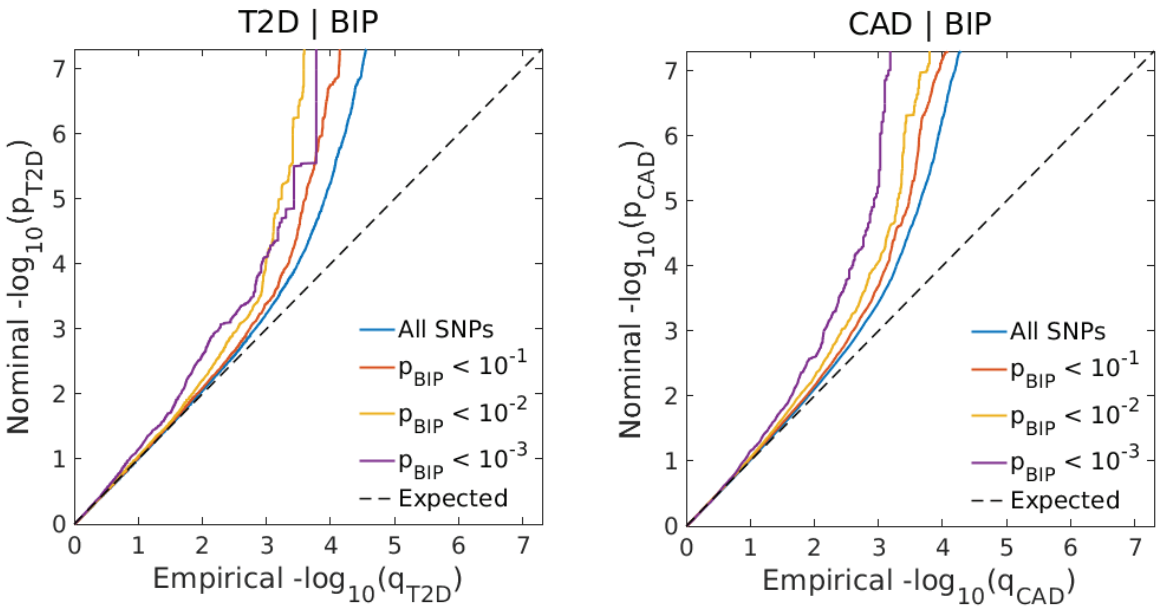

SBP | BIP
Nominal -log10(pSBP)
Empirical -log10(qSBP)
All SNPs
pBIP < 10-1
pBIP < 10-2
pBIP < 10-3
Expected


DBP | BIP
Nominal -log10(pDBP)
Empirical -log10(qDBP)
All SNPs
pBIP < 10-1
pBIP < 10-2
pBIP < 10-3
Expected

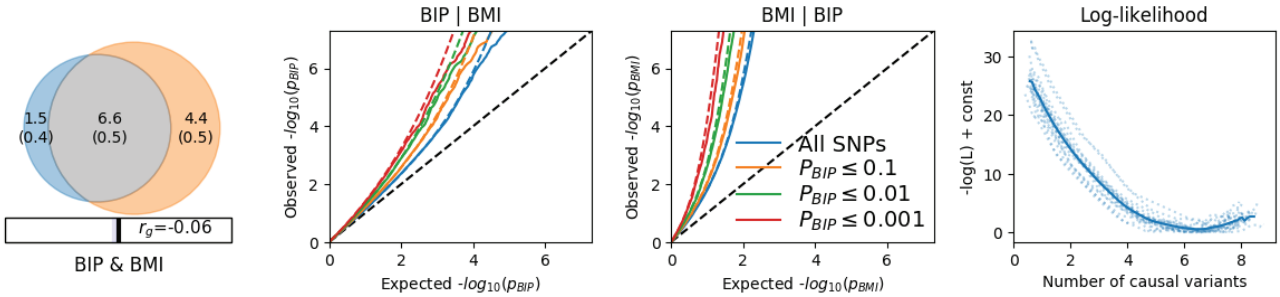

TC | BIP
Nominal -log10(pTC)
Empirical -log10(qTC)
All SNPs
pBIP < 10-1
pBIP < 10-2
pBIP < 10-3
Expected


