UNIVERSITAT DE BARCELONA

Understanding the impact of COVID 19 on individuals with pre-existing mental disorders: mental health burden and biological insights

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SJD Sant Joan de Déu Institut de Recerca

DOCTORAL THESIS

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Mental health burden and biological insights

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Doctoral thesis dissertation presented by

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To apply for the degree of doctor at the University of Barcelona

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Index

Abbreviations

ACE-2	Angiotensin-Converting Enzyme 2
ADHD	Attention Deficit and Hyperactivity Disorder
AIDS	Acquired Immunodeficiency Syndrome
ASD	Autism Spectrum Disorders
BMI	Body Mass Index
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
COVID-19	Coronavirus Disease 19
CRP	C-Reactive Protein
DALYs	Disability Adjusted Life Years
DSM-V	Diagnostic and Statistical Manual of Mental Disorders – 5th edition
GAD	Generalized Anxiety Disorder
HIV	Human Immunodeficiency Virus
HCV	Hepatitis C Virus
HPA	Hypothalamic-Pituitary-Adrenal
MDD	Major Depressive Disorder
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
NPI	Non-Pharmaceutical Interventions
PRS	Polygenic Risk Score
PTSD	Post Traumatic Stress Disorder
RCT	Randomized Controlled Trial

SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
VOC	Variant of Concern
WHO	World Health Organization
YLD	Years Lived with Disability

List of articles in the thesis

Thesis in compendium of publications format. The thesis consists of 5 objectives and 5 studies:

Study I. **Monistrol-Mula A**, Giné-Vázquez I, Caggiu G, Conflitti C, Gemes K, Hecker I, Mediavilla R, Monzio Compagnoni M, Pinucci I, Stoffers-Winterling J, Witteveen AB, Smith P, Walter H, Ayuso-Mateos JL, Melchior M, Mittendorfer-Rutz E, Sijbrandij M, Haro JM, Felez-Nobrega M. SARS-CoV-2 infection and COVID-19 outcomes across mental disorders and the role of sex: A register-based study from Catalonia.

Submitted to: General Hospital Psychiatry

Study II. **Monistrol-Mula A**, Diaz-Torres S, Felez-Nobrega M, Haro JM, Medland SE, Mitchell BL. Genetic analyses point to alterations in immune-related pathways underpinning the association between psychiatric disorders and COVID-19. Accepted in *Molecular Psychiatry. 2024;* doi: 10.21203/rs.3.rs-3791588/v1

JCR journal impact factor and quartile: 11.0 – Q1 (JCR) – Q1 (SJR) [2022]

Study III. **Monistrol-Mula A**, Felez-Nobrega M, Domènech-Abella J, Mortier P, Cristóbal-Narváez P, Vilagut G, Olaya B, Ferrer M, Gabarrell-Pascuet A, Alonso J, and Haro JM. The impact of COVID-related perceived stress and social support on generalized anxiety and major depressive disorders: moderating effects of pre-pandemic mental disorders. *Annals of General Psychiatry*. 2022; 21: 7. doi: 10.1186/s12991-022-00385-3. PMID: 35164779

JCR journal impact factor and quartile: 3.7 – Q2 (JCR) – Q2 (SJR) [2022]

Article IV. **Monistrol-Mula A**, Felez-Nobrega M, Moneta MV, Condominas E, Vilagut G, Martin-Iñigo L, Domènech-Abella J, Sánchez-Niubó A, Mortier P, Cristóbal-Narváez P, Olaya B, Alonso J and Haro JM. Mental health symptoms 1 year after the COVID-19

outbreak in Spain: The role of pre-existing mental disorders and their type. *Journal of Affective Disorders*. 2022; 318: 22–28. doi: 10.1016/j.jad.2022.08.127. PMID: 36058361

JCR journal impact factor and quartile: 6.6 – Q1 (JCR) – Q1 (SJR) [2022]

Article V. Monistrol-Mula A, Felez-Nobrega M, Byrne EM, Lind PA, Hickie IB, Martin NG, Medland SE, Colodro-Conde L, Mitchell BL. The effect of polygenic liability to mental disorders on COVID-19 outcomes in people with depression: the mediating role of anxiety. Accepted in *Psychological Medicine.* 2024

JCR journal impact factor and quartile: 6.9 – Q1 (JCR) – Q1 (SJR) [2022]

Resum de la tesi

Títol. Estudi de l'impacte de la COVID-19 en les persones amb trastorns mentals preexistents: repercussions en la salut mental i aportacions biològiques.

Introducció. La pandèmia de la COVID-19 ha suposat una crisi sanitària global sense precedents. En primer lloc, degut als elevats índexs d'infecció i mortalitat; després, per l'aparició de la COVID-19 persistent; i, finalment, per l'impacte en la salut mental global. Algunes poblacions, com per exemple les persones amb trastorns mentals preexistents, poden ser especialment vulnerables a la COVID-19, tant als efectes directes de la malaltia, com a l'impacte psicològic lligat al context psicosocial de la pandèmia. Malgrat l'augment en la recerca científica, encara hi ha mancances de coneixement pel que fa a la interacció entre la COVID-19 i els trastorns mentals. Per exemple, no hi ha evidència clara sobre si els diferents trastorns mentals presenten riscos similars d'infecció per el virus de la COVID-19, severitat de la malaltia, i mortalitat, ni quins mecanismes biològics hi ha al darrere. Alhora, molts estudis han analitzat canvis en els símptomes de salut mental durant la pandèmia en persones amb trastorns preexistents, però la majoria es centren en el brot epidèmic inicial, mancant informació sobre fases més tardanes, o sobre si aquesta afectació en la salut mental és diferent depenent del tipus de trastorn mental previ. També és rellevant conèixer el rol de factors com l'estrès relacionat amb la COVID-19, el suport social o la resiliència per desenvolupar intervencions que mitiguin l'impacte de potencials futures pandèmies en la salut mental de persones amb trastorns mentals.

Hipòtesi. La hipòtesi principal de la tesi és que l'impacte de la COVID-19 varia segons el tipus específic de trastorn mental preexistent, donant lloc a diferents susceptibilitats a la malaltia i diferents patrons de símptomes de malestar

emocional, els quals podrien estar determinats per diferents factors genètics i psicològics.

Objectius. La present tesi té com a objectiu principal investigar la vulnerabilitat de les persones amb trastorns mentals preexistents a la pandèmia de la COVID-19, tenint en compte tant els efectes directes de la malaltia com l'impacte en la salut mental. A més, busca explorar quins factors psicològics i genètics contribueixen a aquestes associacions.

Mètodes. Aquesta tesi consta de cinc articles, cadascun dels quals correspon a un objectiu de la tesi. Tots els estudis inclosos són observacionals i estan basats en la població adulta (+18 anys), però presenten metodologies diferents. L'estudi I utilitza dades clíniques d'infecció, severitat, i mortalitat de la COVID-19 de més de 785,000 persones provinents de registres sanitaris de Catalunya (Espanya). En l'estudi II es realitzen un seguit d'anàlisis d'estadística genètica utilitzant dades provinents dels majors estudis d'associació genètica disponibles per la COVID-19 i diferents tipus de trastorns mentals. L'estudi III utilitza dades de salut mental d'una mostra representativa de la població espanyola (n = 3,500) provinent de l'estudi MINDCOVID. L'estudi IV utilitza el mateix conjunt de dades però incloent dades de seguiment de 2,000 persones. Finalment, l'estudi V utilitza dades genètiques i de salut mental d'una cohort de 4,405 persones australianes amb depressió provinents de l'estudi AGDS (*Australian Genetics of Depression Study*). Aquest compta amb dades basals pre-pandèmia i dades obtingudes de dos seguiments realitzats durant la pandèmia.

Resultats principals

1. S'observen variacions en el risc d'infecció i hospitalització per COVID-19 en funció del tipus de trastorn mental. Tot i això, tots els trastorns mentals pre-existents, excepte aquells relacionats amb l'estrès, mostren un major risc de

mortalitat per COVID-19 en comparació amb individus sense aquests trastorns.

2. S'identifiquen diferents gens compartits alterats entre diversos trastorns mentals i la COVID-19, tots localitzats al cromosoma 17, i que s'han relacionat amb la funció immune. Es troba una possible causalitat entre tenir un trastorn mental, concretament depressió, trastorn d'estrès post-traumàtic i dèficit d'atenció amb hiperactivitat, i un major risc d'infecció i hospitalització per COVID-19.
3. Un major estrès relacionat amb la COVID i un menor suport social prediuen un major risc de trastorn depressiu major i trastorn d'ansietat generalitzada durant la primera etapa de la pandèmia, amb conseqüències més significatives per a aquells amb trastorns mentals preexistents.
4. S'observa un augment general dels símptomes depressius i d'ansietat a l'etapa intermèdia de la pandèmia en persones amb i sense trastorns mentals preexistents, tot i que aquest augment no sempre és estadísticament significatiu. En el cas de les persones amb trastorn depressiu i d'ansietat comòrbid, els símptomes de depressió es mantenen estables i elevats. El tipus de trastorn mental no modifica l'associació entre l'estrès relacionat amb la COVID-19, el suport social, la resiliència i els símptomes de salut mental.
5. La predisposició genètica a la depressió, el trastorn bipolar, l'esquizofrènia, i l'ansietat no prediu un major risc d'infecció i de COVID persistent en persones amb depressió. Contràriament, una major predisposició genètica a la depressió prediu una major fatiga per COVID-19, però aquesta relació està totalment explicada per els símptomes d'ansietat.

Conclusions. Les persones amb trastorns mentals són més vulnerables als efectes de la COVID-19, possiblement a causa d'alteracions en la funció immune.

Intervencions centrades en augmentar el suport social i la resiliència, així com en reduir els símptomes d'ansietat i d'estrès relacionats amb la pandèmia, podrien ser efectives per mitigar l'impacte de situacions d'emergència, com una pandèmia, en la salut mental d'individus amb trastorns mentals. Aquestes estratègies serien beneficioses independentment del tipus de trastorn mental i de la predisposició genètica a aquests trastorns.

Outline of the thesis

The present thesis is structured into six chapters. **Chapter 1** provides an introduction, summarizing the background and context of the study. It briefly reviews the existing evidence on mental disorders and COVID-19, the interplay between mental disorders and infections, and the impact of the COVID-19 pandemic on mental health. This chapter concludes with a summary of the gaps in the literature and the justification for the thesis. **Chapter 2** outlines the specific hypotheses and objectives of the thesis. **Chapter 3** comprises the five studies that form the core of the thesis. Each study addresses one of the main objectives. **Chapter 4** offers a general discussion, presenting an overview and interpretation of the main findings from each study. This is followed by a discussion of the implications and potential interventions derived from the findings of this thesis. The chapter also addresses the strengths and limitations of the studies, and concludes with future perspectives, outlining how this research should be continued. **Chapter 5** presents the conclusions of the thesis. Finally, **Chapter 6** includes all the references cited throughout the thesis.

1 Introduction

When I'm sad I open up a book and just ignore the world

- Lisa Simpson

1.1. MENTAL DISORDERS

1.1.1. Definition and epidemiology

Mental disorders, or psychiatric disorders, are characterized by significant disturbances in an individual's cognition, emotional regulation, or behaviour (1). There are many different types of mental disorders that vary in degree of severity (1). The present thesis is focused on the following mental disorders: depressive disorders, bipolar disorder, schizophrenia, anxiety, post-traumatic stress disorder (PTSD), substance use disorder, autism spectrum disorder (ASD), and attention deficit and hyperactivity disorder (ADHD). These conditions have been assessed either through self-reported screening scales or via clinical diagnosis (Table 1).

Mental disorders are highly prevalent conditions, affecting 1 in 8 people worldwide. Indeed, it has been estimated that in 2019, more than 970 million individuals were living with a mental disorder (1,2). Among these, depressive and anxiety disorders are the most common. In 2019, 280 and 301 million people worldwide were affected by depressive and anxiety disorders, respectively, meaning a global prevalence of 3.4% and 3.8% (2,3). Depressive disorders manifest through persistent feelings of sadness, irritability, emptiness, or anhedonia, while anxiety disorders are marked by worry, panic attacks, social and performance fears, and avoidance behaviours (4). Conversely, schizophrenia is the least common mental disorder, affecting nearly 24 million people worldwide in 2019, with a global prevalence of 0.3% (2). This severe mental disorder is characterized by significant impairments in perception and changes in behaviour (4). Prevalence estimates for the remaining mental disorders of interest are shown in Table 1.

Table 1

Epidemiologic data of the mental disorders of interest

Mental disorder	Global prevalence (2019)	Sex-based prevalence	Median age of onset	Years of potential life lost	References
SCZ	0.3 %	♂ 0.32% ♀ 0.29%	25 years	15.2	(2–6)
BD	0.5%	♂ 0.48% ♀ 0.54%	33 years	12.5	(2,3,5,6)
DEP	3.4%	♂ 2.83% ♀ 4.43%	30 years	12.8	(3,5,6)
ANX	3.8%	♂ 2.95% ♀ 4.87%	17 years	8.8	(3,5,6)
PTSD	3.9% [1]	♂ 5-6% [1] ♀ 10-12% [1]	30 years	NA	(5)
SUD	3%[1]	♂ 3.8% [1] ♀ 1.9%[1]	25 years	20.4	(3,5–7)
ASD	0.4%	♂ 0.56% ♀ 0.17%	9 years	12.7 [2]	(2,5,6)
ADHD	1.1%	♂ 1.60% ♀ 0.60%	12 years	12.7 [2]	(2,5,6,8)

Note. Table created using information from the references cite within the table. SCZ: Schizophrenia, BD: Bipolar disorder, DEP: Depressive disorders, ANX: Anxiety disorders, PTSD: Post Traumatic Stress Disorder, SUB: Substance Use Disorder (excluding tobacco and alcohol use disorders), ASD: Autism Spectrum Disorder, ADHD: Attention Deficit and Hyperactivity Disorder, NA: Not available, ♂ male sex, ♀ female sex. [1] Lifetime prevalence; [2] Includes all neurodevelopmental disorder

Notably, the prevalence of some mental disorders differs considerably between sexes. Depression, anxiety, and PTSD are more prevalent in females (Table 1). PTSD develops after an exposure to an extremely threatening or appalling event. It is defined by the presence of intrusive memories and nightmares of the traumatic event, avoidance of thoughts, and a persistent sense of heightened danger (4). Alternatively, neurodevelopmental disorders such as ADHD and ASD are particularly prevalent in males. ADHD is characterized by a persistent pattern

of inattention, hyperactivity, and/or impulsivity, while ASD encompasses a range of conditions characterized by ongoing difficulties with social communication and interaction, along with repetitive and inflexible behavioural patterns (4).

It is important to highlight that comorbidity among mental disorders is exceptionally high, with most individuals meeting criteria for multiple mental disorders (9,10). A population-based cohort study including more than 7 million individuals during a follow-up period of 22 years reported that, by the end of follow-up period, 40% of individuals with a mental disorder had been subsequently diagnosed with two or more mental disorders (11). Indeed, having a diagnosis of one mental disorder has been reported to increase the risk for a subsequent mental health diagnosis from 2 to 48 times (10). Depressive and anxiety disorders are the most common form of comorbidity, with nearly 45% of individuals with depressive disorders having a life-time history of anxiety disorders, and 43% of patients with anxiety disorders having a life-time history of depressive disorders, which usually coexist (12).

Mental disorders are the seventh largest cause of disease burden worldwide, with no evidence of reduction since 1990 (2). The huge burden of mental disorders can be explained by the convergence of several factors. First, the age of onset of most mental disorders typically occurs between the mid-teens and late twenties (Table 1), coinciding with crucial stages of human development. This can have a long-term negative impact on social relationships, educational attainment, and employment opportunities (5). Second, mental disorders are leading causes of disability worldwide (2,13), affecting the individual's capacity to function in different life areas, which has a remarkable impact on their quality of life (14,15). In 2019, mental disorders accounted for a total of 125.3 million years lived with disability (YLDs), which represent 14.6% of the global YLDs, making it the second leading cause of YLDs worldwide (2). Third, the efficacy of

current pharmacological treatments for mental disorders is limited, with response rates often lower than 50% (16). Fourth, mental disorders are associated to an excess mortality and a reduced life expectancy (13), particularly in the case of substance use disorders, characterised by the inability of the individual to control their use of substances such as alcohol and drugs, despite harmful consequences (Table 1) (4). This excess mortality is not caused by the condition *per se*; instead, people with mental disorders die of chronic diseases, infections, and suicide (13). Individuals with mental disorders have a higher risk of a wide range of chronic physical disease, particularly cardiometabolic conditions (17). Moreover, individuals with mental disorders have nearly eight times higher odds of suicide compared to the general population (18). This is particularly important for depression and bipolar disorder, given that half the suicides per year worldwide occur within a depressive episode (19). Bipolar disorder, is a severe mental disorder characterized by extreme mood swings. People with bipolar disorder experience alternating depressive and manic or hypomanic episodes that cause serious impairment in functioning (1,4).

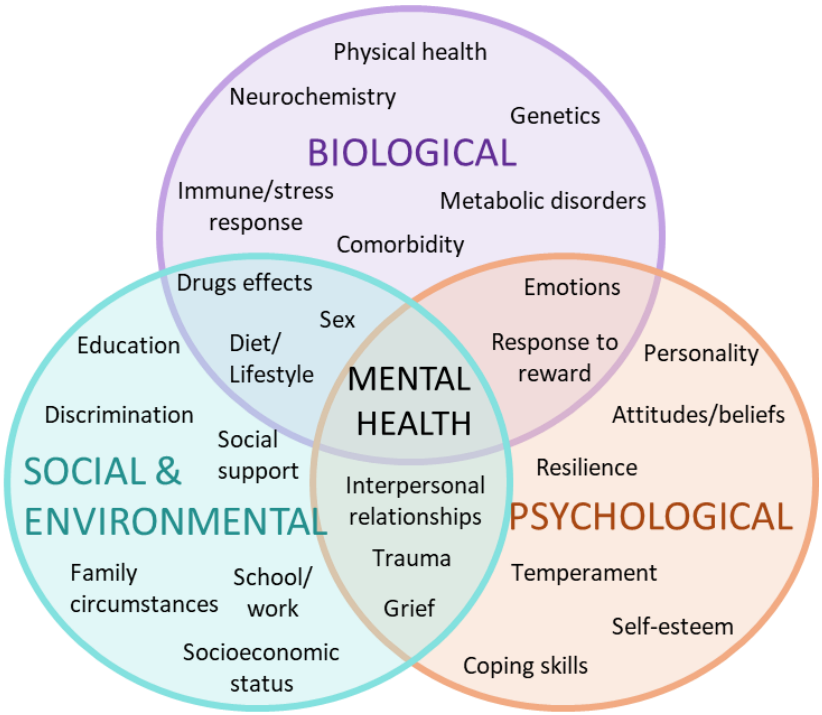
The burden of a disease is usually measured in disability adjusted life years (DALYs), which considers both disability and mortality, and represent the loss of the equivalent of one year of full health. In 2019, mental disorders contributed to 125 million DALYs, accounting for 4.9% of all global burden of disease (2). The economic value associated with this burden was estimated to be 4.7 trillion US dollars (20). Among all mental disorders, depressive disorders are the foremost contributors to the burden of mental disorders, followed by anxiety disorders and schizophrenia (2).

