Cardiovascular disease risk in people with severe mental disorders: an update and call for action

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Purpose of review
Cardiovascular disease (CVD) is a major cause of premature death in people with severe mental disorders (SMDs). This review provides an update on the level of CVD mortality and morbidity, as well as the socioeconomic, psychosocial and genetic factors associated with the comorbidity, and offer directions for improved interventions to reduce CVD in SMDs.

Recent findings
The level of CVD mortality and morbidity has sustained high in people with SMDs during the past decades, but the causal mechanism must be further elucidated. Psychosocial and socioeconomic challenges are frequent in SMDs as well as in CVD. Further, recent studies have revealed genetic variants jointly associated with SMDs, CVD risk and social factors. These findings highlight the need for more targeted interventions, prediction tools and psychosocial approaches to comorbid CVD in SMDs.

Summary
The level of CVD comorbidity remains high in SMDs, indicating that most people with SMDs have not benefitted from recent medical advances. A complex interplay between genetic and social vulnerability to CVD, which differs across subgroups of patients, seems to be involved. Further research is required to meet the urgent need for earlier, more efficient intervention approaches and preventive strategies for comorbid CVD in SMD.

Keywords
bipolar disorder, cardiovascular disease, loneliness, major depressive disorder, schizophrenia

INTRODUCTION

People with severe mental disorders (SMDs), including schizophrenia (SCZ), bipolar disorder (BIP) and major depressive disorder (MDD), have two to three times higher mortality rate than the general population, which corresponds to 10–20 years reduced life expectancy [1–4]. Suicide and accidents contribute to the premature death; however, the main cause of excess mortality is physical diseases, especially cardiovascular disease (CVD) [1–4]. People with SMDs have a higher prevalence and earlier onset of risk factors for CVD, including obesity, hypertension, type 2 diabetes (T2D), dyslipidaemia and smoking [5▪▪,6]. Comorbid CVD is associated with poorer quality of life and more severe illness course [7▪▪,8▪], which underscores the need for better prevention and treatment of CVD in SMDs. The causal mechanisms of the comorbidity are not fully understood, but appear to be associated with metabolic side effects of psychotropic medications, unhealthy lifestyle (e.g. poor diet, physical inactivity, smoking and substance use) and inadequate somatic healthcare [5▪▪,9]. Low socioeconomic status (e.g. unemployment and low educational attainment) has traditionally been linked to cardiovascular morbidity and mortality in the general population [10] as well as to increased risk of SMDs [11]. However, until recently, little has been known about the contribution of socioeconomic disadvantage to the increased rate of CVD-related mortality in SMDs. Recent findings have shed new light on this relation [12▪]. Furthermore, increasing evidence

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KEY POINTS

- The striking disparity in cardiovascular health and mortality between people with SMDs and the general population has remained over time.
- Loneliness appears to be an under-recognized CVD risk factor in individuals with SMDs.
- Educational attainment is less associated with CVD mortality in SCZ compared with the general population.
- The discovery of polygenic overlap between SMDs, loneliness and CVD risk factors indicates complex genetic relationships and possible subgroups of patients with higher genetic liability to CVD and loneliness.
- There is an urgent need to develop and implement multidisciplinary interventions tailored to the individual patient's risk and psychosocial challenges.

highlights the importance of loneliness in the comorbidity [13,14], and genetic overlap is discovered [15,16,17▪,18▪]. The aim of this review is to provide an update on the prevalence of CVD morbidity and mortality among people with SMDs compared with the general population, and present new findings into the role of socioeconomic, psychosocial and genetic factors in the CVD comorbidity. Finally, we will suggest some directions for improved preventive strategies and treatment of CVD in people with SMDs.

CARDIOVASCULAR DISEASE MORBIDITY AND MORTALITY IN SEVERE MENTAL DISORDERS

In the general population of industrialized countries, there has been a marked increase in life expectancy since the 1970 s, largely due to a decline in CVD mortality [19,20]. The incidence of myocardial infarction has decreased, and a smaller portion of the population is suffering from severe CVD [19–21]. The reduction in CVD mortality and morbidity in the general population is largely due to medical advances, stricter tobacco legislation and other health promotion efforts resulting in decreased level of risk factors, including smoking, hypertension and dyslipidaemia [19,20]. People with SMDs do not seem to have benefitted from these advances in CVD prevention and treatment to the same degree as the general population [1,22,23]. Although some Nordic registry studies suggest increased life expectancy for individuals with SMDs during the past 20–30 years, this progress seems mainly due to a decline in unnatural deaths, including suicides and accidents [2,3,22]. By contrast, excess mortality from physical diseases, including CVD and cancer, show increasing trends in SMDs compared with the general population [2,3,22]. Still, recent data from Denmark, Finland and Norway have revealed a mortality gap of approximately 10 years between SMDs and the general population [2,3,12▪,22], which is lower than the previously reported gap of 15–20 years [24]. However, other studies indicate persistent or widening mortality gap over time [25,26]. The inconsistent result may be related to different follow-up duration, selection of patient populations and quality of the healthcare services.