HDL | BIP
Nominal -log10(pHDL)
Empirical -log10(qHDL)
All SNPs
pBIP < 10-1
pBIP < 10-2
pBIP < 10-3
Expected

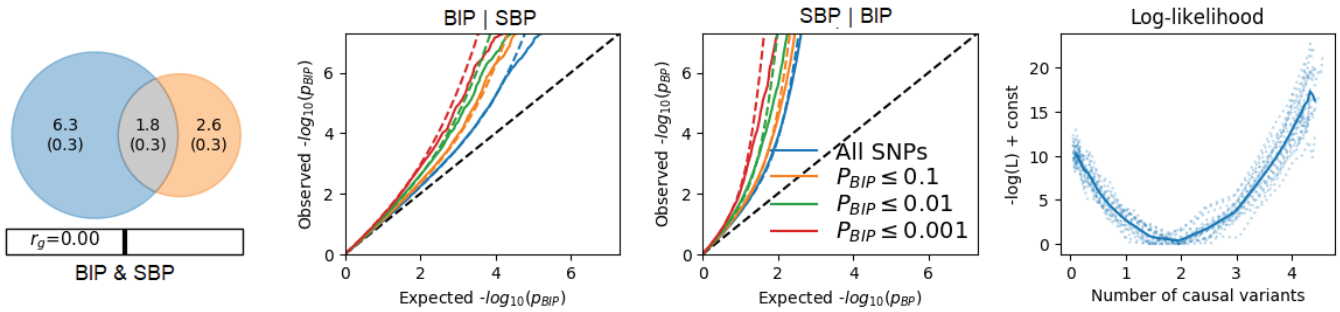

LDL | BIP
Nominal -log10(pLDL)
Empirical -log10(qLDL)
All SNPs
pBIP < 10-1
pBIP < 10-2
pBIP < 10-3
Expected



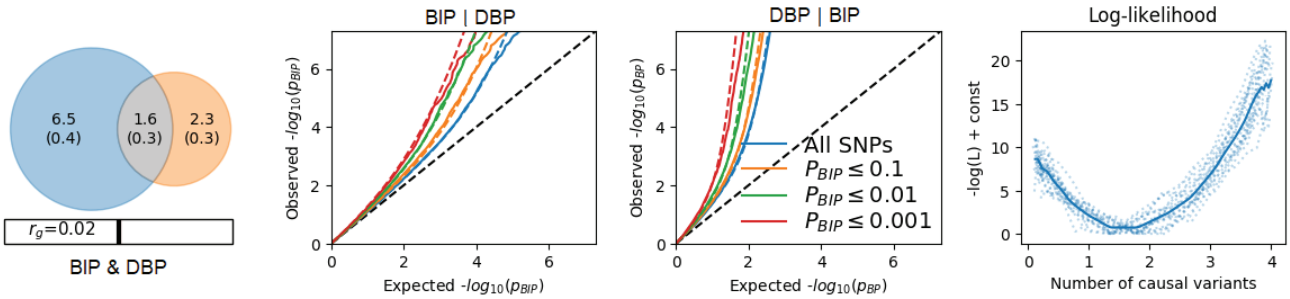
Supplementary Figure 2. Polygenic overlap between BIP and CVD phenotype. Conditional Q-Q plots of nominal versus empirical −log10p values (corrected for inflation) in CVD phenotype below the standard GWAS threshold of $p < 5 \times 10{-}8$ as a function of significance of association with BIP, at the level of $p < 0.1$, $p < 0.01$, $p < 0.001$, respectively. The blue lines indicate all SNPs. The dashed lines indicate the null hypothesis. The Q-Q plot for BIP and BMI is previously published in Bahrami et al. 2020[7]. Abbreviations: BIP, bipolar disorder; CVD, cardiovascular disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; T2D, type 2 diabetes; CAD, coronary artery disease. The conditional Q-Q plots build on the condFDR method.