1.1.2. Etiology of mental disorders

To date, the exact mechanisms underlying most mental disorders remain poorly understood (21). Mental disorders are multifactorial in nature, meaning that these conditions do not arise from singular causes but instead emerge from the interplay of several biologic and psychosocial factors (21). Thousands of genetic variants and dozens of psychosocial factors have been reported to contribute to the development of mental disorders, but none of these on its own is sufficient to cause a mental disorder (21). In addition, there is the added complexity that multiple combinations of genetic and psychosocial factors can lead to the development of the same mental disorder, whereas a single gene variant or psychosocial factor can contribute to several mental disorders (22). This complexity has been addressed within the biopsychosocial model, which posits that mental disorders arise from multiple concurrent causes. This model systematically explains the intricate interplay of three major dimensions—biological, psychological, and social/environmental—in the development of mental disorders (Figure 1). Extensive research and clinical evidence support this assumption, making this model widely accepted as a comprehensive framework for understanding the development of mental disorders (23).

Figure 1

Biopsychosocial model for mental disorders



Note. Adapted from: The Open University (24).

Biological/genetic factors

Biological determinants of mental disorders refer to genetic, neurobiological, and physiological factors that influence the development and expression of mental disorders. In the context of the present thesis, this section will specifically address genetic factors.

The observation that mental disorders ran in families has been noted throughout history, which has been confirmed by large family, twin, and population-based studies (25). These studies reported that all major mental disorders had a significant heritability, meaning the proportion of variation in a trait attributable to genetics. The heritability of neurodevelopmental, bipolar, and psychotic

disorders (68-80%) (25) tends to be higher compared to PTSD, depressive, substance use, and anxiety disorders (37-60%) (25,26). These high heritabilities were initially thought to suggest the presence of genetic variants with large effects in candidate genes responsible for mental disorders. However, this approach did not consistently identified any specific variant with such significant effects (27). A major turning point in psychiatric genetics came with genome-wide association studies (GWAS), which showed that mental disorders were highly polygenic, with thousands of variants of tiny effect collectively contributing to the condition (25). GWAS is a research approach that systematically examines millions of common genetic variants (frequency >1%), known as Single Nucleotide Polymorphisms (SNPs), to assess their association with a specific phenotype or disease. This approach is hypothesis-free and involves comparing the frequency of variants between affected individuals (cases) and unaffected individuals (controls) (28). The fact that genetic variants identified by GWAS are predominantly common variants implies that every individual harbors some genetic risk for each mental disorder. This risk ranges from low to high, with a threshold beyond which the individual is likely to be affected by the disorder.

Current GWAS for mental disorders have identified thousands of SNPs associated to these conditions (29). Each individual SNP explains only a small fraction of the heritable variance for mental disorders (with odd ratios usually below 1.2). However, these effects can be consolidated into polygenic risk scores (PRSs), which capture the additive effects of several SNPs, thereby accounting for larger fractions of the heritability (25). Nevertheless, it is important to highlight that the heritability estimates obtained from common variants only explain between 5-26% of the risk of these major mental disorders, which is far lower than the estimates reported from twin studies (30–35). This *missing*

heritability could be explained by rare variants –which are not included in GWAS and usually have larger effects than common variants–, gene-environment or gene-gene interactions, or by an inflated heritability estimated from twin studies (29). Table 2 shows the most robust GWAS available for each mental disorder included in the present thesis, the proportion of heritability explained by the identified SNPs, the heritability estimated by twin studies, and the number of genome-wide significant loci identified.

Table 2

Twin heritability and characteristics of genome-wide association studies (GWAS) included in the present thesis.

Mental disorder	Cases	Controls	Twin heritability	SNP-based heritability	GWAS loci	GWAS reference
SCZ	76,755	243,649	60-80%	24%	287	(33)
BD	41,917	371,549	60-85%	18.6%	64	(32)
DEP	371,184	978,703	37-45%	16.7%	243	(36)
ANX	25,453	58,113	20-60%	26%	5	(34)
ADHD	38,691	186,843	74%	14%	27	(30)
ASD	18,381	27,969	50-90%	11.8%	5	(31)
PTSD	137,136	1,085,746	49%	5.3%	95	(37)

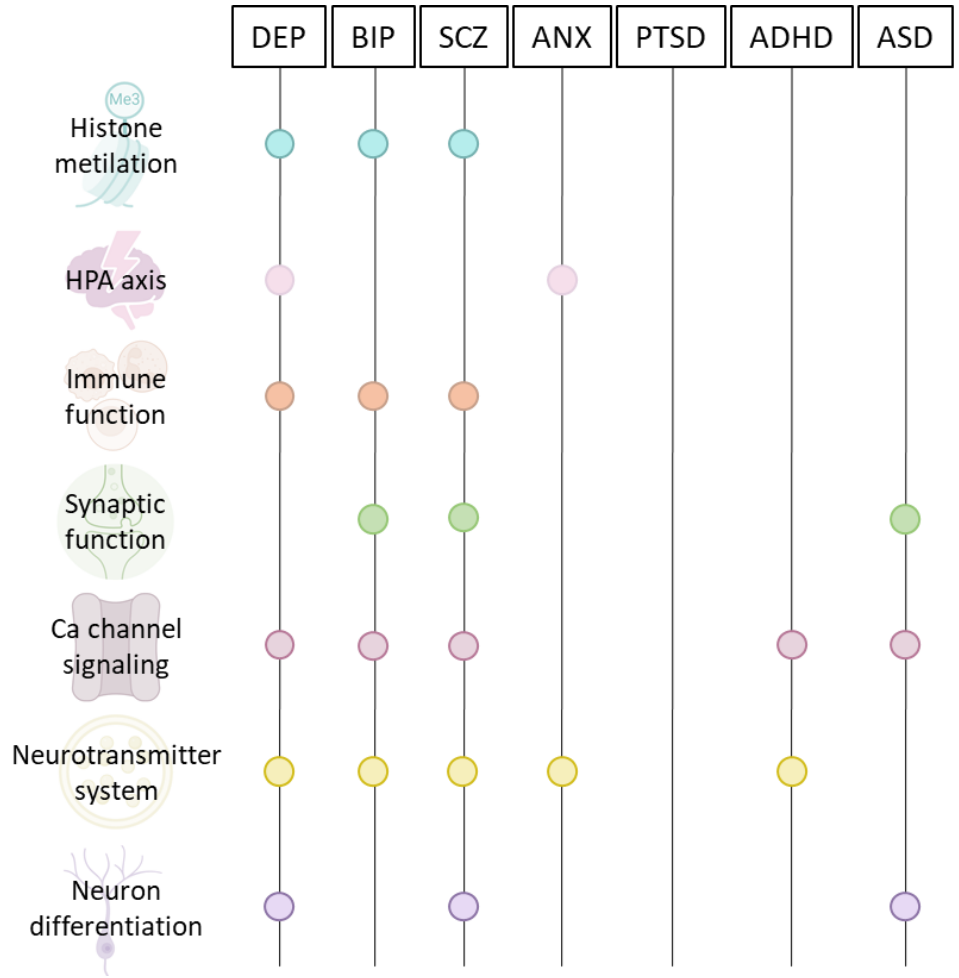
Note. Table created using information from the references cited within the table. SNP: Single nucleotide polymorphism, GWAS: Genome-wide association study, SCZ: Schizophrenia, BD: Bipolar disorder, DEP: Depressive disorders, ANX: Anxiety disorders, ADHD: Attention Deficit and Hyperactivity Disorder, ASD: Autism Spectrum Disorder, PTSD: Post Traumatic Stress Disorder.

Furthermore, findings from GWAS studies have revealed that, while certain identified loci are specific to a single mental disorder (38) or exhibit opposite directional effects on two or more mental disorders (39), such instances are in the minority. Instead, the prevailing pattern suggests a significant genetic

overlap among the majority of mental disorders (40), with a high number of the identified loci for mental disorders (>150) being pleiotropic, meaning that each variant influences two or more mental disorders (39). Therefore, considering the polygenic nature of mental disorders, where only a small number of genes operate independently, and most of them interact within intracellular networks of pathways to shape specific traits, the biological significance of these risk loci remains unclear. Nevertheless, recent results suggest that these risk loci for mental disorders converge on similar biological pathways, including neuronal, immune, and epigenetic pathways (41). Figure 2 shows the main biological pathways that have been linked to two or more mental disorders according to current literature. Importantly, the absence of a specific biological pathway for a given mental disorder does not necessarily indicate a lack of association; it may simply mean that it has not been evaluated in the context of that specific mental disorder yet.

Figure 2

Biological pathways associated with multiple mental disorders



Note. Original figure created using results from Gandal et al., (2018) (42); Levey et al., (2020) (43); Smoller et al., (2013) (44); Gatt et al., (2015) (45); O'dushlain et al., (2015) (46); and Zuo et al., (2021) (47). DEP: Depressive disorders, BD: Bipolar disorder, SCZ: Schizophrenia, ANX: Anxiety disorders, PTSD: Post Traumatic Stress Disorder, ADHD: Attention Deficit and Hyperactivity Disorder, ASD: Autism Spectrum Disorder.

Psychological factors

Psychological determinants of mental disorders encompass various factors related to an individual's thoughts, emotions, and behaviours that contribute to the development or exacerbation of mental health conditions (23). Cognitive patterns, such as negative self-perceptions, low self-esteem, or negative thinking, are often observed in disorders like depression and anxiety (48,49). Additionally, emotional factors, such as intense stress, can also play a significant role in the onset of schizophrenia, anxiety, and depression (48,49).

On the other hand, resilience is a known protective psychological factor for mental illness. Resilience is defined as "*the ability to adapt to stress while maintaining a healthy mental and physical performance"* (50). High levels of resilience have the potential to prevent the development of mental disorders or minimize the severity of the disease following stressful events (51–53). Conversely, lower levels of resilience have been reported among individuals with mental disorders (54). Furthermore, the presence of adaptive cognitive strategies, such as problem-solving skills or coping strategies, can enhance resilience and mitigate the impact of stressors. For instance, several studies suggest that how a person copes during a traumatic event or stressor and afterwards predicts the risk of PTSD, with factors such as positive emotion-focused coping and greater sense of purpose in life being negatively associated with symptomatic trajectories (55).

Social/environmental factors

Social and environmental determinants of mental health encompass a set of structural conditions encountered at different points in life, encompassing prenatal, perinatal, childhood, adolescent, and adult phases, that affect the individual's mental health outcomes (22,56). Social factors are diverse, but we

can classify them in five main domains: demographic, economic, community, environment, and sociocultural (Figure 3) (57,58).

The demographic domain encompasses factors such as age, sex[1], and ethnicity. Sex is both a biological and social factor. It is one of the most significant risk factors for several mental disorders, with certain diagnoses being more prevalent in women while others in men. For example, depression and anxiety are approximately twice as common in women as in men (59), whereas this trend seems to be reversed in conditions like ADHD, ASD, and substance use disorders (60). While biological factors such as hormones and neurotransmitters explain part of these differences, current evidence suggests that they are not solely biologically determined. Social factors including family environment, social norms, and strongly gendered risk factors such as intimate partner violence also contribute to these variations (56). In fact, in countries with a dual-earner model, where employment, wage earning, and domestic and childcare tasks are shared more equally between men and women, gender inequality in mental health risks is smaller (61,62).

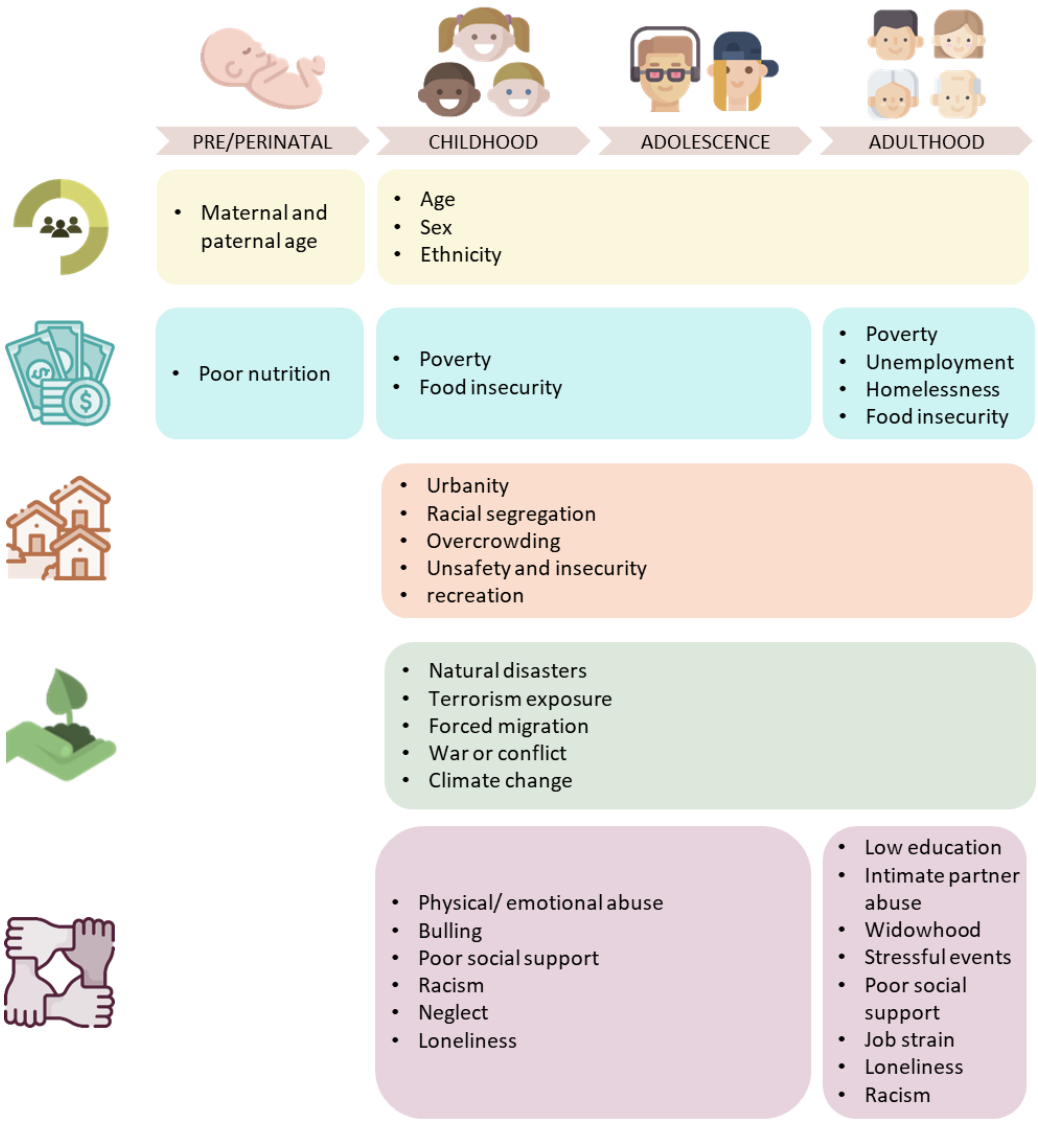
The economic domain includes factors such as poverty, unemployment, financial strain, and food insecurity (56). Socioeconomic disadvantage, which is a complex construct involving education, finance, occupation, and living standards, is a key determinant of mental health outcomes over the life course. Indeed, strong socioeconomic gradients are evident in various mental conditions, both in high- and low-/middle- income countries (63,64). Importantly, socioeconomic disadvantage can also be a consequence of mental disorders, as mental

[1] The studies included in the present thesis collect the variable 'sex', which refers to the biological sex as 'female' and 'male'. However, the thesis also considers 'gender,' defined as the social, cultural, political, psychological, juridical, and economic characteristics that society assigns based on biological sex. Concepts such as 'gender identity' and 'gender expression' are not covered in this thesis.

disorders can decrease employment opportunities, resulting in reduced income, which can potentially lead to poverty (65–67).

Figure 3

Examples of demographic, economic, community, environment, and sociocultural environmental risk factors for mental disorders across life stages.



Note. Figure adapted from Lund, et al., (2018) (57) and Kirkbride et al., (2024) (56).

The neighbourhood domain, closely related to economic factors, includes aspects such as urbanity, unsafety, recreation, and overcrowding. For instance, there is consistent evidence that individuals born and raised in urban and socially disadvantaged neighbourhoods are at a greater risk of non-affective psychotic disorders (68–70). Furthermore, the environment domain includes several factors such as climate change, natural disasters, terrorism, or war. For example, exposure to war and terrorism are known risk factors for PTSD (22). In addition, results from a meta-analysis suggest that short- and long-term exposure to air pollutants is associated with increased risk of both depression and anxiety (71). Finally, the sociocultural domain encompasses aspects such as bullying, poor social support, and physical or emotional abuse in childhood. For instance, poor social support, has been associated with higher rates of depression and other mental disorders, as well as more severe symptoms in individuals with mental health conditions (72,73). Moreover, experiences of physical or emotional abuse during childhood can have long-lasting effects on mental health. Children who experience abuse are more likely to develop mental disorders such as depression, anxiety, and PTSD later in life (22).