Moreover, the level of CVD risk factors has remained high in SMDs over time [27,28,29▪], although there is recent evidence of modest reductions in hypertension, obesity and dyslipidaemia in BIP during the past decade [27]. One study indicated a lower incidence of coronary artery disease (CAD) and stroke in people with SMDs from 1990 to 2015, but the relative risk was 2 to 2.5-fold greater compared with the general population [30]. However, another study of patients with SMDs found no decrease in the incidence of ST-elevation myocardial infarction, which is a more severe type of infarction with a greater risk of complications and mortality [31]. A registry study from Denmark confirmed the increased prevalence of CVD risk factors and diagnosis in SMDs [32].

In summary, there is still a major disparity in mortality in people with SMDs compared with the general population, largely due to high rate of CVD comorbidity. It is a public health concern that there has been limited improvement in the cardiovascular health of people with SMDs, including patients living in countries with universal health coverage designed to limit socioeconomic differences in healthcare provision [1,22,27]. Moreover, even countries with the highest ranked healthcare system in the world, such as Norway [33], have failed to effectively address these health disparities [1,27]. Thus, there is an urgent need for improved prevention and treatment of CVD in SMDs, which requires a better understanding of the underlying causes of the increased comorbidity and mortality related to CVD in SMDs.

POSSIBLE CONTRIBUTORS TO THE CARDIOVASCULAR DISEASE COMORBIDITY

The causes of the increased CVD risk in SMDs are likely to involve an interplay between several genetic and environmental factors. Here, we focus on recent research into socioeconomic and

psychosocial challenges, such as loneliness, and the genetic relationship between SMDs and CVD.

SOCIOECONOMIC FACTORS

Low socioeconomic position (SEP) is associated with an increased risk of CVD and CVD-related mortality in the general population, as well as with an increased risk of SMDs. In the general population, socioeconomic measures, such as household income, have been shown to be associated with reduced life expectancy due to CVD and all-cause mortality [34], and educational attainment has been found to be negatively correlated with CVD risk factors [35] and CVD-related mortality [10]. Despite a decline in premature mortality and CVD during the last decades [36], social inequalities in health have remained high in high-income countries [37]. Disadvantaged SEP has consistently been reported in individuals with SMDs such as SCZ [11], but it is unknown whether socioeconomic factors are causally involved in the development of SMDs (social causation hypothesis), or if reduced social function leading to lower SEP results from SMDs symptoms (social drift hypothesis) [11,38]. Moreover, we still lack a comprehensive overview on the interplay between socioeconomic factors, SMDs and CVD. This issue is important to address, as different interventions might be effective in different scenarios. For instance, if socioeconomic factors account for most of the life years lost in SMDs, interventions should focus on these factors, whereas if factors related to SMDs symptoms are more important, interventions aiming at attenuating the illness progress should be emphasized.

A few recent studies have investigated this issue. One British study found reduced life expectancy among individuals with SCZ, BIP and MDD irrespective of residence area in east London, thus suggesting that a diagnosis of SMD has a larger impact on life years lost than social inequality [39▪▪]. A recent study assessed the association of educational attainment on CVD and all-cause mortality in people with SCZ in the entire Norwegian population [12▪]. The main finding was that although individuals with SCZ have a reduced life expectancy and lower educational attainment than the general population, there was a weaker association between educational attainment and mortality in individuals with SCZ than the general population. Further, parents' educational attainment was similar between people with SCZ and the general population [12▪], supporting the hypothesis of a social drift, which is in accordance with a Danish nationwide study [11]. However, these findings might have limited generalizability to other countries, in particular those with larger socioeconomic differences and warrant further exploration.