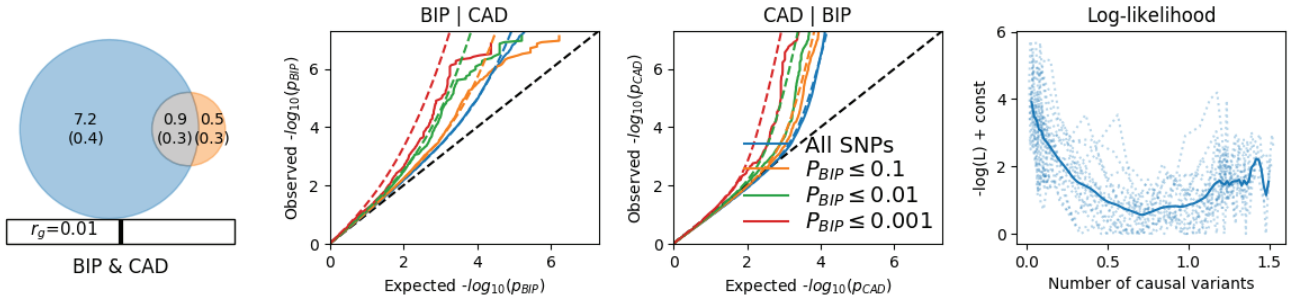
Supplementary Figure 3. Venn Diagrams, conditional Q-Q plots, and negative log-likelihood plot, respectively. *Venn diagrams* of shared and unique trait-influencing variants, showing polygenic overlap (gray) between bipolar disorder (BIP) (blue) and body mass index (BMI) (orange). The numbers in the Venn diagram indicate the estimated quantity of trait-influencing variants (in thousands), explaining 90% of SNP heritability in each phenotype, followed by standard error. *Conditional Q–Q plots* of observed versus expected $-\log_{10}$ *p*-values in the primary trait as a function of significance of association with a secondary trait at the level of $p < 0.1$, $p < 0.01$, $p < 0.001$. Blue line indicates all SNPs. Dotted lines in blue, orange, green, and red indicate model predictions for each stratum. Black dotted line is the expected Q–Q plot under null hypothesis. *Negative log-likelihood plot*: minus log-likelihood calculated for the bivariate model as a function of π parameter. The remaining parameters of the model were constrained to their fitted values. Figure generated from MiXeR.



Supplementary Figure 4. Venn Diagrams, conditional Q-Q plots, and negative log-likelihood plot, respectively. *Venn diagrams* of shared and unique trait-influencing variants, showing polygenic overlap (gray) between bipolar disorder (BIP) (blue) and systolic blood pressure (SBP) (orange). The numbers in the Venn diagram indicate the estimated quantity of trait-influencing variants (in thousands), followed by standard error. Appearance of the Q-Q plot and negative log-likelihood plot are described below Supplementary Figure 3. Figure generated from MiXeR.