1.2. INFECTIONS AND MENTAL DISORDERS

The complex interplay between infections and mental disorders has been long since investigated. It is well known that infections can trigger a broad spectrum of mental health impairments (e.g. delirium, psychotic experiences, and mood disorders) (74). Moreover, several studies suggest that infections and the activation of the immune system might play a causative role in various mental disorders, particularly depression and schizophrenia. For instance, maternal infections during pregnancy and early childhood infections are known risk factors for schizophrenia and ASD (75–78). Furthermore, severe adult infections,

particularly viral infections, have been associated with increased risk of major depressive disorder (MDD), schizophrenia, and bipolar disorder (79,80), with some studies showing that even mild infections could increase the risk of mental disorders (81).

Importantly, mental disorders have been also reported to be risk factors for infections (82). For instance, the presence of a mental disorder has been associated with increased incidence of influenza, pneumococcal, herpes zoster, human immunodeficiency virus (HIV), and hepatitis B/C infections (83,84), and even mild infections such as the ones causing the common cold (85). In addition, a diagnosis of bipolar disorder, schizophrenia, or PTSD has been associated with increased prevalence of life-threatening infections (86,87). Although infections are inherently caused by external microorganisms, inter-individual differences influence the susceptibility to infections, which is influenced by both environmental and genetic factors (88–90).

Several biological mechanisms have been proposed to explain the association between infections and mental disorders, with immune dysregulation emerging as the most compelling explanation. Growing evidence suggests a chronic dysregulation of the immune response and a pro-inflammatory state among individuals with mental disorders (74). In fact, a higher prevalence of alterations in cellular and humoral immunity has been reported among individuals with mental disorders compared to healthy controls (91). This is further supported by genetic studies reporting associations between mental disorders such as schizophrenia, depression, and bipolar disorder and genes of the immune system (92–94). Moreover, higher levels of pro-inflammatory cytokines in blood (e.g. IL-1, IL-6, TNFα…) have been reported in people with schizophrenia, depression, bipolar disorder, anxiety disorders, and PTSD compared to people without these disorders (95). These heightened cytokine levels appear to

correlate with anxiety and depressive symptoms (96,97). Furthermore, consistently elevated levels of C-reactive protein (CRP), a protein produced by the liver in response to inflammation, have been associated to mental disorders such as depression and schizophrenia (98). Interestingly, different patterns of pro-inflammatory biomarkers have been reported across mental disorders, with closely related mental disorders such as bipolar disorder and schizophrenia sharing similar patterns of inflammatory profiles (95,99).

There are numerous factors, including genetic susceptibility, that promote immune dysregulation in mental disorders, but there is clear evidence that chronic stress exposure is related to increased levels of pro-inflammatory cytokines, as well as a higher risk for developing mental disorders (89). In addition, psychological stress has been associated with an increased incidence of various infections (100). Genetic studies show a considerable genetic overlap between susceptibility to infections and mental disorders (90). Thus, it has been suggested that cumulative exposure to infections, particularly early-life infections, along with other stressful environmental insults, might cause persistent disruptions of immune homeostasis in those individuals genetically susceptible, and thereby potentially increasing the risk for some mental disorders (101). On the other hand, stress and mental health symptoms have been reported to supress the immune system by dysregulating inflammatory responses (97,102). This can result in an increased susceptibility to infections, which might underlie the heightened vulnerability and severity of infections reported in individuals with mental disorders (82).

1.3. CORONAVIRUS DISEASE 19

Coronavirus Disease 19 (COVID-19) is a highly contagious respiratory illness caused by a novel coronavirus named Severe Acute Respiratory Syndrome

Coronavirus 2 (SARS-CoV-2). The first cases of COVID-19 were reported in Wuhan (China) in December 2019, and rapidly disseminated to every corner of the world, becoming the most significant global health crisis since the influenza pandemic in 1918 (103). By March 2024, more than 774 million cases of COVID-19 had been reported globally, resulting in more than 7 million deaths (104).

1.3.1. SARS-CoV-2 virus

SARS-CoV-2 is a coronavirus, which are single-stranded RNA viruses composed of 4 main structural proteins: the nucleocapsid, the membrane protein, the envelope glycoprotein, and the spike protein, which is key to infect the host cells (105). SARS-CoV-2, like all known human coronaviruses, is thought to have a zoonotic origin, although the exact origin remains elusive. The most likely hypothesis is that it emerged from bats, from which it jumped to an intermediate host before infecting humans (106).

SARS-CoV-2 is the seventh coronavirus that can infect humans. Coronaviruses mainly cause seasonal mild respiratory infections, with symptoms resembling those of the common cold. However, three of them, the prior Severe Acute Respiratory syndrome Coronavirus (SARS-CoV), the Middle East respiratory syndrome Coronavirus (MERS-CoV), and the SARS-CoV-2 itself, are highly pathogenic and can cause life-threatening respiratory infections and lung injuries (105,107).

The SARS-CoV-2 virus is primarily transmitted through respiratory droplets during close contact, although transmission through aerosols containing the virus is also possible (108). Inhalation of droplets allows the SARS-CoV-2 to enter the host cell by specific binding of its spike proteins to the angiotensin-converting enzyme 2 (ACE-2) receptors in the respiratory epithelium (108). In addition to the respiratory system, ACE-2 receptors are also present in the

intestinal tract, heart, kidneys, gallbladder, pancreas, and testis (109), which dictates viral tropism and pathogenicity of SARS-CoV-2. Once inside the host cell, the virus starts to replicate itself, increasing its viral load. As the viral load increases, so does the risk for SARS-CoV-2 transmission when an infected individual talks, coughs or sneezes (105). SARS-CoV-2 infectivity begins two days prior the symptom onset, then peaks, and remains in the host for approximately seven days, when it rapidly declines (108,110).

Since its emergence, SARS-CoV-2 has evolved rapidly, which has facilitated the emergence of many mutational variants across the world (107). Variants are the result of beneficial mutations, changes in the virus genome that entail an advantage over prior strains. Although several SARS-CoV-2 variants have been reported, to date, the World Health Organization (WHO) has only declared five of them to be variants of concern (VOCs), meaning that they have an impact on transmissibility, disease severity, and vaccine efficacy (111). The characteristics of these five VOCs, named alpha, beta, gamma, delta, and omicron, are presented in Table 3. Notably, as of March 2024, only the omicron variant remains a VOC, it is the only variant that remains circulating (112).

Table 3

Characteristics of the five variants of concern for SARS-CoV-2 identified so far

VOC	Country of emergence (date)	Infectivity	Mortality	Neutralization	Vaccine Effectiveness
Alpha	United Kingdom (10/2020)	Higher [1]	Higher [1]	No effect	88%
Beta	South Africa (12/2020)	Higher [1]	Higher [1]	Reduced	73%
Gamma	Brazil (1/2021)	Higher [1]	Equal [1]	Not clear	63%
Delta	India (11/2020)	Higher [2]	Higher [2]	Reduced	77%
Omicron	South Africa (11/2021)	Much higher [3]	Lower [3]	Reduced	55%

Note. Table created using information from Shao et al., (2022) (113); Lin et al., (2021) (114); Fan et al., (2022) (115); and Zeng et al., (2022) (116). The table displays the countries where each variant was first reported and the respective dates, along with its infectivity and mortality compared to previous strains. In most high-income countries, vaccination campaigns began on early 2021. The table also indicates whether the variant of concern (VOC) affected neutralization from both natural infection and vaccination, and vaccine effectiveness against the mentioned strain.

1 Compared to baseline, 2 compared to alpha, 3 compared to delta.

1.3.2. Pathogenesis of COVID-19 disease

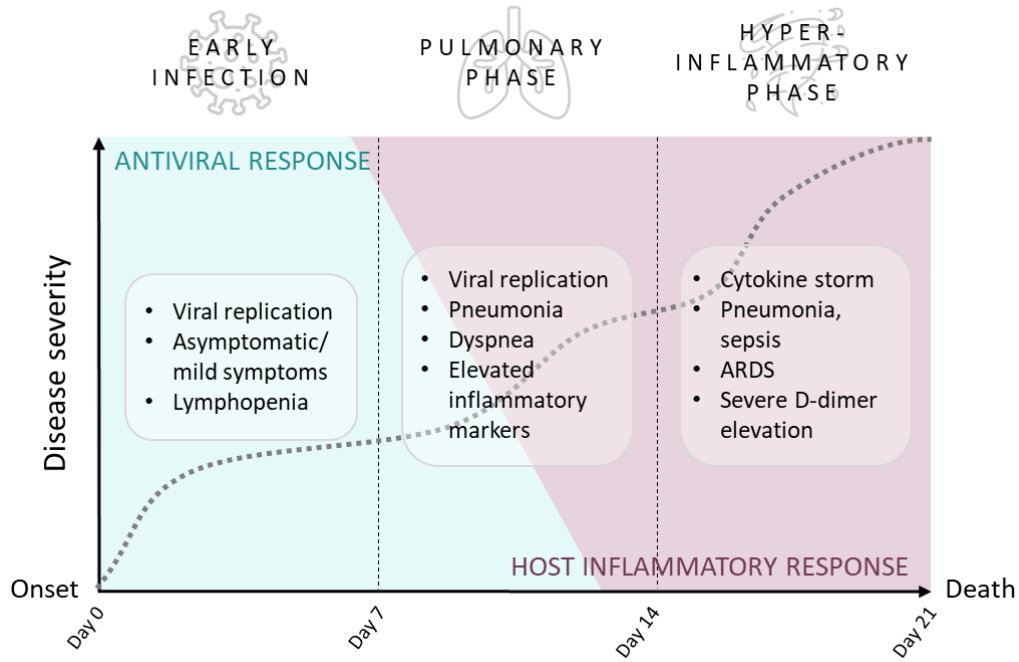
COVID-19 is a highly heterogeneous systemic disease with a clinical spectrum ranging from asymptomatic cases to severe illness (117). A distinctive feature of COVID-19 is the presence of asymptotic patients, which account for 40% of COVID-19 cases. No other coronavirus infection can present asymptomatically (118,119). Despite the lack of symptoms, multiple studies have documented that

asymptomatic cases are still able to transmit the infection, although the risk is lower than for symptomatic cases (120).

The SARS-CoV-2's incubation period is around 6.3 days, with most cases developing symptoms between 2 and 12 days after the infection (121). In the early phase of the disease the main processes driving the pathogenesis of COVID-19 are the direct tissue damage caused by SARS-CoV-2 in respiratory tract cells during replication. Whereas systemic immune responses triggered by the infected host cells to recruit T lymphocytes, monocytes, and neutrophils to fight the virus occur in the late phase (122) (Figure 4).

Figure 4

COVID-19 disease course



Note. Figure adapted from Wagner Gouvea dos Santos (2020) (123). The figure illustrates the three phases of COVID-19, detailing the symptom progression over a 21-day period. It also indicates the timeline for antiviral responses and host inflammatory reactions.

The most common symptoms of the disease are fever, fatigue, and upper respiratory tract manifestations (such as sore throat and cough), while less common symptoms include nausea, diarrhoea, muscle aches, headache, and ageusia/anosmia (i.e., loss of sense of taste/smell) (103,124). These symptoms are shown in mild cases of the disease, while moderate cases may also present difficulty of breathing or mild pneumonia. These cases, together with asymptomatic cases, account for 80% of the infections (125).

In severe COVID-19 cases, which account for around 20% of the infections (125), SARS-CoV-2 infection induces an over-activation of the immune system accompanied by a *cytokine storm* (i.e. heightened levels of circulating cytokines), which are intended to kill the virus. However, this immune dysregulation results in an unintentionally harmful systemic inflammatory response against the host (126). Symptoms of severe COVID-19 include severe pneumonia, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction (103). Finally, COVID-19 is fatal in around 2% of cases (127).

Although all individuals are at risk of contracting COVID-19, not everyone is equally susceptible to the infection or similarly affected by the disease. A recent meta-analysis has identified a cluster of host genetic variants in chromosome 3 associated with increased susceptibility and severity of COVID-19. The SNP-based heritability estimates reported are 4.6% for susceptibility and 7.6% for severity (128). Further from genetic factors, some populations have been identified as particularly vulnerable to severe COVID-19. Age is the strongest predictor of severe COVID-19. Once infected, adults older than 65 years are 6 times more likely to develop a severe disease course than younger individuals (129). Another risk factor for severe COVID-19 is male sex. Men have a higher risk of severe COVID-19 and higher mortality rates than women (130). In terms of lifestyle habits, smoking is a strong predictor of severe COVID-19. Smokers

have 2.5 higher odds of developing a severe COVID-19 than non-smokers (130). Several chronic conditions such as cardiovascular disease, chronic obstructive pulmonary disease, diabetes, hypertension, cancer, or acute kidney injury have also been associated with an increased risk of severe COVID-19 and mortality (130).

1.3.3. Prevention of COVID-19

Given the absence of a definitive treatment for COVID-19 or its related complications, preventive measures proved crucial to prevent the spread and reduce the mortality rates of COVID-19. Preventive measures primarily relied on non-pharmaceutical interventions (NPIs), and were complemented by vaccines as they became available in January 2021 (131). NPIs encompass public health measures designed to reduce the mortality of COVID-19 through the prevention and control of SARS-CoV-2 transmission (132). These include lighter measures such as hand-washing, social distancing, teleworking, and contact tracking, as well as more restrictive measures such as curfews, isolation, mandatory face masks, travel restrictions, lockdowns, and the closure of schools, shops, and leisure facilities (133). NPIs were essential in the first stages of the COVID-19 pandemic, when effective vaccines to protect from symptomatic infections and severe COVID-19 were not yet available, but remained necessary in later phases due to barriers such as misinformation, vaccine hesitancy and unequal access to vaccination (134,135). Notably, although essential, most NPIs had a negative impact on the general well-being of people, the economy, and the functioning of society (132,136).

1.3.4. Long COVID

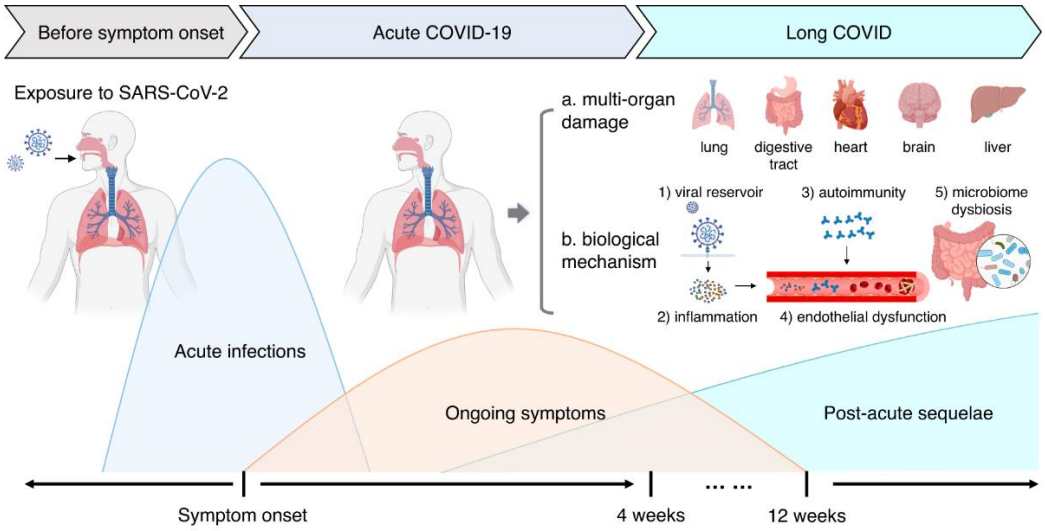
Long COVID, also known as post COVID-19 condition, is a multisystemic condition that follows a history of COVID-19 and a failure to fully recover (137). In general terms, long COVID includes both the continuation of COVID-19 symptoms for more than 4 weeks, and the conditions that develop during or after the infection that cannot be attributed to any other disorder (Figure 5) (138,139). The estimated incidence of long COVID is around 6-10%, with more than 65 million individuals affected by long COVID worldwide (137,140).

More than 200 symptoms of long COVID have been reported, the most common being generalized pain, fatigue, shortness of breath, chest pains, muscle aches, persisting fever, and cognitive dysfunction (137,141). Moreover, several new-onset conditions have been reported, including cardiac impairment, diabetes, and mental disorders such as depression, anxiety, or, less frequently, psychotic disorders (137,142). These can persist for months to years, and in certain instances, may persist for a lifetime, which can impact the ability to work and general quality of life of individuals with long COVID (137). Notably, a comprehensive study analysing psychiatric risk trajectories over two years following SARS-CoV-2 infection in a sample of more than 1 million individuals found that the increased risk of affective disorders after COVID-19 was short-lived, disappearing 6 months later, while the increased risk of psychotic disorders following COVID-19 persisted over time (143). This suggests that the main factor causing affective disorders after SARS-CoV-2 infection might be the stress related to COVID-19, while the onset of psychotic disorders may be due to the infection directly affecting the brain. Research on the pathogenicity of long COVID is still ongoing, but several biological mechanisms have been suggested to underlie the wide spectrum of long COVID symptoms, including the persistence of SARS-CoV-2 reservoirs, immune dysregulations caused during the

acute SARS-CoV-2 infection, autoimmunity, or microbiome dysfunction (Figure 5) (137,144).

Figure 5

Timeline of long COVID



Note. Figure obtained from Li et al., (2023) (145). The figure highlights the commonly affected organs as well as the biological mechanisms involved.

As with COVID-19, not everyone is equally at risk of developing long COVID. For instance, survivors of severe COVID-19 are at an increased risk of long COVID (146), while preliminary research indicates that SARS-CoV-2 reinfections might increase the risk of developing long COVID, even in vaccinated individuals (147). Other known risk factors for long COVID are female sex, which have 1.5 (95%CI 1.41-1.73) higher odds of developing long COVID than men, older age, high body mass index (BMI), smoking, and poor pre-pandemic general and mental health (148,149). A recent study examining the risk of developing long COVID in those with pre-existing mental health diagnoses reported that these individuals were 1.36 (95%CI 1.30–1.42) times at higher risk of developing long COVID than those without a mental health diagnosis (150).