PSYCHOSOCIAL CHALLENGES

Over the past years, there has been a growing interest in loneliness as a psychosocial risk factor for CVD [40,41]. Loneliness is a distressing feeling resulting from a discrepancy between the desired and achieved level of social relationships [42]. Loneliness is more related to the perceived quality than the quantity of social relationships [42]. Feeling lonely is frequent in people with SMDs, with an annual rate two to three times higher than the general population [43,44]. Epidemiological studies indicate that up to nearly 80% of patients with SMDs report feeling lonely [43–45], and they rank loneliness as a major life challenge [46] associated with reduced quality of life [8▪]. Notably, longitudinal data indicate that loneliness is associated with around 30% increased risk of CVD and premature death, even after adjustment for factors such as lifestyle, age, sex, socioeconomic status and depressive symptoms [40,41]. Loneliness and poor social relationships are also related to cardiometabolic disturbances, including obesity, hypertension and dyslipidaemia in the general populations [47] and SMDs [13,48]. The adverse health effects associated with loneliness are comparable to those of well known CVD risk factors, such as smoking, obesity and physical inactivity [49].

Research has implicated multiple pathways by which loneliness can influence CVD development [14,47,50▪▪]. Loneliness may have *indirect* effects through lifestyle behaviour (e.g. physical inactivity, poor diet and smoking) and psychological factors (e.g. stress, emotional regulation and depressive symptoms) as well as *direct* effects on biological mechanisms [14,47,50▪▪]. In particular, loneliness is associated with higher cortisol levels, reflecting activation of the hypothalamus-pituitary-adrenal (HPA) axis, as well as increased inflammation and autonomic dysregulation [50▪▪]. Individuals with SMDs may be particularly prone to the adverse effects of loneliness due to a vulnerability to stress, in line with the diathesis-stress model [51]. Still, the mechanisms underlying the relationship between loneliness and CVD comorbidity remain elusive. Although longitudinal data indicate that loneliness may play a causal role in the development of CVD, causal inferences from these data should be made with caution and a bidirectional relationship is possible [40,52]. A complementary explanation for the co-occurrence of loneliness, SMDs and CVD is shared genetic underpinnings [18▪] (see in the following section).

SHARED GENETIC MECHANISMS

There are observations of cardiometabolic disturbances among people with SMDs in the preantipsychotic era, which suggest that part of the increased CVD risk is inherent to the mental illness [53]. Moreover, recent studies show an increased risk of T2D and other metabolic abnormalities in drug-naive first-episode patients [54▪▪] and unaffected relatives [55▪,56▪]. However, findings are mixed [57], and these investigations cannot rule out the effect of lifestyle and other environmental factors relevant to CVD comorbidity.

Increasing efforts have been made during the past decade to delineate the genetic relationship between complex diseases and traits, including SMDs and CVD [15], with the development of novel statistical tools. The conditional/conjunctional false discovery rate (cond/conjFDR) approach can improve gene discovery associated with a phenotype (e.g. SCZ) and detect shared genetic loci with associated phenotypes (e.g. SCZ and CVD risk factors) by leveraging the combined power of two genome-wide association studies (GWAS) [15]. The cond/conjFDR method [15] has been used in several studies to improve understanding of the polygenic architecture of SMDs and their genetic relationships with CVD morbidity [15,16,17▪,18▪]. ConjFDR analyses have revealed overlapping genetic loci between SCZ and CVD risk factors, including lipids, blood pressure and BMI [15,16]. Interestingly, the majority of SCZ risk loci appear to be associated with reduced BMI, resulting in a negative genetic correlation [16]. The inverse association may seem unexpected, as patients with SCZ on average have higher BMI than the general population [27]. However, low BMI is implicated as a risk factor for SCZ [58] and higher prevalence of underweight is reported in SCZ than in the general population [59▪]. Thus, these genetic findings suggest that obesity in SCZ is mainly driven by unhealthy lifestyle factors (such as poor diet and physical inactivity) and metabolic side effects of antipsychotics rather than disease-specific genetics [16].