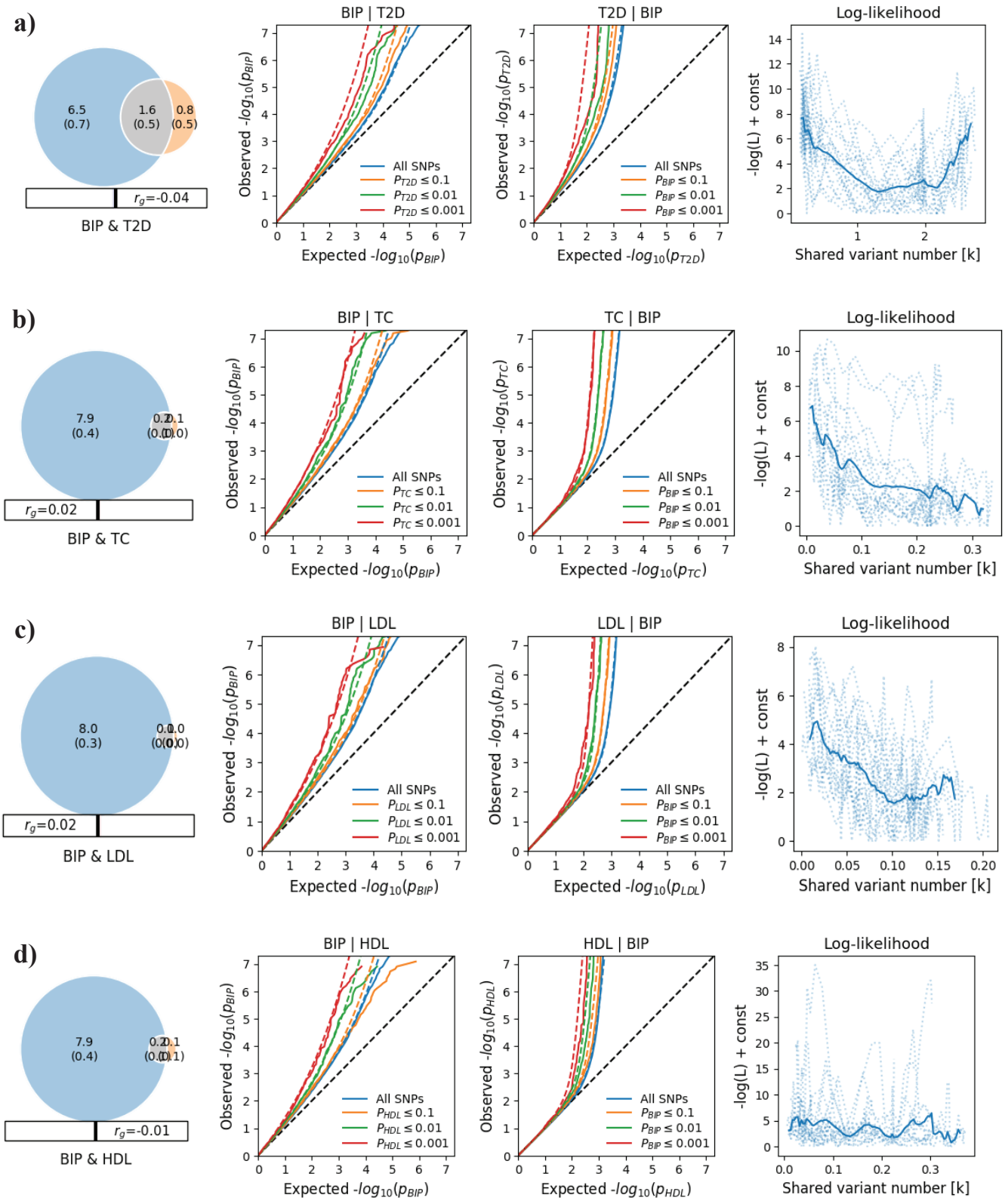


Supplementary Figure 5. Venn Diagrams, conditional Q-Q plots, and negative log-likelihood plot, respectively. *Venn diagrams* of shared and unique trait-influencing variants, showing polygenic overlap (gray) between bipolar disorder (BIP) (blue) and diastolic blood pressure (DBP) (orange). The numbers in the Venn diagram indicate the estimated quantity of trait-influencing variants (in thousands), followed by standard error. Appearance of the Q-Q plot and negative log-likelihood plot are described below Supplementary Figure 3. Figure generated from MiXeR.



Supplementary Figure 6. Venn Diagrams, conditional Q-Q plots, and negative log-likelihood plot, respectively. *Venn diagrams* of shared and unique trait-influencing variants, showing polygenic overlap (gray) between bipolar disorder (BIP) (blue) and coronary artery disease (CAD) (orange). The numbers in the Venn diagram indicate the estimated quantity of trait-influencing variants (in thousands, followed by standard error. Appearance of the Q-Q plot and negative log-likelihood plot are described below Supplementary Figure 3. Figure generated from MiXeR.