1.4. GLOBAL DYNAMICS OF THE COVID-19 PANDEMIC

Given the high transmissibility of the virus and the existence of asymptomatic cases, which complicated accurate tracking exposure in populations, the spread of the SARS-CoV-2 virus was rapid and extensive (107). Nevertheless, the impact of the COVID-19 pandemic was not equal across countries. Several factors, including the virulence of the outbreak, the population density, the application of NPIs, or the circulation of determinate VOCs, among others, influenced the dynamics and the fatality of COVID-19 in each country (151). This thesis is mainly based on studies from the Spanish population, but also includes results from the Australian population. Therefore, this section will outline the worldwide progression of the COVID-19 pandemic, emphasizing Spain, followed by a comparative analysis of the Spanish and Australian contexts (Figure 6).

One month after the first COVID-19 cases were reported in December 2019 in China, cases had spread to 21 countries across Europe, Asia, and North America (107,122). The initial viral spread was caused by international passengers that left Wuhan before the Hubei province was placed under lockdown on the 23rd of January 2020, which caused the WHO to declare a Public Health emergency of International Concern on January 30th (107). Spain reported the first case of COVID-19 on January 31st (152).

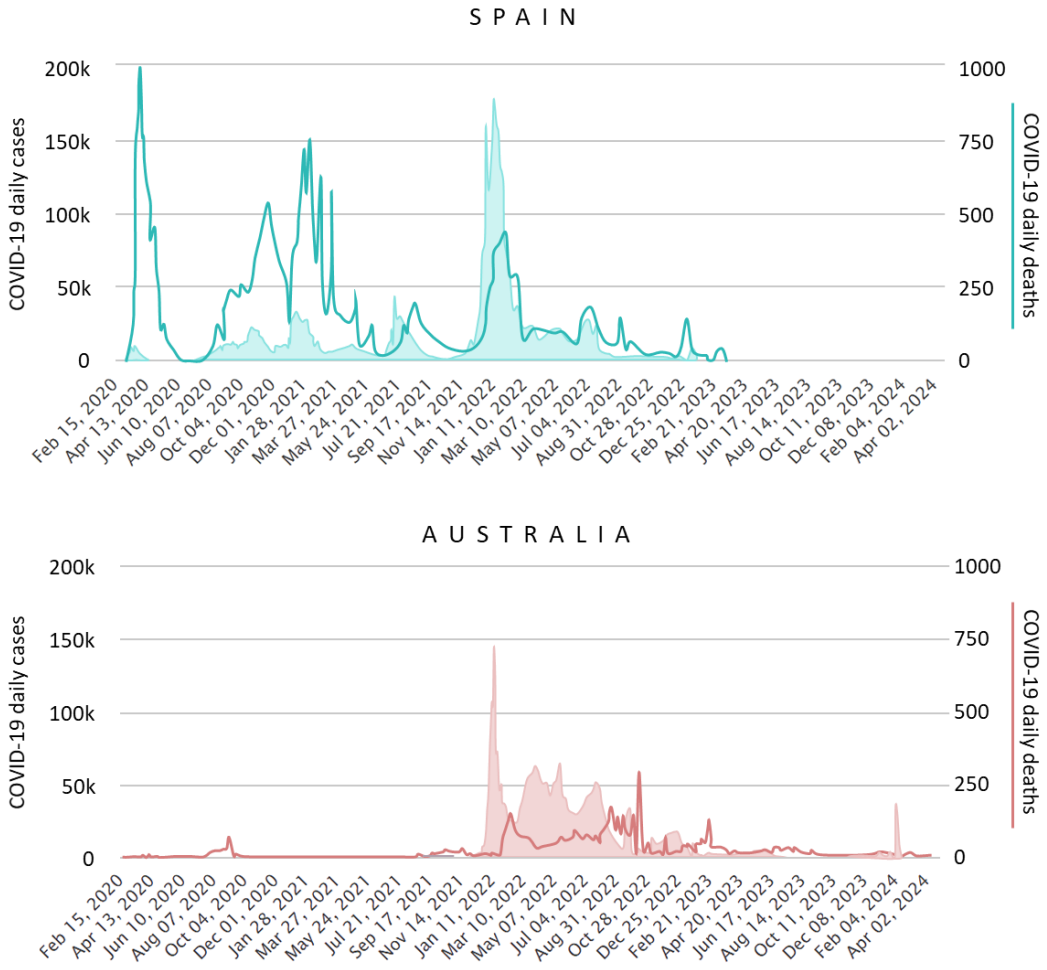
From mid-February to mid-March 2020, international travel outside China facilitated the second spread of the virus, changing the epicentre of the epidemic from China to Europe. At the beginning of March 2020, more than 100,000 cases had been confirmed globally (153). The major hotspots in Europe were Italy and Spain, with Spain reporting the highest mortality rates, rapidly surpassing China's death toll (154). On the 11th of March 2020 the WHO declared a pandemic (155), and most countries started to implement drastic NPIs to contain

the virus (107). Spain was among the countries with the most restrictive NPIs, which included lockdown, isolation, mandatory face masks, travel restrictions, and closure of schools, shops, and leisure facilities (156). By the end of March, nearly a third of the global population was under lockdown (154). The number of confirmed cases rose to 1 million in April, meaning a ten-fold increase in less than a month (157). However, this number is thought to be greater, given that the number of cases was greatly underestimated during the outbreak given the limited availability of COVID-19 tests to detect mild cases (154). In Spain, the first wave of the pandemic lasted until the end of May, 2020, when most of the NPIs were relaxed with the decrease in the number of cases (Figure 6) (104).

The relaxation of measures facilitated the circulation of the virus during the boreal summer, which boosted the emergence of mutational variants with an effect on fitness. The alpha variant caused an increase of cases between October 2020 and January 2021, which marked the initiation of the second and third wave of the pandemic, respectively (158). This caused the reimplementation of strict NPIs such as curfew to contain the spread of the virus (159), which lasted until May 2021, marking the end of the third wave (104). Subsequently, peaks of cases (or waves) were observed in August 2021 and in January 2022 (104), which coincided with the spread of the Delta and Omicron variants (160,161), respectively (Figure 6). Notably, although the number of cases during these phases was higher, the number of reported deaths was not as high as in the first waves (104). This decrease in mortality can be partly attributed to the effect of vaccines, which began to be administered in early 2021 in most European countries, including Spain (162). The WHO declared the end of the global emergency of COVID-19 on May 2023 while emphasising that it remained a global health threat (163). By March 2024, Spain had reported almost 14 million cases and 121,852 deaths (164).

Figure 6

Comparison of COVID-19 daily cases and daily deaths between Spain and Australia across the COVID-19 pandemic timeline



Note. Original figure created using information from the World Health Organization (WHO) (104) and the Worldometer (165).

In Australia, the course of the COVID-19 pandemic differed significantly from that of other countries. Its remote geographical location, coupled with the swift and stringent closure of borders and mandatory quarantine for returning travellers, which lasted nearly two years, facilitated the containment of COVID-19 cases (166). Consequently, during the first and second waves of the pandemic, Australia reported very few cases and low mortality rates (164). Indeed, it was not until the late 2021-early 2022 that Australia experienced a significant peak of cases and deaths (Figure 6). This event was caused by the arrival of the Omicron variant coinciding with the lifting of restrictions such as the reopening of borders to all vaccinated travellers in February 2022 (167). However, by that time the great majority of the adult population (93%) had been vaccinated. The higher vaccination coverage of the population, together with the lower fatality of the Omicron variant, meant that, despite the high number of cases, the total mortality in Australia was not as high as in other countries (168). By March 2024, Australia had reported nearly 12 million cases and 24,782 deaths.

1.5. PANDEMICS AND MENTAL HEALTH

Pandemics are large-scale outbreaks of infectious diseases that rapidly spread globally, affecting many people simultaneously across multiple countries (169). Throughout history, catastrophic pandemics have occurred. The most known examples of prior pandemics are the Bubonic plague in the 14th century, which killed between 30-50% of the European population (170), and the 1918 Spanish influenza, which affected more than one-third of the global population, killing near 50M people. Most recent epidemics are the acquired immunodeficiency syndrome (AIDS) pandemic in the 80s, caused by the HIV, and the severe acute respiratory syndrome (SARS) epidemic in 2003 (169).

Pandemics are associated with a multitude of stressful events such as uncertainty, fear, economic disruption, social isolation, stigma, and high mortality rates. Additionally, they often necessitate severe restrictions aimed at controlling the spread of the disease, resulting in serious disruptions to daily life. Not surprisingly, pandemics are related to long-term psychological consequences (171). Experience from the past indicates that prior epidemics/pandemics such as the Spanish Influenza, SARS, and Ebola were associated with increased levels of distress, depression, anxiety, and PTSD (172,173). Furthermore, one systematic review analysing the long term mental health trajectories after such pandemics reported that, while the prevalence of PTSD improved over time, depression and anxiety remained elevated for years following the pandemic (174). Indeed, the psychological morbidity of some epidemics such as SARS has been suggested to be even larger than its medical morbidity, both in terms of numbers of individuals impacted and duration of the impact (175–177).

Furthermore, pandemics can impact mental health through the direct effects of infectious agents. Infectious agents can significantly contribute to the onset or exacerbation of several mental disorders (79–81). For instance, viral infections like influenza and SARS have been associated with an increased risk of depression, anxiety, and psychosis (178,179). Similarly, bacterial infections such as tuberculosis, have been linked to psychosis and depression (180–183). Furthermore, chronic infections like HIV and hepatitis C virus (HCV) have been implicated in the development of mood disorders (184,185).

1.5.1. COVID-19 pandemic and mental health

In addition to being a public health emergency, the COVID-19 pandemic has profoundly impacted global mental health, both indirectly through disruptive

societal changes and directly via long-lasting neuropsychiatric sequelae following SARS-CoV-2 infection (186). Given the major role of environmental stressors in the aetiology of most mental disorders, the disruptive and unpredictable pandemic context was expected to increase the distress levels of the population. Moreover, research on past pandemics indicates that many people can exhibit stress-related responses focused on fear (e.g. of infection, of foreigners carrying the infection, of the socio-economic consequences, etc.) (187). The term COVID-related stress has been coined to account for the psychological and emotional strain experienced by individuals due to the COVID-19 pandemic, including health concerns, social isolation, loss, economic impact, and information overload (188). Additionally, the prolonged exposure to these stressors and to the uncertainty surrounding the duration of the pandemic can contribute to burnout, known as COVID-19 burnout or pandemic fatigue, potentially exerting a detrimental effect on mental health (189).

Available meta-analyses comparing levels of self-reported symptoms of mental health before and during the COVID-19 pandemic, predominantly in Europe and North America, reach consistent conclusions and indicate a heterogeneous small but significant increase in mental health symptoms, including psychological distress, anxiety, and depressive symptoms (190–194). Conversely, levels of self-reported well-being (190) and alcohol use remained unchanged, while a slight decrease has been reported for psychotic symptoms (190). Nevertheless, these results are mainly based on the first year of the pandemic, and particularly during the outbreak, when there were strict restrictions and high mortality rates of the disease. Further studies reported a decrease of mental health symptoms in subsequent months, when infection and mortality rates were lower and the social restrictions eased, but they did not return to pre-pandemic levels (190,194).

It is important to mention that although levels of self-reported mental health symptoms show an increased risk for mental disorders, they cannot be directly translated to clinical diagnoses. The Global Burden of Disease estimated that the COVID-19 pandemic led to a 28% increase in cases of MDD and a 26% increase in cases of generalized anxiety disorder (GAD) (195). However, these numbers might be substantially overestimated (196). Several longitudinal studies, all of them from Europe and United States, have compared the prevalence of depressive and anxiety disorders before and during the pandemic, but results are highly heterogeneous (197–199). Moreover, a recent study using data from electronic health records from different high income countries reported that the incidence of mental health diagnoses declined during the first phase of the COVID-19 pandemic, probably because of the difficult access to mental health care during the lockdown and other restrictions, and it gradually returned to or exceeded pre-pandemic levels in 2021 (200). Finally, one study from United States comparing mental health utilization rates from January 2020 to December 2020 found a sharp decline in in-person mental health care service utilization rates, but when combining in-person and telehealth service utilization rates, they observed an increase in care for depressive and anxiety disorders over the period (201).

In sum, although a global increase in mental disorders prevalence during the first year of the pandemic was expected, consistent evidence for this increase remains absent. This observation, together with the only modest increase in mental health symptoms found, might imply remarkable levels of resilience and adaptation. However, the considerable heterogeneity across studies analysing the impact of the COVID-19 pandemic on mental health suggest that any potential improvement in mental health in certain population groups could have masked underlying mental health problems in other groups (186).

1.6. PRE-EXISTING MENTAL DISORDERS AND COVID-19

Immediately following the onset of the COVID-19 pandemic, several researchers expressed their concerns about the vulnerability of individuals with pre-existing mental disorders to COVID-19, both to the disease outcomes and to the mental health impact of the pandemic and its restrictions (202–204). As previously mentioned, individuals with mental disorders, and particularly severe mental disorders, present physiological dysregulations that can alter their immune function (95,98), increasing their susceptibility to SARS-CoV-2 infection and the severity of the disease when contracted, as well as the likelihood to develop long COVID (205). In addition, higher rates of smoking, unhealthy habits, and comorbidities might confer a worse prognosis among those infected (17,206). Moreover, this population often face socioeconomic disparities, including inadequate housing conditions and limited access to healthcare, which can further exacerbate their risk of infection and severe disease (207,208). Finally, cognitive impairment, reduced risk awareness, and potential confined conditions in psychiatric wards might increase their risk of infection (204).

Despite this increased vulnerability to COVID-19, higher vaccine hesitancy and lower vaccination rates have been reported in individuals with mental disorders compared to the general population, further contributing to their increased risk of severe COVID-19 outcomes (209,210). Several barriers including misinformation, difficulties in understanding the benefits of vaccination, and reduced access to healthcare may explain their lower adherence to vaccination (211). Numerous studies have assessed the risk of SARS-CoV-2 infection and severe COVID-19 outcomes in individuals with pre-existing mental disorders. The latest meta-analysis on this topic, encompassing 81 studies from diverse, predominantly high-income countries, reported increased risks of severe COVID-19 and mortality, but not infection, in this population (212). Nevertheless,

nuanced distinctions across mental health diagnoses might shape different risks of infection and severe COVID-19 outcomes.

Furthermore, the pandemic's disruptive effects to daily life, including financial stress and uncertainty can exacerbate existing mental health conditions, while the limited access to mental health services, discontinuation of treatment, and reduced social support networks during the pandemic can further contribute to their symptomatology (213). Nevertheless, current evidence does not support the hypothesis that people with pre-existing mental disorders were disproportionately affected by the pandemic (194). However, in absolute terms, they showed higher levels of depressive symptoms, anxiety symptoms, and COVID-related stress during the first phase of the pandemic (214,215). Moreover, certain mental health diagnoses might have been more affected by the pandemic compared to others. Thus, improvements in mental health symptoms for certain disorders might mask the mental health impact within particular diagnoses.

1.7. JUSTIFICATION OF THE THESIS

The growing global population, interconnectedness, globalization, urbanization, food production, animal activity, and climate change, coupled with microbial adaptation and resistance, projects an escalation in the occurrence of emerging infectious diseases (i.e., those diseases that are newly identified or previously unknown) (216). In fact, from the 1970s to 2015, nearly 50 new human pathogens were identified and characterized (217,218). Therefore, it is almost certain that COVID-19 is only one of the many pandemics that will hit our population. At the same time, the burden of mental disorders is increasing worldwide, with projections indicating a persistent increase in both incidence rates and mortality in the coming years (219). The concurrent rise of emerging

infectious diseases and mental disorders, both top causes of disability worldwide (220), underscores the urgent need for comprehensive research into their interplay, and the recent COVID-19 pandemic has brought this need into sharp focus.

Pandemics can significantly impact mental health through various mechanisms, and the impact of the COVID-19 pandemic on mental health is undeniable. The implementation of strict public health measures, economic instability, and misinformation about the disease, has led to increased feelings of isolation, anxiety, fear, distress, and depression, which can exacerbate already existing mental health conditions. Furthermore, it is essential to acknowledge the relationship between mental health and COVID-19. Not only does the pandemic impact the mental health of individuals with mental health conditions, but pre-existing mental disorders can also increase the susceptibility to the virus and worsen clinical outcomes. Importantly, given that mental health diagnoses differ in behavioural aspects, health behaviours, and clinical factors, the type of pre-existing mental disorder should also be considered, as the impact of COVID-19 might not be equal across disorders.

In addition, genetic factors can contribute to differences in transmissibility and pathogenicity of SARS-CoV-2 among people with mental disorders (128). While it is well-known that genetic factors play a role in the development of mental disorders, their interaction with infections such as COVID-19 is less understood. Recent studies have reported common alterations in biological pathways for mental disorders and COVID-19 (221), which suggests a potential role for shared common genetic risk factors between both conditions. Investigating which specific genes are shared between these two traits could provide valuable insights into the underlying mechanisms linking infectious diseases and mental health outcomes.

Understanding whether pre-existing mental disorders (and their genetic predispositions) are associated with COVID-19 outcomes, and the impact of the pandemic on mental health indicators among such population group is key to mitigate health disparities across people with mental disorders and develop targeted interventions and public health strategies (207).

2 Hypotheses and Objectives

What's the use of doing all this work if we don't get some fun out of this?

- Rosalind Franklin

2.1. HYPOTHESIS

The present thesis explores the impact of COVID-19, on individuals with pre-existing mental disorders, incorporating clinical, psychosocial, and biological perspectives. We hypothesize that the impact of COVID-19 varies depending on the specific type of pre-existing mental disorder, leading to distinct patterns of mental health symptoms and susceptibilities to the disease, which might be influenced by genetic and psychological factors.

To address various aspects pertinent to this main hypothesis, we have formulated several specific hypotheses:

1. Different types of pre-existing mental disorders do not present the same pattern of risk of SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19 mortality, when compared to individuals without these mental disorders.
2. We expect to find shared genomic alterations between pre-existing mental disorders and COVID-19 outcomes, which underlie the increased risks of infection and severe COVID-19 reported in epidemiological studies.
3. We expect to find causal genetic associations that support the identified associations between specific types of mental disorders and risk of SARS-CoV-2 infection and COVID-19 hospitalization.
4. Having a pre-existing mental disorder may affect the impact of psychological factors like COVID-related stress and social support on major depressive and generalized anxiety disorders during the early pandemic.
5. The type of pre-existing mental disorder influences changes of depressive and anxiety symptoms experienced from the early to mid-phase of the COVID-19 pandemic.