By comparison, major depression (including MDD and self-reported depression) appears to be associated with increased genetic liability to weight gain [60]. This was corroborated by the discovery of shared genetic loci with mostly concordant effect directions in major depression and BMI [16]. Similarly, major depression demonstrates positive genetic correlations with CAD and triglycerides [60]. Furthermore, we recently discovered considerable genetic overlap between BIP and CVD risk factors (BMI, lipids, blood pressure, T2D) and CAD [17▪]. The shared loci possessed a mixture of effect directions, with ca. half of BIP risk loci associated with increased liability to CVD, while the other half of BIP risk loci were linked to reduced CVD risk. These mixed effect directions 'cancel each other out' resulted in nonsignificant genetic correlations [17▪]. Using the novel statistical tool MiXeR [61], we also estimated the total number of shared SNPs between BIP and CVD risk factors [17▪]. MiXeR analysis indicated that most of the SNPs influencing BIP are associated with BMI, despite a genetic correlation close to zero. The results illustrate the utility of conjFDR and MiXeR to uncover considerable genetic overlap even in the absence of genetic correlation [17▪,61], providing insights into the complex genetic relationship between SMDs and CVD. Other studies have also implicated shared variants between SCZ and BIP and CVD risk factors despite no significant genetic correlations [29▪,62].

The mixed effect directions of the overlapping loci are in line with prior findings of bidirectional effects of shared loci between SCZ and CVD risk factors except from BMI [15,16]. The inconsistent effect directions of the shared genetic variants may partly underlie the observed variation in the CVD comorbidity. In particular, there is considerable individual variation in CVD risk in SMDs, with dyslipidaemia (~25–50%), overweight (~50–80%), T2D (~5–20%) and hypertension (~35–60%) being restricted to the subsets of patients with SCZ and BIP [13,27,28,29▪]. This heterogeneity in CVD comorbidity may, at least partly, be genetically driven. Thus, subgroups of patients with BIP may carry a higher genetic liability to CVD [17▪]. Patients with BIP with more depressive symptomatology may represent such a subgroup, as depressive symptoms are associated more with increased CVD risk than manic symptoms [63,64]. However, larger GWAS cohorts with more comprehensive clinical characterization are necessary to determine genetically influenced subgroups with potentially different vulnerability to CVD.

The identified common genetic variants between SMDs and CVD explain a small proportion of the predisposition [15,16,17▪]. The remaining liability is probably the result of several undetected SNPs, rare variants and gene–gene and gene–environment interactions [17▪]. This further highlights the importance of increasing GWAS sample sizes as well as investigating the interplay between genetic and environmental factors. Moreover, environmental and psychosocial factors are under some genetic influence. For instance, the heritability of loneliness is 40–50% [65]. We recently revealed several loneliness risk loci shared with SMDs and CVD risk factors with mainly concordant effect directions

[18▪]. The findings suggest that people with SMDs, especially major depression, may have an inherent propensity to loneliness, which in turn was associated with an increased genetic risk of CVD [18▪]. Together with the evidence of a genetic overlap between SMDs and CVD [15,16,17▪,60], the results suggest overlapping genetic loci between loneliness, SMDs and CVD risk factors, which may underlie part of the clinical relationship between loneliness, SMDs and CVD comorbidity [18▪]. Furthermore, functional analysis of shared loci between SMDs, loneliness and CVD risk factors implicates plausible biological processes related to neurodevelopment, HPA axis, immune system and metabolic pathways [15,16,17▪,18▪]. However, experimental studies are needed to identify the causal genetic variants and clarify how they – in interplay with environmental factors – influence the brain and various biological systems and pathways.

INTEGRATED AND TARGETED HEALTHCARE

The persistent high level of CVD risk and mortality in SMDs during the past decades highlights the importance of more tailored lifestyle interventions and personalized psychopharmacological treatment [5▪▪,27]. There is also a need for improved screening procedures and treatment of CVD among people with SMDs [9,66▪▪]. In addition, accumulating evidence calls for greater recognition and integration of loneliness in the treatment for people with SMDs [18▪]. Moreover, the discovery of shared genetic loci can form the basis for developing prediction tools, enabling more targeted prevention [15,16,17▪,18▪]. In the following section, we review recent literature on loneliness interventions in SMDs and emerging prediction models, which can facilitate precision medicine approaches.