Supplementary MiXeR Table. Results of cross-trait analysis with the MiXeR model			
Trait1	**Trait2**	**AIC**	
		best vs min. overlap	best vs max. overlap
BIP	BMI	52.14	5.69
BIP	SBP	23.21	35.21
BIP	DBP	17.68	36.64
BIP	CAD	6.00	3.69
AIC - results from Akaike information criterion, showing AIC calculated for the full versus reduced bivariate MiXeR model, constrained to minimal feasible polygenic overlap ("best vs min.") or to the complete polygenic overlap ("best vs max."). A positive AIC value provides evidence for the polygenic overlap, shown in the MiXeR Venn diagram. BIP: Bipolar disorder; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease.			


a)
6.5
(0.7)
1.6
(0.5)
0.8
(0.5)
r_g=-0.04
BIP & T2D
BIP | T2D
Observed -$log_{10}(p_{BIP})$
Expected -$log_{10}(p_{BIP})$
All SNPs
$P_{T2D} \le 0.1$
$P_{T2D} \le 0.01$
$P_{T2D} \le 0.001$
T2D | BIP
Observed -$log_{10}(p_{T2D})$
Expected -$log_{10}(p_{T2D})$
All SNPs
$P_{BIP} \le 0.1$
$P_{BIP} \le 0.01$
$P_{BIP} \le 0.001$
Log-likelihood
-log(L) + const
Shared variant number [k]
b)
7.9
(0.4)
r_g=0.02
BIP & TC
BIP | TC
Observed -$log_{10}(p_{BIP})$
Expected -$log_{10}(p_{BIP})$
All SNPs
$P_{TC} \le 0.1$
$P_{TC} \le 0.01$
$P_{TC} \le 0.001$
TC | BIP
Observed -$log_{10}(p_{TC})$
Expected -$log_{10}(p_{TC})$
All SNPs
$P_{BIP} \le 0.1$
$P_{BIP} \le 0.01$
$P_{BIP} \le 0.001$
Log-likelihood
-log(L) + const
Shared variant number [k]
c)
8.0
(0.3)
r_g=0.02
BIP & LDL
BIP | LDL
Observed -$log_{10}(p_{BIP})$
Expected -$log_{10}(p_{BIP})$
All SNPs
$P_{LDL} \le 0.1$
$P_{LDL} \le 0.01$
$P_{LDL} \le 0.001$
LDL | BIP
Observed -$log_{10}(p_{LDL})$
Expected -$log_{10}(p_{LDL})$
All SNPs
$P_{BIP} \le 0.1$
$P_{BIP} \le 0.01$
$P_{BIP} \le 0.001$
Log-likelihood
-log(L) + const
Shared variant number [k]
d)
7.9
(0.4)
r_g=-0.01
BIP & HDL
BIP | HDL
Observed -$log_{10}(p_{BIP})$
Expected -$log_{10}(p_{BIP})$
All SNPs
$P_{HDL} \le 0.1$
$P_{HDL} \le 0.01$
$P_{HDL} \le 0.001$
HDL | BIP
Observed -$log_{10}(p_{HDL})$
Expected -$log_{10}(p_{HDL})$
All SNPs
$P_{BIP} \le 0.1$
$P_{BIP} \le 0.01$
$P_{BIP} \le 0.001$
Log-likelihood
-log(L) + const
Shared variant number [k]

Supplementary Figure 7a-d. Venn Diagrams, conditional Q-Q plots, and negative log-likelihood plot, respectively. *Venn diagrams* of shared and unique trait-influencing variants, showing polygenic overlap (gray) between bipolar disorder (BIP) (blue) and **a)** type 2 diabetes (T2D) (orange), **b)** total cholesterol (TC) (orange), **c)** low-density lipoprotein (LDL) (orange) and **d)** high-density lipoprotein (HDL) (orange). The numbers in the Venn diagram indicate the estimated quantity of trait-influencing variants (in thousands), explaining 90% of SNP heritability in each phenotype, followed by standard error. *Conditional Q–Q plots* of observed versus expected $-\log_{10} p$-values in the primary trait as a function of significance of association with a secondary trait at the level of $p < 0.1$, $p < 0.01$, $p < 0.001$. Blue line indicates all SNPs. Dotted lines in blue, orange, green, and red indicate model predictions for each stratum. Black dotted line is the expected Q–Q plot under null hypothesis. *Negative log-likelihood plot*: minus log-likelihood calculated for the bivariate model as a function of π parameter. The remaining parameters of the model were constrained to their fitted values. Figure generated from MiXeR.

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