6. The effect of COVID-related stress, social support, and resilience on these mental health symptoms is moderated by the type of mental disorder.
7. In people with pre-existing depression, a higher genetic predisposition to depression and other mental disorders predicts higher risk of SARS-CoV-2 infection and long COVID.
8. In people with pre-existing depression, a higher genetic predisposition to depression and other mental disorders predicts higher levels of COVID-related stress and burnout, and anxiety symptoms and resilience levels influence this association.

2.2. OBJECTIVES

The present thesis aims to investigate the vulnerability of individuals with pre-existing mental disorders to both the mental health impact of the COVID-19 pandemic and the direct effects of the COVID-19 disease. Additionally, it seeks to explore psychological and genetic factors contributing to the identified associations. The following specific objectives have been proposed:

1. Explore the association between different types of pre-existing mental disorders and risk of SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19-related death (Study I).
2. Examine whether shared genetic factors contribute to the increased transmissibility and pathogenicity of COVID-19 observed in mental disorders, identify the specific genomic regions shared between each disorder and COVID-19, and test for causal associations (Study II).
3. Identify whether having a pre-existing mental disorders moderated the association between COVID-related stress and social support, and screening positive for major depressive and generalized anxiety disorders during the early pandemic (Study III).
4. Explore changes of anxiety and depressive symptoms from the early to mid-phase of the COVID-19 pandemic among those with different pre-existing mental disorders and assess the influence of psychological factors on these associations (Study IV).
5. Investigate if a higher genetic predisposition to different mental disorders is associated with an increased risk of SARS-CoV-2 infection, long COVID, COVID-related stress, and COVID-19 burnout in individuals with pre-existing depression, while also examining the influence of anxiety symptoms and resilience on the associations with COVID-related stress and COVID-19 burnout (Study V).

3 Materials, Methods, and Results

We realize the importance of our voices

only when we are silenced

- Malala Yousafzai

STUDY I

SARS-CoV-2 infection and COVID-19 outcomes across mental disorders and the role of sex: A register-based study from Catalonia

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Submitted to General Hospital Psychiatry

SARS-CoV-2 infection and COVID-19 outcomes across mental disorders and the role of sex: A register-based study from Catalonia

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ABSTRACT

Introduction: This study aimed to study the risk of SARS-CoV-2 infection and severe COVID-19 outcomes across different mental diagnoses and to assess the role of sex in these associations.

Methods: We used electronic health records from Catalonia to identify adults receiving inpatient/outpatient mental health care between 2017-2019 with diagnosis of non-affective psychosis (NAP), bipolar disorder (BD), depressive disorder (DEP), stress-related disorders, neurotic/somatoform disorders (NSD), and substance misuse (SUB) (exposed). Outcomes included SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19-related death. Adjusted logistic regression analyses were conducted.

Results: 785,378 adults were included (70.3% < 65 years old; 57.1% women). Compared to unexposed, those with NAP [OR (95%CI): 0.84 (0.80-0.88)], BD [0.80 (0.75-0.86)], DEP [0.97 (0.94-1.00)] and SUB [0.81 (0.78-0.84)] had a lower risk of SARS-CoV-2 infection, while people with NSD presented an increased risk [1.03 (1.01-1.06)]. Among those infected, people with DEP, NSD, and SUB had a lower risk of COVID-19 hospitalization, but higher risk of COVID-19-related death [1.23 (1.07-1.41); 1.26 (1.07-1.48); 1.48 (1.24-1.71), respectively]. A higher COVID-19-related death was also found in people with NAP and BD [1.68 (1.34-2.12); 2.02 (1.50-2.73)]. Sex-stratified analysis showed that women with NSD were especially vulnerable to

infection [1.07 (1.03-1.11)], and women with DEP and NSD to COVID-19-related death [1.24 (1.05-1.47); 1.26 (1.02-1.54)].

Conclusions: These results suggest different vulnerabilities to infection and COVID-19 hospitalization and death across mental disorders. These findings have implications for pandemic preparedness, highlighting the need for specific public health strategies to mitigate the excess of mortality of people with certain mental disorders

1. INTRODUCTION

People with pre-existing mental disorders are particularly vulnerable to the impact of the COVID-19 disease. This population not only faces a higher risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, but also experiences worse COVID-19 outcomes and subsequent health complications [1,2]. However, it is unclear if this vulnerability is present in all mental disorder groups. Types of mental disorders differ in behavioural factors (e.g. stress response, cognitive impairment) 3, biological factors, and health behaviours (e.g. smoking, sleeping habits) [4,5]. For instance, the prevalence of smoking is not equal across disorders, being higher in individuals with bipolar and drug misuse disorders, while different mental disorders exhibit distinct clusters of altered inflammatory markers [6,7]. In addition, mental disorders differ in clinical factors such as medication patterns or the prevalence of physical comorbidities [8]. Given that most of these factors directly influence the risk of infection and COVID-19 severity [9–11], the impact of COVID-19 disease might not be equal across mental disorders. Understanding the individual risks of SARS-CoV-2 infection and severe COVID-19 outcomes among mental health diagnoses is important to mitigate health disparities across people with mental disorders [12] and to develop targeted interventions and public health strategies.

To date, several studies have analysed the association between specific mental health diagnoses and SARS-CoV-2 infection and severe COVID-19 outcomes, but results are inconsistent for most diagnostic groups. Current literature suggests an increased risk of COVID-related death in people with pre-existing psychotic and drug misuse disorders compared to individuals without mental disorders, but the results are diverse regarding their risk of infection [1,13]. Likewise, the association between other mental disorders such as depression, anxiety or neurodevelopmental disorders and SARS-CoV-2 infection and mortality is unclear [13], while evidence is limited for some mental disorders such as stress-related disorders. One potential reason for the divergence of results across studies is the heterogeneity in grouping of mental disorders. For instance, the latest systematic review reported an increased COVID-19 mortality in people with mood disorders (which included both depression and bipolar depression into a single category) [13]. Yet, results from other studies in which such disorders were examined individually showed that people with bipolar disorder faced an elevated risk of COVID-19-realted death [14], while results were mixed for depression [2,15], with some studies suggesting a lower risk of COVID-19 mortality [15].

Another factor that has the potential to play a significant role in these divergent findings is sex. Studies from the general population revealed that men had higher odds of SARS-CoV-2 infection, a severe course of the disease and COVID-19-related death than women. [16] In addition, women and men present differences both in the manifestation and prevalence of several mental disorders [17]. This is mainly caused by disparities in brain structure and function, stress response, socio-cultural norms and sex hormones [18]. Some of these factors, such as sex hormones, have been reported to contribute to the risk of severe COVID-19 [19]. However, we have only identified one study from the United States showing different risks of COVID-related outcomes between men and women across different pre-existing mental disorders [20]. This study found that women with ADHD, depression, bipolar disorder, and schizophrenia had an increased risk of SARS-CoV-2 infection when compared to men, while COVID-19 hospitalization and death rates remained higher in men with any mental disorder than in women. However, the role of sex in the risk of COVID-19 hospitalization and COVID-19 death was not explored in the different diagnostic groups [20]. Therefore, further studies from diverse countries are required to better understand the prognosis of individuals with COVID-19 according to their psychiatric diagnosis and sex.

This study used health registers from the region of Catalonia (Spain) to assess the association between several types of mental disorders (i.e., non-affective psychosis, bipolar disorder, depression, stress-related disorders, neurotic/

somatoform disorders and substance misuse) and risk of SARS-CoV-2 infection, hospitalization and COVID-19-related death employing health registers from Catalonia, Spain. Importantly, analyses were also stratified for sex to explore whether there are sex-specific patterns in the aforementioned associations.

2. METHODS

2.1 Study design and population

An observational retrospective matched cohort study was performed using anonymized data from electronic health records from Catalonia, Spain. Data were retrieved from the Health Quality and Assessment Agency of Catalonia (AQuAS), which is responsible and manages the Public Data Analysis for Health Research and Innovation Programme (PADRIS) 21. Clinical information on users of the Catalan public health system, serving a population of 6,358,740 inhabitants older than 18 years in the first semester of 2021, were here collected [22]. These registers used the 9th and 10th versions of the International Classification of Diseases (ICD-9/ ICD-10) (Annex 1).

We selected all adults ≥ 18 years in 2017 and still alive on 31st of December 2019, that received specialized inpatient or outpatient mental health care between January 1, 2017, and December 31, 2019, for the following mental disorders: non-affective psychosis, bipolar disorder, depressive disorder, stress-related disorders, neurotic/somatoform disorders, and substance misuse (ICD-10 codes in Annex 1). For patients having more than one diagnosis of mental disorder, we used the following hierarchical order based on DSM-V to classify them [23]: non-affective psychosis > bipolar disorder > depressive disorder > stress-related disorders > neurotic/somatoform disorders > substance misuse. That is, those having any diagnosis of non-affective psychosis were classified as “non-affective psychosis”; participants without a diagnosis of non-affective psychosis but a diagnosis of bipolar disorder were classified as “bipolar disorder”; individuals without non-affective psychosis or bipolar disorder but diagnosed with depressive disorder were classified as “depressive disorder”, and so on.

Each individual with one of the mental disorders of interest (exposed) was matched to a random individual from the Catalonia health registry who did not receive specialized inpatient or outpatient mental health care for the mental disorders of interest between January 1, 2017, and December 31, 2019, according to sex, 3-years age band and living area (unexposed).

According to the current regulation for the use of registry-based health data, informed consent was not required. This study was approved by the ethics committee of Fundació Sant Joan de Déu (PIC-160-21).

2.2 SARS-CoV-2 infection and COVID-19 outcomes

The primary outcomes of our study were SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19-related death. These data were retrieved from February 25, 2020 (the date of the first official reported case of COVID-19 in Catalonia) up to December 31, 2020 (before the vaccination campaigns began). SARS-CoV-2 infection was defined by a positive PCR/antigen test or a clinical diagnosis of COVID-19. None of the individuals included had a SARS-CoV-2 reinfection during the study period. COVID-19 hospitalization was defined by admissions caused by the following ICD-10 diagnosis: COVID-19, coronavirus infection, coronavirus causing other diseases and other viral pneumonia (Annex 1). COVID-19-related deaths were ascertained using mortuary records. Dichotomous variables were created for the outcomes (yes/no).

2.3 Covariates

We included the number of physical diagnoses and nursing home/sheltered accommodation stay as covariates in all the analyses. Data on physical diseases was obtained from primary care registries between 2017 and 2018, since no more recent data was accessible at the time of data extraction. Physical diseases included asthma, cardiovascular diseases, chronic pulmonary disease, diabetes, dyslipidaemia, heart failure, hypertension, ischemic heart disease, malignant neoplasia and obesity (ICD-10 codes in Annex 1), which have been related to severe COVID-19 outcomes [24]. Following previous studies, a 3-level variable was created: 0, 1, ≥2 25. We also accounted for individuals who stayed in nursing homes (irrespective of the duration) throughout the study period encompassing the pandemic (February 25, 2020, to December 31, 2020). This is because they experienced a unique environment, which could potentially lead to distinct implications for their health outcomes and risk factors. Thus, a dichotomous variable for those who were admitted to nursing homes (yes/no) was created.

2.4 Statistical analysis

Categorical variables were summarized by frequency tables. In addition, chi-squared tests were used to assess differences in clinical characteristics between exposed and unexposed. Then, we employed multivariable logistic regression analysis to assess the association between the presence of mental disorders and SARS-CoV-2 infection while adjusting for physical diseases and nursing homes stay. Analyses were not adjusted by sex or age because we matched the exposed and unexposed groups by these variables. We further employed multivariable logistic regression analysis in a sub-cohort containing only those individuals who had tested positive for COVID-19 to test the association between each mental health diagnosis and COVID-19 hospitalization and COVID-19-related death. These analysis were adjusted for age, sex, number of physical diseases and nursing homes stay. Multivariable logistic regression analyses were also conducted stratified by sex to account for the role of sex in the association between the six mental disorder groups of interest and risk of SARS-CoV-2 infection adjusting for physical diseases and nursing homes stay. Furthermore, multivariable logistic regression analyses were conducted stratified by sex in the sub-cohort containing only individuals who had tested positive for COVID-19, to account for the role of sex in the association between the six mental disorders groups and COVID-19 hospitalization and COVID-19-related death.

The level of statistical significance was set at alpha level of 0.05. All analysis were performed in R, version 4.3.1.

3. RESULTS

3.1 Sample characteristics

Between the 1st of January 2017 and the 31st of December 2020, 392,689 people were diagnosed with a mental disorder of interest. After the 1:1 matching procedure, the total sample size for this study comprised 785,378 individuals. In both groups, 70.3% were younger than 65 years old and 57.1% were women. The demographic characteristics of the study population are shown in Table 1. Compared to unexposed, people with diagnoses of mental disorders had a higher prevalence of more than one physical diagnosis (35.5% vs 28.9% in unexposed) and were more likely to be staying in nursing homes (2.6% vs 1.6% in unexposed). The proportion of individuals infected with SARS-CoV-2 was similar between groups. The proportion of COVID-19 hospitalizations among individuals with a SARS-CoV-2 infection was lower in exposed than in unexposed (10.7% vs 11.5%), while COVID-19-related death was significantly higher in exposed (4.4% vs 3.3%).

Table 1. Sociodemographic characteristics of the study population

N (%)		Total (n = 785,378)	Exposed (n = 392,689)	Unexposed (n = 392,689)	p-value[2]
Sex	**Men**	336,646 (42.9%)	168,323 (42.9%)	168,323 (42.9%)	-
	Women	448,732 (57.1%)	224,366 (57.1%)	224,366 (57.1%)	
Age	**18 - 64**	552,278 (70.3%)	283,917 (72.3%)	268,361 (68.3%)	-
	≥ 65	233,100 (29.7%)	108,772 (27.7%)	124,328 (31.7%)	
Mental disorder	**Non-affective psychosis**	26,665 (3.4%)	26,665 (6.8%)	-	-
	Bipolar disorder	15,000 (1.9%)	15,000 (3.8%)	-	
	Depressive disorder	98,434 (12.5%)	98,434 (25.1%)	-	
	Stress-related disorders	51,944 (6.6%)	51,944 (13.2%)	-	

	Neurotic and somatoform disorders	103,048 (13.1%)	103,048 (26.2%)	-	
	Substance misuse	97,598 (12.4%)	97,598 (24.9%)	-	
Nursing homes stay	**Non-user**	768,641 (97.9%)	382,315 (97.4%)	386,326 (98.4%)	<0.001
	User	16,737 (2.1%)	10,374 (2.6%)	6,363 (1.6%)	
Physical comorbidities	**0**	348,153 (44.3%)	157,672 (40.2%)	190,481 (48.5%)	<0.001
	1	184,225 (23.5%)	95,694 (24.4%)	88,531 (22.5%)	
	≥2	253,000 (32.2%)	139,323 (35.5%)	113,677 (28.9%)	
SARS-CoV-2 infection	**No**	738,842 (94.1%)	369,429 (94.1%)	369,413 (94.1%)	0.942
	Yes	46,536 (5.9%)	23,260 (5.9%)	23,276 (5.9%)	
COVID-19 hospitalization[1]	**No**	41,368 (88.9%)	20,764 (89.3%)	20,604 (88.5%)	0.012
	Yes	5,168 (11.1%)	2,496 (10.7%)	2,672 (11.5%)	
COVID-19 related death[1]	**No**	44,738 (96.1%)	22,230 (95.6%)	22,508 (96.7%)	<0.001
	Yes	1,798 (3.9%)	1,030 (4.4%)	768 (3.3%)	

[1] Sample size restricted to COVID-19 positive cases (n = 46,536). [2]P-values were calculated using 20000 Monte Carlo simulations of the χ^2 test facing exposed and unexposed.

3.2 Mental disorders and risk of SARS-CoV-2 infection and COVID-19 outcomes

Results from multivariate logistic regression analysis are shown in Table 2. Our results showed that people with non-affective psychosis, bipolar disorder, depression and substance misuse had a significant reduced risk of SARS-CoV-2 infection compared to unexposed [OR (95%CI): 0.84 (0.80-0.88); 0.80 (0.75-0.86); 0.97 (0.94-1.00); 0.81 (0.78-0.84), respectively], although in the case of depression the effect size was small. Conversely, individuals with neurotic/somatoform disorders exhibited a slightly elevated risk of infection [OR (95%CI): 1.03 (1.01-1.06)]. No significant differences were found in people with stress-related disorders.

Among those who tested positive for COVID-19, we explored differences in the risk of COVID-19 hospitalization and COVID-19-related death across the six groups of mental disorders (Table 2). We observed that individuals with depression, neurotic/somatoform disorders, and substance misuse disorders had a lower risk of COVID-19 hospitalization compared to unexposed [OR (95%CI): 0.90 (0.82-0.98); 0.86 (0.78-0.95); 0.83 (0.75-0.91), respectively], while no significant differences were found for non-affective psychosis, bipolar disorder, and stress-related disorders. Regarding COVID-19-related death, we found that all mental health groups (with the exception of stress-related disorders) had a greater risk of COVID-19-related death when compared to unexposed [ORNAP (95%CI): 1.68 (1.34-2.12); ORBIP: 2.02 (1.50-2.73); ORDEP: 1.23 (1.07-1.41); ORNSD: 1.26 (1.07, 1.48); ORSUB: 1.48 (1.24, 1.71)].

3.3 Mental disorders and risk of SARS-CoV-2 infection and COVID-19 outcomes stratified by sex

Among COVID-19 outcomes, sex differences were only observed for depression and neurotic/somatoform disorders (Figure 1, Annex 2). As regards to the risk of SARS-CoV-2 infection, only men with depression showed a lower risk of SARS-CoV-2 infection [AOR: 0.90 (95%CI 0.85-0.95), p < 0.001] when compared to unexposed. Moreover, only women with neurotic/somatoform disorders presented an increased risk of SARS-CoV-2 infection [AOR: 1.07 (95%CI 1.03-1.11), p < 0.001] when compared to their unexposed counterparts. No sex differences were found in terms of COVID-19 hospitalization. Regarding COVID-19-related death, people with depression and neurotic/somatoform disorders had a significant increased risk of COVID-related death when compared to unexposed, but this was only significant for women [AORDEP: 1.24 (95%CI 1.05-1.47), p = 0.013; AORNEU: 1.26 (95%CI 1.02-1.54), p = 0.029].