Currently, there is a shortage of evidence-based interventions that effectively reduce loneliness in people with SMDs [67,68]. Although there is a variety of psychosocial approaches focusing on increasing social interactions and support in SMDs (e.g. group therapy, social skills training and Assertive Community Treatment) [52,67,68], these efforts appear to have limited effect on the subjective feeling of loneliness in people with SMDs [67,68]. However, promising developments have emerged; interventions targeting social cognitions offer an opportunity to alleviate loneliness in SMDs [67]. Such cognitive approaches are aimed at changing maladaptive expectations and interpretations of social exchanges that are considered important determinants of loneliness [67,68]. However, reducing loneliness in people with SMDs probably also requires addressing other barriers to social connections that the individual patient face, such as stigma, symptoms, social anxiety and social skills deficits [52,67]. To obtain sustainable effects on loneliness, cognitive approaches should be integrated with broader societal efforts that facilitate social inclusion, education and employment [52,69]. Alleviating loneliness in SMDs may help improve psychosocial functioning and quality of life and alleviate symptoms, in line with loneliness correlating with these clinical factors [8▪,69]. Importantly, the beneficial effects of reducing loneliness may also extend to the cardiovascular health of people with SMDs [52], but this remains to be investigated.

Developing prediction tools for CVD comorbidity is necessary to guide more effective prevention. Cardiovascular risk scores validated for the general population do not appear to be suitable for young people with SMDs and may underestimate their cardiometabolic risk [70]. Thus, a prediction model tailored to young people with psychosis is developed that integrates established risk factors (age, sex, BMI, smoking status and blood lipid profile) along with antipsychotics with metabolic side effects [71▪▪]. The results indicate that the risk calculator can reliably predict metabolic syndrome, an important CVD risk factor, in young people with psychosis and those at risk of developing psychosis [71▪▪]. Still, further validation in larger samples is necessary before such tools can be implemented in the clinic to improve management of CVD [71▪▪]. Another prediction model (PRIMROSE) is based on traditional CVD risk factors combined with SMD diagnosis, use of antidepressants and antipsychotics, excessive alcohol use and deprivation [72]. The analysis suggests that PRIMROSE performs better for people with SMDs compared with models that only contain the standard CVD risk factors (i.e. blood pressure, smoking, BMI and T2D) [72]. Despite these promising results, the use of this CVD risk algorithm is not associated with improved CVD outcome compared with the use of traditional risk prediction models [73]. Nevertheless, there is evidence that the PRIMROSE model is more cost-effective in terms of total health-care costs [74].

Importantly, the CVD prediction tools tested for individuals with SMDs have not incorporated individual genetic risk, such as polygenic risk score (PRS). Although family history for CVD is included in some studies [70], family history does not serve as a substitute for genetic risk assessment [75,76▪▪]. Data from the general population demonstrate that PRS provides complementary information that improves cardiovascular risk stratification [76▪▪]. Moreover, in a study of ca. 480 000 people from

the UK Biobank, a cardiovascular PRS had higher discriminative ability for CAD than family history and any of the other conventional risk factors (e.g. smoking, T2D, hypertension, BMI and dyslipidaemia) [75]. The value of including genetic risk in the prediction tools is expected to apply to SMD populations. Importantly, increased genetic risk for CVD can be detected at a younger age, long before traditional CVD risk factors have manifested. Early detection of high-risk individuals is a crucial step towards more tailored and personalized prevention of the CVD comorbidity. Increasing research suggests that prediction tools including genotyping help identify people who are more likely to benefit from certain pharmacologic and nonpharmacological interventions [77▪▪]. Thus, improving the current CVD algorithms for people with SMDs is likely to promote the management of their cardiovascular health by highlighting modifiable risk factors and guide the selection of medication and lifestyle interventions [71▪▪].

CONCLUSION

The level of CVD comorbidity and mortality has remained high in people with SMDs. Moreover, the cause of the CVD comorbidity is still a puzzle. However, new pieces to the puzzle are starting to emerge; accumulating evidence suggests that loneliness plays a role in the CVD comorbidity, while educational attainment may be less associated with CVD mortality in SCZ compared with the general population. Moreover, research into the molecular genetic underpinnings of SMDs, CVD and loneliness has made advances that offer new insights into the potential genetic mechanisms underlying the clinical relationships. The findings stress the importance of more timely and effective somatic healthcare and psychosocial interventions to reduce the CVD comorbidity and mortality in SMDs. These improvements require better collaboration across disciplines and further investigation of the genetic and environmental sources of the comorbidity. Such progress will facilitate the development of tools for risk stratification and more targeted interventions.

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Conflicts of interest

Ole A. Andreassen is a consultant for HealthLytix and has received speaker's honoraria from Lundbeck and Sunovion. The other authors report no conflicts of interest.

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This article provides an overview of the current knowledge about the potential clinical utility of PRS for CVD. The review describes possibilities and limitations of the genetic risk scores, and outline directions to improve the implementation and utility of such tools in clinical practice.