Table 2. Logistic regression analysis for risk of SARS-CoV-2 infection, COVID-19 hospitalization and COVID-19-related death

		SARS-CoV-2 infection AOR (95%CI)	COVID-19 hospitalization AOR (95%CI)[1]	COVID-19-related death AOR (95%CI)[1]
Physical diseases	1	1.08 (1.05, 1.11) p <0.001	1.14 (1.04, 1.24) p = 0.006	1.00 (0.84, 1.19) p = 0.999
	≥2	1.26 (1.23, 1.29) p <0.001	1.44 (1.33, 1.55) p <0.001	1.18 (1.03, 1.36) p = 0.021
Nursing homes stay	yes	7.90 (7.63, 8.18) p <0.001	0.83 (0.75, 0.91) p <0.001	0.93 (0.82, 1.06) p = 0.277
Mental disorder	Non-affective psychosis	0.84 (0.80, 0.88) p <0.001	1.08 (0.93, 1.26) p = 0.307	1.68 (1.34, 2.12) p <0.001
	Bipolar disorder	0.80 (0.75, 0.86) p <0.001	1.00 (0.81, 1.24) p = 0.957	2.02 (1.50, 2.73) p <0.001
	Depression	0.97 (0.94, 1.00) p = 0.030	0.90 (0.82, 0.98) p = 0.014	1.23 (1.07, 1.41) p = 0.003
	Stress-related disorder	1.02 (0.98, 1.06) p = 0.315	0.92 (0.80, 1.06) p = 0.245	0.94 (0.69, 1.28) p = 0.695
	Neurotic and somatoform disorder	1.03 (1.01, 1.06) p = 0.026	0.86 (0.78, 0.95) p = 0.004	1.26 (1.07, 1.48) p = 0.006
	Substance misuse	0.81 (0.78, 0.84) p <0.001	0.83 (0.75, 0.91) p <0.001	1.48 (1.24, 1.71) p <0.001

Analysis were adjusted for number of physical diseases and nursing home stay. [1] Sample size restricted to COVID-19 positive cases (n = 46,536), analysis were adjusted by age, sex, number of physical diseases, and nursing home stay. OR: Odd ratio, CI: Confidence Interval, p: p-value

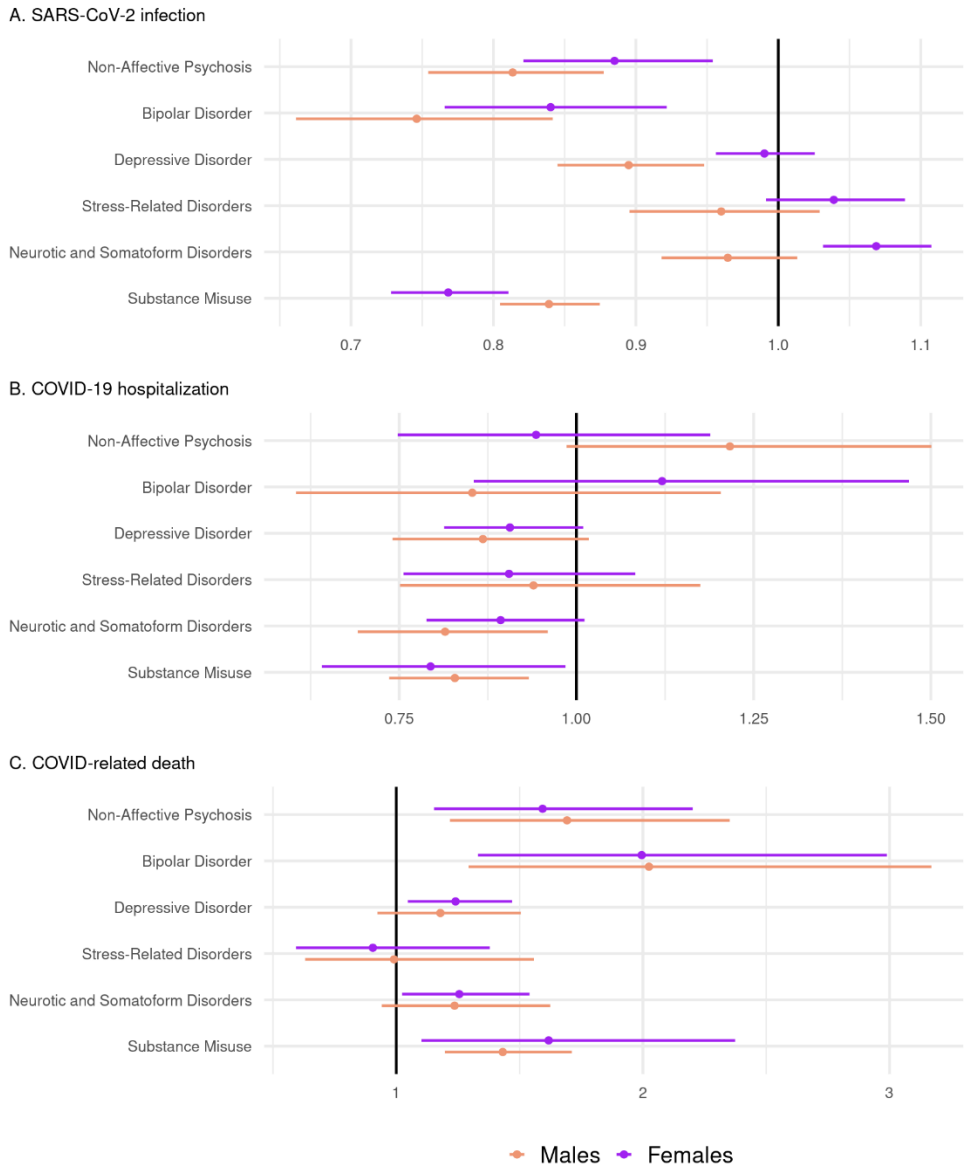

Figure 1. Sex-stratified Forest plots of the association between mental disorder groups and SARS-CoV-2 infection, COVID-19 hospitalization and COVID-19-related death. Figure shows model coefficients in its odd ratio (OR) form. Models were adjusted for physical diseases and nursing homes stay (A) and for age, physical diseases and nursing homes stay (B,C)

DISCUSSION

To the best of our knowledge, this study is one of the largest population-based studies from Europe on the risk of infection and severe COVID-19 outcomes across mental disorders. We found different risks of SARS-CoV-2 infection, hospitalization, and COVID-19-related death across pre-existing mental disorders. In addition, this study is among the few that also explored the role of sex in the association between diverse psychiatric conditions and COVID-19 outcomes.

Our results showed that people with pre-existing non-affective psychosis, bipolar disorder,

depression, and substance misuse had a lower risk of SARS-CoV-2 infection, which is in line with prior studies [26,27]. This reduced risk could be explained by social factors such as the decreased social activity observed in individuals with mental disorders, particularly in individuals with severe mental illnesses like schizophrenia or bipolar disorder [28]. Alternatively, the use of psychotropic drugs such as antidepressants or antipsychotics, which have been reported to reduce the risk of SARS-CoV-2 infection, could also explain these findings [29]. Importantly, it should be noted that other studies reported a heightened risk of infection for these population groups [20,30,31]. One potential factor that could explain divergences across studies might be that, due to their life circumstances, people with pre-existing mental disorders, and especially those with severe mental illness, are more prone to be living in nursing homes, therapeutic communities, or hospitals, where infections can spread more rapidly [32]. However, none of the prior studies accounted for the fact of staying in these facilities. Thus, the increased risk of infection reported in some studies might be biased by the higher rate of people staying in mental health facilities or hospitals.

Conversely, we found a modest increased risk of SARS-CoV-2 infection in people with neurotic/somatoform disorders compared to unexposed, which is in line with findings of an umbrella review reporting a higher risk of infection in people with anxiety [1]. The increased risk of COVID-19 (and other infectious diseases) [33] reported in people with anxiety disorders might be due to a compromised immune system [34], caused by the impact of anxiety-related factors such as high psychological stress or sleep insufficiency on the immune system [33,35]. Alternatively, this increased risk of infection could actually mean a greater inclination towards getting tested due to an exacerbated response to stress [36].

Among those that were infected, we further examined whether there were differences in the risk of COVID-19 hospitalization and COVID-19-related death. We found that, compared to unexposed, people with pre-existing depression, neurotic/somatoform disorder, and substance misuse disorder had a lower risk of COVID-19 hospitalization, but a higher risk of COVID-related death. This decreased risk of hospitalization found in these populations might be explained by a neglect in seeking medical treatment due to a lack of energy, social withdrawal, feelings of hopelessness, and lower self-worth [37–39], which would ultimately lead to an increased mortality. Notably, the increased risk of COVID-19-related death was not exclusive to these diagnostic groups, since we also observed a higher risk of COVID-19-related death in people with non-affective psychosis and bipolar disorder when compared to unexposed. Overall, the increased COVID-19 mortality of people with these mental disorders has been widely reported in literature [13,40,41], with numerous factors contributing to these associations, including a poor socioeconomic status [42], poor lifestyle habits such as smoking or unhealthy diet [10,43], and increased prevalence of comorbid medical conditions [44,45]. Interestingly, all these factors converge to a higher pro-inflammatory state [10,45,46], which seems to be the baseline reason for the increased COVID-19-related death reported in people with these mental disorders [7,10]. Conversely, the increased risk of COVID-19-related death observed for those with neurotic/somatoform disorders in our study contradicts prevailing evidence 1, which indicates that people with pre-existing anxiety face a similar risk of COVID-19-related death than unexposed individuals. As previously mentioned, anxiety disorders have been related to a compromised immune system [34], caused in part by the effects of stress on the immune system [47]. Chronic stress can lead to both pro-inflammatory and immunosuppressive processes, so people with neurotic/somatoform disorders might have a highly heterogeneous immunological dysregulation [48]. A pro-inflammatory environment could lead to higher inflammation levels, what could explain the increased risk of COVID-19-related death found in people with neurotic/somatoform disorders in our study [49]. Furthermore, anxiety has been associated to acute respiratory distress syndrome resulting from viral respiratory infections, which is a risk factor for COVID-19 mortality [33,50,51]. Nevertheless, the divergence of results across studies suggest that further research is needed in order to elucidate the link between neurotic/somatoform disorders and the risk of COVID-19-related death, as well as the biological pathways behind them.

Finally, we explored the role of sex in the associations between the six mental disorders of interest and SARS-CoV-2 infection, COVID-19 hospitalization and COVID-19-related death. Our results showed a higher vulnerability to SARS-CoV-2 infection in women, but not men, with pre-existing neurotic/somatoform disorders, while the decreased risk of infection observed in people with

depression was only present in men. The higher risk of infection found in women with depression and neurotic/somatoform disorders could be explained by a greater inclination of women towards getting tested, which is supported by studies suggesting greater health care-seeking behaviours among women than among men. [52] Furthermore, we found that women with depression and neurotic/somatoform disorders had a significantly higher risk of COVID-19-related death compared to unexposed women, while no significant differences were identified for men. The increased vulnerability to COVID-19-realted death found in women with affective disorders might be influenced by ovarian hormones. Ovarian hormones fluctuations influence susceptibility to stress and inflammatory responses in women, both of which contribute to the risk of affective disorders and COVID-19 [19,53]. For instance, oestrogens dysregulations have been reported in women with affective disorders, which have been reported to stimulate the production of pro-inflammatory cytokines in low concentrations [53]. Moreover, psychological stress can strongly upregulate inflammatory pathways [53]. Indeed, several studies have reported higher inflammation levels in women with depression than men [54], and inflammation is crucial in depression onset in women but not in men [55]. Thus, the higher risk of COVID-19 death found in women with depression and neurotic/somatoform disorders than in unexposed women might be related to higher inflammation levels, which are directly linked to a higher COVID-19 mortality. Nevertheless, it worth mentioning that our results could be influenced by the smaller sample size of men with depression and neurotic/somatoform disorders compared to women. Thus, further studies including a sex-perspective are needed in order to determine whether women with affective disorders present a higher risk of COVID-19-related death, and the underlying factors of this association.

The main strength of the present study is the use of a large database of electronic health records from Catalonia. The use of electronic health records offers the opportunity to generate reliable real-world evidence reflecting routine clinical practice, without being affected by selective participation or recall biases. However, our results should be interpreted in light of several limitations, also related to the data source. First, mental disorders were defined based on ICD9/10 codes in patients who had received specialized inpatient and outpatient mental health care between 2017 and 2019. Thus, we had no information regarding the current symptomatology or severity of the mental disorder. Second, given that our analysis focus on the first wave of the pandemic, hospitalization was defined by ICD-10 codes based on viral respiratory diseases, and not only COVID-19, so misclassification is possible. Nevertheless, it is improbable that this has impacted our results, given the decline in the occurrence of non-COVID-19 respiratory infections throughout the pandemic [56]. Third, we had no information regarding the use of psychotropic drugs, which have been reported to have a protective effect against infection and severe COVID-19 [2,29]. Fourth, we could not include data on lifestyle factors such as smoking, which is a known risk factor for COVID-19 mortality [57] and is strongly associated to some mental disorders [43]. Importantly, it worth mentioning that the associations between pre-existing mental disorders and COVID-19 outcomes are complex and it is likely that multiple genetic factors, social variables and clinical decisions not assessed in the current study may also be important determinants of the disease progression.

Despite the abovementioned limitations, our results suggest different COVID-19 risk profiles across mental disorders. Nevertheless, an increased risk of COVID-19-realted death was found for almost all mental health diagnoses. Moreover, we found that sex influenced the risk of COVID-19 in some psychiatric groups, with women with depression and neurotic/somatoform disorders being especially vulnerable to the disease. Therefore, our results suggest that the type of mental disorder should be considered when addressing the impact of COVID-19 and potential future epidemics on individuals with mental disorders, and highlights the need for tailored public health strategies and medical interventions for individuals with specific mental disorders. Finally, given the complexity of these findings, further research including data from different countries is needed to understand the specific mechanisms linking mental disorders and infectious diseases, also taking into account sex perspectives.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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STUDY II

Genetic analyses point to alterations in immune-related pathways underpinning the association between psychiatric disorders and COVID-19

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Genetic analyses point to alterations in immune-related pathways underpinning the association between psychiatric disorders and COVID-19

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ABSTRACT

Current literature suggests that people with psychiatric disorders have higher risk of COVID-19 infection and a worse prognosis of the disease. We aimed to study the genetic contribution to these associations across seven psychiatric disorders as well as a general psychopathology factor (P-factor), and determine whether these are unique or shared across psychiatric disorders using statistical genetic techniques. Using the largest available genome-wide association studies (GWAS), we found a significant genetic overlap between depression, ADHD, PTSD, and the P-factor with both COVID-19 infection and hospitalization, and between anxiety and COVID-19 hospitalization. We used pairwise GWAS to examine this overlap on a fine-grained scale and identified specific regions of the genome shared between several psychiatric disorders, the P-factor, and COVID-19. Gene-based analysis in these genomic regions suggested possible links with immune-related pathways such as thyroid homeostasis, inflammation, and stress response. Finally, we show preliminary evidence for causal associations between depression, ADHD, PTSD, and the P-factor, and higher COVID-19 infection and hospitalization using Mendelian Randomization and Latent Causal Variable methods. Our results support the hypothesis that the relationship between psychiatric disorders and COVID-19 risk is likely due to shared alterations in immune-related pathways and are not as a result of environmental factors alone, shedding light on potentially viable therapeutic targets.

1. INTRODUCTION

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to an unprecedented global health problem due to the high contagion and mortality rates of the virus, the existence of a persistent form of the disease, known as long COVID, and its impact on mental health. (1–3) Nevertheless, not everyone is equally affected by the disease. One population particularly vulnerable to the effects of COVID-19 disease is people with pre-existing psychiatric disorders. A recent umbrella review showed that this subgroup is more susceptible to SARS-CoV-2 infection, more likely to develop a severe form of the disease, and has a higher risk of COVID-19-related mortality. (4) Moreover, one study including data from different longitudinal studies as well as electronic health records reported poor pre-pandemic mental health as a risk factor for long COVID. (3) However, the association between psychiatric disorders and COVID-19 outcomes is variable. For instance, while evidence supports an increased risk of COVID-19 hospitalization and mortality in people with schizophrenia, mood disorders, and autism spectrum disorders (ASD), (4–6) this is not observed in people with anxiety, (4) and results are

mixed for people with attention deficit and hyperactivity disorder (ADHD) and stress-related disorders. (6–8) Likewise, higher infection rates have been reported in people with anxiety (4,7), while results from recent systematic reviews and meta-analyses did not find significant associations between neurodevelopmental disorders, schizophrenia, and mood disorders, and higher risk of infection. (4,9) These observations indicate that there may be differences in both the susceptibility to COVID 19 and the severity of symptoms experienced in individuals with various psychiatric disorders.

Differences in transmissibility and pathogenicity of SARS-CoV-2 among people with psychiatric disorders might be explained by both psychosocial factors such as cognitive impairment, shared living facilities, psychotropic medication, health behaviours, and biological factors such as sex and genetics. (10–12) Some studies have reported common alterations in biological pathways for psychiatric disorders and COVID-19, (13) which suggests a potential role for shared common genetic risk factors between both conditions. In line with these observations, a genetic predisposition to psychiatric disorders has been associated with COVID-19 infection and hospitalization, (14) and recent studies have reported significant genetic correlations between depression and COVID-19. (15) Despite shared genetic overlap, studies using genetic data have failed to find evidence of causal associations between selected psychiatric disorders and COVID-19 in support of the results obtained in observational studies. (16,17) Additionally, more studies are needed focusing on other psychiatric disorders, such as anxiety, ASD or Post-Traumatic Stress Disorder (PTSD), for which literature is scarce.

While there is some evidence pointing towards shared biological aetiology underpinning the vulnerability to certain psychiatric disorders and COVID-19 outcomes, little is known about which biological pathways or genes may contribute to these observations, or whether these mechanisms are unique or shared across psychiatric disorders. A recent study has identified a number of differentially expressed immune-related genes that are shared across psychiatric disorders such as mood disorders and schizophrenia, and COVID-19. (18) However, no study has yet compared the shared and unique genomic overlap across a wide array of psychiatric disorders and COVID-19, nor investigated the extent of this overlap when examining a general psychopathology factor (P-Factor) and COVID-19.

We aimed to extend current knowledge regarding the genetic links between seven psychiatric disorders, a general psychopathology factor, and COVID-19, and test for any causal associations. To do this we i) examined whether shared genetic factors may underpin differences in transmissibility and pathogenicity of SARS-CoV-2 observed among different psychiatric disorders, ii) identified which specific regions of the genome are shared between each disorder and COVID-19 and iii) tested for causal associations using Mendelian Randomization and Latent Causal Variable (LCV) analysis.

2. METHODS

2.1 Data

2.1.1 Psychiatric disorders

We examined the relationship between seven psychiatric disorders and two COVID-19 traits. We selected traits based on i) results from several epidemiological studies suggesting increased risks of infection and/or severe COVID-19/COVID-19 mortality in individuals with these specific mental disorders and ii) the public availability of moderate- to well-powered genome-wide association studies (GWAS) summary statistics for the disorders. We used the summary statistics from the latest GWAS available of depression (371,184 cases and 978,703 controls), (19) ADHD (38 691 cases and 186 843 controls), (20) ASD (18 381 cases and 27 969 controls), (21) bipolar disorder (41 917 cases and 371 549 controls), (22) schizophrenia (76 755 cases and 243 649 controls), (23) anxiety (25 453 cases and 58 113 controls), (24) and PTSD (137,136 cases and 1,085,746 controls). (25) For further information regarding data acquisition and phenotype definitions for each trait, see the corresponding reference.

2.1.2 COVID-19

We obtained the summary statistics of SARS-CoV-2 infection (159 840 cases and 2 782 977 controls) and COVID-19 hospitalization (44 986 cases and 2 356 386 controls) from the release 7 of the COVID-19 Host Genetics Initiative GWAS meta-analyses, (26) excluding 23andMe Inc. data. Infection cases were defined as individuals with a laboratory confirmed SARS-CoV-2 infection (RNA and/or serology based), a diagnosis of COVID-19 made by a physician or self-reporting a positive COVID-19 test (e.g. through a questionnaire). Hospitalization cases were defined as individuals hospitalized due to COVID-19 related symptoms and with a laboratory confirmed SARS-CoV-2 infection. (27)

2.1.3. P-factor

Given the substantial genetic overlap among the included mental disorders, in order to test the relationship between general psychopathology and COVID-19 infection and hospitalization, we constructed a latent psychopathology (P) factor using a common factor model in genomic structural equation modelling (gSEM). (28) Genomic SEM uses GWAS summary statistics to fit structural equation models based on genetic correlations. To do this, we first estimated a genetic covariance matrix across our seven mental disorders using LD Score regression (LDSC). (29) In the second step, we utilized the usermodel() function in GenomicSEM to specify a common factor model across our seven traits using diagonally weighted least squares (DWLS) estimation.

2.2 Genetic correlations between psychiatric disorders and COVID-19 traits

We estimated genetic correlations between the seven psychiatric disorders of interest, the common P-factor, and COVID-19 infection and hospitalization using LDSC. (29) For all the disorders and COVID-19 phenotypes, we obtained their European-only summary statistics. Significance values were corrected for multiple testing bias using a Bonferroni correction (0.05/14 = 0.003).

2.3 Pairwise GWAS

We used the pairwise GWAS method (GWAS-PW) (30) to identify shared causal risk loci between each of the seven psychiatric disorders, the P-factor, and COVID-19 infection and hospitalization. This method tests four models of local genetic association between two traits to determine the likelihood of a shared genetic signal being truly causal (rather than correlated) in a single analysis. As GWAS-PW directly compares two traits and leverages the observed correlation structure between them at each independent genomic region, this method has increased power to detect causal genetic associations than methods that average genetic covariation across the genome. To do this, GWAS-PW splits the genome into 1703 independent regions and calculates, for each region, the posterior probability of association (PPA) of four different models: (1) the region is unique to the psychiatric disorder, (2) it is unique to the COVID-19 trait, (3) it is shared by both traits through the same causal variants and (4) it is associated with both traits but through independent causal variants. GWAS-PW method needs the correlation between effect sizes in non-associated regions of the genome to avoid potential confounding due to sample overlap between traits. Thus, we used the command-line tool fGWAS, implemented in PW-GWAS, to calculate the PPA for each region separately, for both traits. In order to obtain a proxy estimate of sample overlap, regions with a PPA <0.2 in both traits were selected and the correlation in SNP effect sizes between the two traits was determined and incorporated into the models. We selected those regions with the highest PPA for model 3 (with a cut-off of PPA > 0.5), as we were only interested on those regions shared between the psychiatric disorder and the COVID-19 trait through the same causal variants. An ideogram showing these shared regions was created using http://visualization.ritchielab.org/phenograms/plot.

2.4 Gene mapping of shared regions and drug-gene interactions

We uploaded (31) the summary statistics of the seven psychiatric disorders, the P-factor, and the two COVID-19 traits to the FUMA platform v1.5.4 (31) for putative functional annotation. Then, we

used MAGMA v1.10, a tool for gene-based analysis and generalized gene-set analysis of GWAS data, to map protein-coding genes in the identified regions. (32) A Bonferroni correction was applied (0.05/total number of genes in shared regions). We uploaded the results to Cytoscape software v3.10.0 to create an association network. (33) Finally, the identified genes were uploaded to Drug Gene Interaction Database (DGIdb) (34) to check for potential interactions with drugs.

2.5 Causality tests

We used Mendelian randomization (MR) methods to determine whether any of the psychiatric disorders of interest or the P-factor were causally associated with COVID-19 infection and hospitalization, or if there was evidence of reverse causality. This method identifies causal associations between traits using SNPs that are robustly associated with your exposure trait as instrumental variables (IVs). To be IVs, these SNPs have to be associated with your exposure trait and only be associated with the outcome trait through the exposure. Moreover, these SNPs cannot be associated with a confounding variable (horizontal pleiotropy). The rationale of the method is based on the natural randomization of SNPs happening during meiosis, when the population is divided into case and control groups for a given risk factor based on the genetics of each individual, akin to randomized control trials. Therefore, MR can infer causality because the direction of the effect is clear, going always from the IV to the risk factor. (35)

We used generalized summary-data-based Mendelian randomization (GSMR) for our primary analysis. (36) Using full GWAS summary statistics, GSMR clumps SNPs using a linkage disequilibrium reference panel derived from 50,000 individuals from the UK Biobank while adjusting for heterogeneous SNP-outliers using HEIDI-filtering to provide a single MR estimate, adjusted for pleiotropic effects between traits. (36) Moreover, we performed four different MR analyses (IVW, penalized weighted median, weighted median and weighted mode) as sensitivity analyses. We used Plink to select the IVs through clumping of genome-wide significant SNPs (--clump kb 1000 kb, --clump r2 <0.001), (37) and then we performed the MR analyses using the 'TwoSampleMR' package from MR-Base. (38)

A caveat of traditional MR methods is that the assumptions for instrument selection are often violated when traits have overlapping participants (such as the UK Biobank), leading to correlated horizontal pleiotropy and false positives biased towards the observation. Therefore, we further tested for causality among our traits using a non-MR causality method, Latent Causal Variable (LCV), which is better able to differentiate causal effects from horizontal pleiotropy. LCV does not directly test for causality but rather estimates a 'genetic causality proportion' (GCP) parameter that mediates an association between two traits; a GCP of 0 indicates no causal association and a GCP of 1 indicates partial genetic causality. (39)

2.6 Code Availability

All code used in this study will be made available upon request to the authors.

3. RESULTS

3.1 P-factor creation

We created a common latent psychopathology factor across our seven mental disorders using gSEM. Model fit indices indicated an acceptable model fit (CFI = 0.83; SRMR 0.09) given the substantial heterogeneity across our disorders. The resulting common factor GWAS was highly polygenic (lambda = 1.8; Supplementary figure 1) with 319 genome-wide independent SNPs (using parameters –clump-r2 0.01 and –clump-kb 5000 in Plink; Supplementary Figure 2).

3.2 Genetic correlation analysis

Depression, ADHD, and PTSD were positively correlated with COVID-19 infection (rg DEP = 0.170, SE: 0.038, p = 6.4 x10-6; rg ADHD = 0.274, SE: 0.040, p = 4x10-12; rg PTSD = 0.198, SE: 0.038, p = 1.5x10-7, Figure 1) and COVID-19 hospitalization (rg DEP = 0.179, SE: 0.033, p = 5.5x10-8; rg ADHD = 0.251, SE: 0.041, p = 1.2x10-9, rg PTSD = 0.247, SE: 0.04, p = 2.3x10-9; Figure 1). Anxiety was positively correlated only with COVID-19 hospitalization (rg ANX = 0.145, SE: 0.041, p = 0.0004). Bipolar disorder, schizophrenia, and ASD

were not significantly correlated with either COVID-19 infection or hospitalization. The P-factor was genetically correlated with both infection (rg P-FAC = 0.179, SE: 0.031, p = 1.09 x10-4) and hospitalization (rg P-FAC = 0.226, SE: 0.032, p = 6.8x10-9).

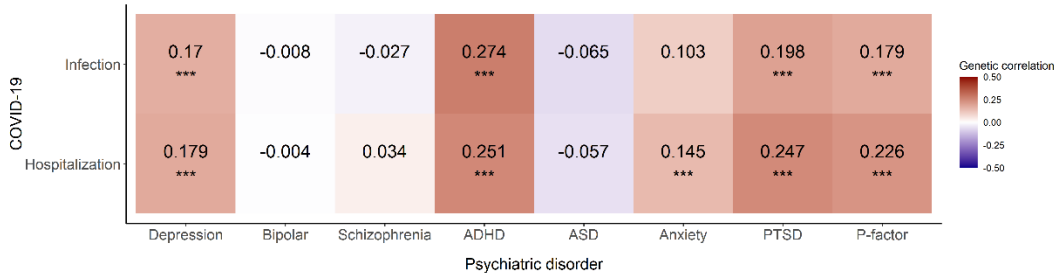

*Figure 1. Genetic correlation estimates between psychiatric disorders, the psychopathological factor (P-factor), and COVID-19 infection and hospitalization. ADHD: Attention Deficit Hyperactivity Disorder, ASD: Autism Spectrum Disorder, PTSD: Post-Traumatic Stress Disorder. ***p-value < 0.001.*

3.3 Pairwise GWAS

We used PW-GWAS to identify the specific regions shared between the seven psychiatric disorders, the P-Factor and COVID-19 infection and hospitalization, regardless of whether a global genetic correlation had been found. Using a PPA cut-off of > 0.5, we identified six different regions of the genome that were causally shared between any of the examined psychiatric disorders and COVID-19 infection, and seven between any of the psychiatric disorders and COVID-19 hospitalization (Supplementary Tables 1-16). Three of these regions were on chromosome 17 (chr17q12, chr17q21.3, chr17q24.1-q24.2), two on chromosome 4 (both in chr4q24), and single regions on chromosome 1 (chr1p31.1), chromosome 7 (chr7p22.1), chromosome 16 (chr16p12.1-p11.2), and on chromosome 19 (chr19q13.32-q13.33) (Figure 2, Supplementary table 15). Interestingly, despite global genetic correlations, we did not identify any shared local genomic regions between ADHD or anxiety, and either COVID-19 infection or hospitalization. On the contrary, despite non-significant global genetic correlations, we found specific shared genomic regions between schizophrenia, bipolar and ASD, and both COVID-19 traits. One region on chromosome 17 (chr17q12) was largely split between being associated with model 3 (PPA: 0.43) and model 4 (PPA: 0.57) for bipolar disorder. Two of the above identified regions were also found to be shared between the P-factor and infection (chr4q24 and chr17q12), and three between the P-factor and hospitalization (chr4q24, chr17q24.2-q24.3, chr7p22.1), indicating common biological pathways shared across both specific and general psychopathology. Additionally, a previously unidentified region on chromosome 9 (chr9p22.2) was found to be shared between the P-factor and hospitalization.

3.4 Gene mapping of shared regions and drug-gene interactions

We mapped SNPs in the identified genomic regions that are shared through the same causal variants to protein-coding genes. Five of our seven psychiatric disorders had significantly enriched genes for at least one of the shared genomic regions after Bonferroni correction for multiple testing. As no shared genomic regions were found between COVID-19 infection or hospitalization, and anxiety or ADHD, these phenotypes were not included in gene-based tests. In total, we identified 23 overlapping genes between any of the psychiatric disorders of interest and either COVID-19 infection or hospitalization, the majority of them mapping to chromosome 17 (Figure 3, Supplementary table 17). Across the seven psychiatric disorders, schizophrenia had the most shared genes with COVID-19 infection and hospitalization (6 and 13 genes, respectively). Bipolar disorder shared genes with COVID-19 infection but not hospitalization. Among the identified genes for COVID-19 infection, PSMD3

was significant for depression, bipolar disorder, and PTSD, while THRA was significant for both depression and bipolar disorder. Among the identified genes for hospitalization, CRHR1, SPPL2C, MAPT, STH, NSF, PLEKHM1, ARL17B, ARHGAP27 and KANSL1 genes were shared between schizophrenia and ASD, and BPTF among depression, ASD, PTSD and the general P-factor. None of the identified genes were significant across all five psychiatric disorders. Results from the gene-based tests for each psychiatric disorder and the P-factor and COVID-19 traits can be found in Supplementary tables 18-29.

Finally, we uploaded the identified genes in DGIdb to search for potential interactions with drugs. Among all 23 genes, CRHR1 was significant for ASD, schizophrenia, hospitalization, and infection (Supplementary table 30). CRHR1 interacted with Verucerfont, Pexacerfont or Emicerfont, CRF1 antagonists that are under investigation as potential treatments for anxious alcoholism, and Fluoxetine, a known antidepressant. On the other hand, CRHR1 also interacted with drugs related to lung diseases such as Budesonide and Triamcinolone, corticosteroids used to treat asthma, and Telavancin, used to treat pneumonia. Furthermore, we found an interaction between THRA (significant for depression, bipolar disorder and COVID-19 infection) and lithium, a mood stabilizer.

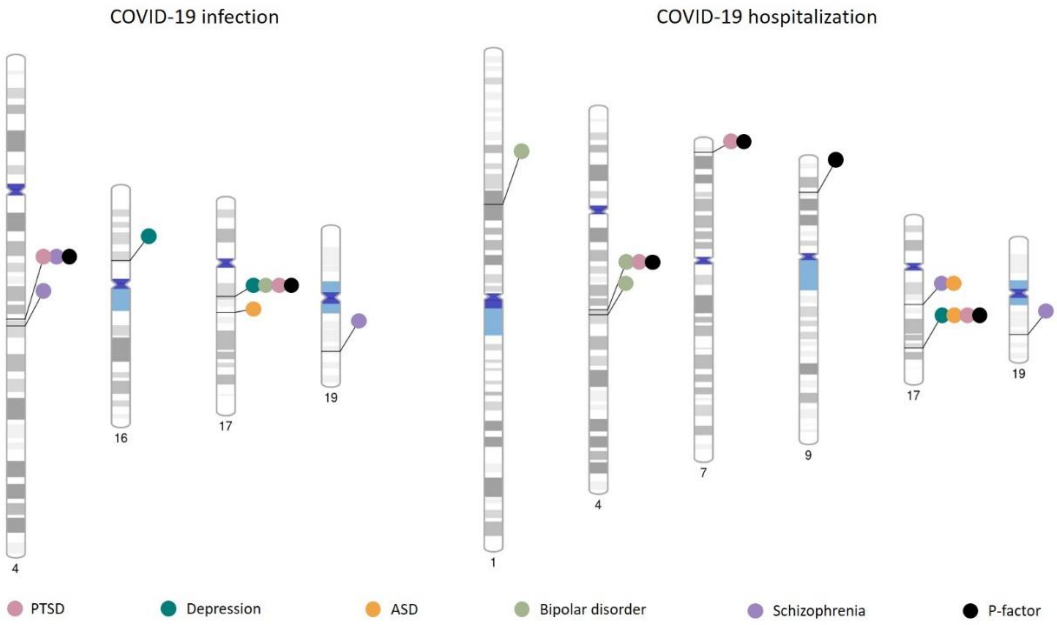

Figure 2. Ideogram showing the chromosomes with their corresponding regions identified by pairwise GWAS as likely to be causally shared between the examined psychiatric disorders and COVID-19 hospitalization and COVID-19 infection, respectively. No regions were identified for anxiety or Attention Deficit and Hyperactivity Disorder. ASD: Autism Spectrum Disorders, PTSD: Post-Traumatic Stress Disorder, P-factor: Psychopathological factor.

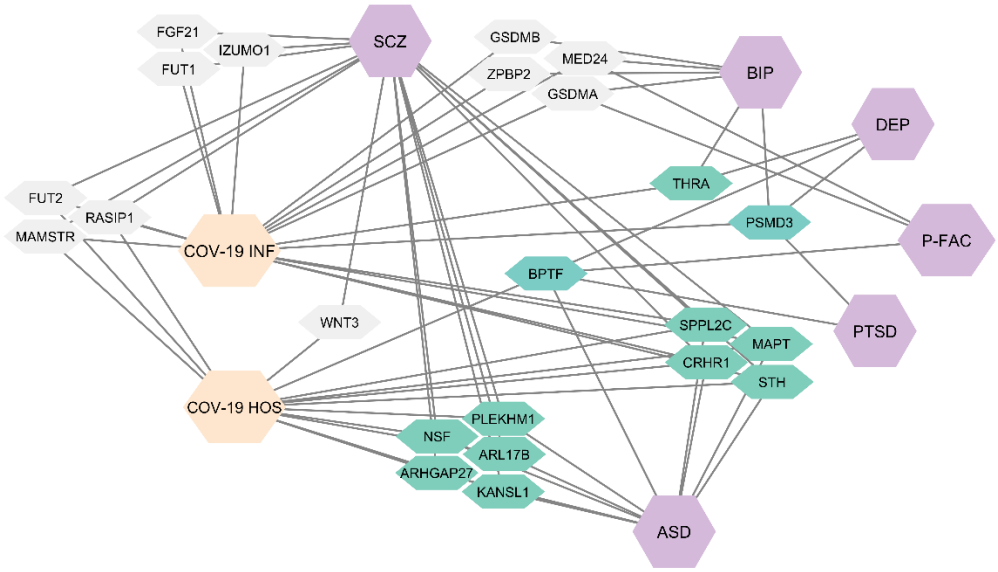

Figure 3. Association network of the significant genes identified in genomic regions shared between COVID-19 infection (COV-19 INF) and COVID-19 hospitalization (COV-19 HOS), and depression (DEP), bipolar disorder (BIP), schizophrenia (SCZ), Post-traumatic stress disorder (PTSD), autism spectrum disorder (ASD), and the psychopathological factor (P-FAC). Highlighted in green are those genes significant for more than one psychiatric disorder.

3.5 Causality Tests

Using GSMR (Instrumental variants shown in Supplementary table 27), we observed a potential causal relationship between genetic risk for depression, ADHD, and PTSD, and COVID-19 infection [ORDEP = 1.07, 95%CI: 1.02-1.13, p = 0.010; ORADHD = 1.03, 95%CI: 1.00-1.06, p = 0.041; ORPTSD = 1.17, 95%CI: 1.05-1.30, p = 0.005] (Figure 4). However, although all MR methods showed an aligned positive effect of depression, ADHD, PTSD and the P-factor on COVID-19 infection, not all MR estimates reached statistical significance (Supplementary table 31). Furthermore, ADHD and PTSD were causally associated with increased COVID-19 hospitalization risk [ORADHD = 1.11, 95%CI: 1.04-1.18, p = 0.001; ORPTSD = 1.65, 95%CI: 1.32-2.07, p = 0.013], while a tendency was observed for depression [ORDEP = 1.11, 95%CI: 0.99-1.24, p = 0.076]. Again, although all MR methods agreed on a positive effect on COVID-19 hospitalization, not all MR estimates reached statistical significance. A potential causal association was also observed between the P-factor and both infection [ORP-FAC = 1.36, 95%CI: 1.12-1.65, p = 0.002] and hospitalization [ORP-FAC = 1.56, 95%CI: 1.03-2.35, p = 0.034], although not all MR estimates validated these results. Remarkably, a significant causal association was observed between bipolar disorder and lower COVID-19 hospitalization [ORBIP = 0.93; 95%CI: 0.88-0.98, p = 0.005]. However, sensitivity analyses did not corroborate this result (Supplementary table 31).

Interestingly, bidirectional GSMR analyses, but not any of the other MR estimates, showed evidence of reverse causality between schizophrenia and COVID-19 infection, indicating that genetic predisposition to COVID-19 infection might influence risk of schizophrenia [ORSCZ = 1.17, 95%CI: 1.04-1.33, p = 0.009], and not the other way around. Evidence of reverse causality was not found for any of the other psychiatric disorders (Supplementary table 31).

As a further sensitivity analysis, we used LCV to test the causal association between genetically correlated disorders and COVID-19 infection and hospitalization (Figure 1; Supplementary table 32).

In line our MR results, we found support of a positive causal effect of mental health disorders on COVID infection and hospitalization, and not the reverse. However, only PTSD and the general P-factor were statistically significantly causal of COVID hospitalization (GCP=0.28, p<0.001 and GCP=0.59, p=0.009 respectively), albeit at weak to moderate proportion estimates. No disorder was significantly causal of COVID infection.

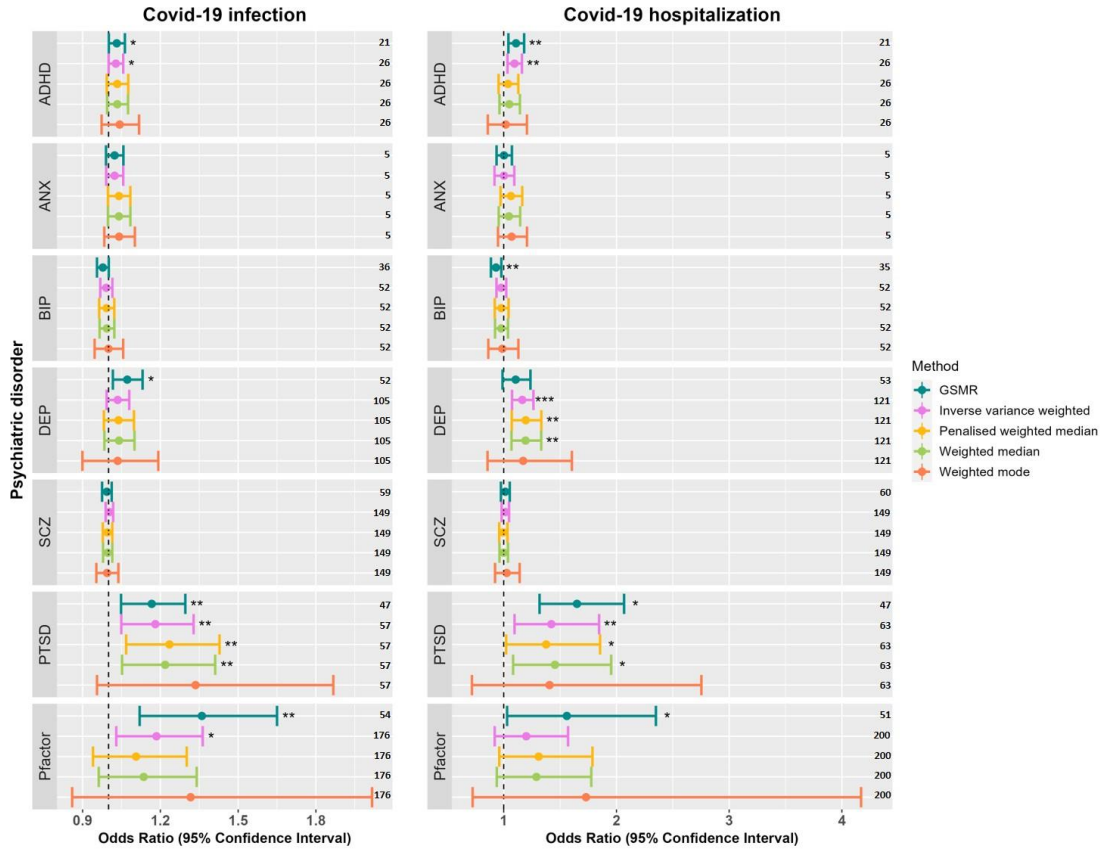

*Figure 4. Mendelian Randomization results for six of the psychiatric disorders of interest and the psychopathological factor (P-factor), and COVID-19 infection and hospitalization. The direction of the association represented is from psychiatric disorder to COVID-19. The numbers on the right of each graph represent the number of SNPs used in the instrument in each method, for each psychiatric disorder. ASD was not included due to the lack of valid instruments to perform the analyses. DEP: depression, BIP: Bipolar disorder, ADHD: Attention Deficit and Hyperactivity Disorder, ANX: anxiety, PTSD: Post-traumatic Stress Disorder, SCZ: Schizophrenia. Bars indicate 95% CIs. *p-value < 0.05, **p-value < 0.01, ***p-value < 0.001.*

4. DISCUSSION

The aim of this study was to examine the genetic relationship between seven psychiatric disorders (depression, bipolar disorder, schizophrenia, ASD, ADHD, anxiety, and PTSD), a general psychopathology factor, and COVID-19 infection and hospitalization using post-GWAS statistical methods. After correcting for multiple testing, we found evidence of significant genetic correlations between depression, ADHD, PTSD, and the P-factor, and COVID-19 infection and hospitalization, as well as between anxiety and hospitalization. While prior studies have reported significant genetic correlations between depression and COVID-19 outcomes, (15) our study is the first to report significant positive correlations between ADHD, anxiety, PTSD, and a general P-factor, and COVID-19. In contrast, we did not find significant

genome-wide genetic associations between bipolar disorder, schizophrenia, and ASD, and any COVID-19 outcome, which is in line with current literature. (40,41)

To further investigate the shared genetic architecture between our psychiatric disorders of interest and COVID-19, we examined local genetic overlap at 1703 independent regions across the genomes. We identified 4 regions that were shared between at least two psychiatric disorders and COVID-19 infection or hospitalization. One of these, located in chromosome 4, was shared between schizophrenia, PTSD, bipolar disorder, and the P-factor, and both COVID-19 outcomes. However, gene-based tests conducted on this region did not reveal any significant gene. The other three regions were located in chromosome 17. We found one region, located in 17q12, for COVID-19 infection, which was shared with depression, bipolar disorder, PTSD, and the P-factor. Gene-based tests revealed the PSMD3 gene, which was significant for the three psychiatric disorders and COVID-19 infection, and the THRA gene, significant for depression, bipolar disorder, and COVID-19 infection. However, none of the two genes were significant for the P-factor. PSMD3, which encodes a proteasome subunit, has been associated with white cell count. (42) However, the role of this gene in psychiatric disorders is still unclear. THRA is a thyroid hormone receptor (THR) gene. (43) THRs are involved in brain development and function, (44) and alterations in THRs, including THRA, have been reported in many psychiatric disorders. (45,46) Interestingly, mutations in THRA have been associated to a reduced white blood cell count (42) and B cell deficiency in mice, (47) suggesting a role in the immune response. Although the exact role of THRA in both mood disorders and COVID-19 infection is unclear, evidence suggests that alterations in THRA could potentially increase the risk of mood disorders while also leading to a compromised immune system, what may underlie, at least in part, the increased risk to COVID-19 infection reported in people with mood disorders in some epidemiological studies. (8) Therefore, further studies are needed in order to elucidate the role of THRA in the interplay between mental disorders and infections.

The other two regions found in chromosome 17 were found for COVID-19 hospitalization. One of them, located in 17q21.31-q21.32, was shared between schizophrenia and ASD. Gene-based analysis conducted on this region identified nine genes that were significantly enriched in schizophrenia, ASD, and COVID-19. These included CRHR1, the corticotropin releasing hormone receptor 1, which plays a role in the hypothalamic-pituitary-adrenal (HPA) axis activation and is crucial in the physiological response to stress. (48) Moreover, CRHR1 is important for the immune response as it exerts both indirect anti-inflammatory effects through the production of cortisol, which supress immune function, and direct proinflammatory effects on immune cells. (49)

Given its role in stress response, CRHR1 has been associated with several psychiatric disorders. For instance, increased methylation levels in CRHR1 have been linked to more negative effects on health care workers' mental health during the COVID-19 pandemic. (50) In addition, alterations in CRHR1 have been linked to higher levels of proinflammatory cytokines in people with schizophrenia. (51) Results from animal studies showed that blockage of CRHR1 receptor in mice infected with streptococcus pneumonia increased neutrophil infiltration in lungs but did not confer resistance to the infection, (52) and mutations in CRHR1 have been associated with neutrophil and lymphocyte count. (53) Neutrophils are important in the fight against pulmonary infections, but dysregulations in neutrophil's function are linked to uncontrolled inflammatory reactions that can result in lung damage and sepsis. (54) Thus, it is possible that in people with psychiatric disorders, and specifically schizophrenia and ASD, alterations in CRHR1 are contributing to the increased hospitalization and mortality reported in observational studies (4) through the dysregulation of neutrophil's function. In order to validate these biological pathways, we sought for drug-gene interactions with the CRHR1 gene. We identified interactions with CRF1 antagonists such as Verucerfont, Pexacerfont or Emicerfont, which are under investigation as potential treatments for stress-induced alcoholism, (55,56) and also with the antidepressant Fluoxetine. Interestingly, Fluoxetine has been reported to exert antiviral and

anti-inflammatory activities against SARS-CoV-2 infection. (57,58) Furthermore, CRHR1 also interacted to Budesonide and Triamcinolone, corticosteroids used to treat asthma, and Telavancin, an antibiotic used to treat pneumonia.

The other region found for COVID-19 hospitalization, located in 17q24.2-q24.3, was shared with depression, ASD, PTSD, and the P-factor. Subsequent gene-based tests revealed the BPTF gene, which was significant for the three psychiatric disorders, the P-factor, and COVID-19 hospitalization. This gene encodes the BPTF transcription factor, which has been reported to be key for T cell homeostasis and function (59). Moreover, BPTF has been related to neurodevelopmental alterations (60), although the role of this gene in specific mental health diagnoses is limited. Hence, evidence indicates a potential involvement of BPTF in both immune and neurological function, potentially contributing to the interplay between infections and psychiatric disorders, thereby potentially warranting further investigation.

These results are further supported by the potential causal associations observed between the P-factor and increased COVID-19 hospitalization and infection, albeit to a lesser extent, which, to the best of our knowledge, no study has reported yet. Moreover, putative causal associations were also identified for depression and PTSD, and increased COVID-19 infection and hospitalization. While prior studies have reported potential causal associations between depression and COVID-19 infection, they failed to identify causality between depression and COVID-19 hospitalization (15,17). Additionally, as far as we know, our study is the first to report a causal association between PTSD and both increased risk of COVID-19 infection and COVID-19 hospitalization, which is in line with epidemiological studies reporting an increased vulnerability to COVID-19 and other infections in individuals with PTSD. (6,61,62)

Surprisingly, despite global genetic correlations, we did not find any genomic region shared between ADHD or anxiety and any COVID-19. The polygenic architecture of these traits might explain the lack of shared genomic regions; while we could observe a strong association at a global level, caused by multiple genes with tiny individual effects, it might be challenging to identify specific genomic regions with substantial effects shared between our traits. Another reason might be the lack of statistical power to detect causal variants in the anxiety and ADHD GWAS, which is key to identify shared genomic regions with confidence. (63) Nevertheless, we observed a potential causal association between ADHD and increased infection and hospitalization of COVID-19, which confirm prior results obtained in smaller samples. (17) Demontis et al., found that almost all variants influencing ADHD also influenced smoking, 79% of which had concordant directions. (20) Given that smoking is a known risk factor for severe COVID-19, (64) it is plausible that the causal association between ADHD and increased hospitalization of COVID-19 is driven by smoking habits rather than by shared genetic causes.

Importantly, we should highlight that all significant genes shared between more than one psychiatric disorder and COVID-19, as well as all genes shared between the P-factor and COVID-19, were located on chromosome 17, specifically in 17q12-q24, a region that has been previously linked to immune response. (65,66) Thus, while different genes have been identified across different psychiatric disorders in relation to COVID-19 infection and hospitalization, our results suggest that altered immune responses may be behind the increased vulnerability of people with psychiatric disorders to COVID-19. These results, if confirmed, might open the way for new targets for suitable transdiagnostic therapeutic approaches.

The main strength of our study is the use of datasets from the largest available GWAS of various psychiatric disorders and COVID-19 traits. Moreover, to the best of our knowledge, it is the first study to explore shared causal risk loci between seven different psychiatric disorders and COVID-19 traits using consistent methodology. However, this study should be considered in the light of several limitations. First, all GWAS results used in this study were obtained from cohorts of European ancestry, so our results might not represent other ancestry groups. Second, the power of the original GWAS is key for most of the analysis performed in our study. Thus, a non-significant result does not necessary reflect a true

lack of association. Third, our study was constrained by the unavailability of sex-specific data, which hindered our exploration of potential sex differences in the genetic associations between the seven psychiatric disorders and COVID-19 infection and hospitalization. Given the reported sex disparities in both psychiatric disorders and COVID-19 outcomes, future investigations should prioritize the inclusion of sex-specific data in order to unravel potential sex-related differences in the genetic underpinnings of psychiatric disorders and COVID-19 outcomes. Likewise, we are missing the role of potential cofounding variables such as BMI or vaccination on COVID-19 infection and hospitalization, which could not be taken into account due to the study design and data availability. Fourth, MR needs a strict list of assumptions to be met and may be biased due to overlapping samples included in the originating GWAS studies, which is challenging when analysing large GWAS studies of polygenic traits. Even though we have endeavoured to include multiple sensitivity analyses, our results may be influenced by existing sample overlap or assumption violation. Finally, our study does not account for complex gene-gene interactions that may play a significant role in the observed relationships between psychiatric disorders and COVID-19.

In conclusion, our results support that the relationship between psychiatric disorders and COVID-19 risk is likely due to shared alterations in immune-related pathways such as thyroid and inflammatory dysfunction, and impaired stress response, and is not as a result of environmental factors alone. A convergence of evidence combining our results with future studies using the constantly evolving statistical genetic methods to examine genetic overlap and causality will further improve the mechanistic insights into the relationship of mental health disorders and infectious disease. Exploring new targets and drug repositioning strategies for medications traditionally employed in the treatment of immune-related disorders holds promising potential to enhance COVID-19 and similar viral infection outcomes among individuals with psychiatric disorders.

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6. DISCLOSURES

The authors declare no competing interests.

Supplementary information is available at MP's website

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STUDY III

The impact of COVID-related perceived stress and social support on generalized anxiety and major depressive disorders: moderating effects of pre-pandemic mental disorders

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The impact of COVID-related perceived stress and social support on generalized anxiety and major depressive disorders: moderating ef ects of pre-pandemic mental disorders

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Abstract

Background: We assessed the moderating ef ect of pre-pandemic mental disorders on the association of COVID-related perceived stress and social support with mental health.

Methods: A nationally representative sample of 3500 Spanish adults was interviewed in June 2020 (mean age 49.25 years, ± 15.64; 51.50% females). Mental health included Generalized Anxiety Disorders (GAD; GAD-7, cut-of point of ≥ 10), Major Depressive Disorders (MDD; PHQ-8, cut-of point of ≥ 10) and the comorbid form (those screening positive for GAD and MDD). COVID-related stress was assessed using an adapted version of the Peri Life Events Scale, and social support using the Oslo Social Support Scale. Logistic regression models were used to assess if COVID-related stress and social support were related to mental health outcomes and interactions were conducted to examine whether these relationships dif ered according to the presence of pre-pandemic mental disorders.

Results: Higher COVID-related stress was associated with a higher risk of lower mental health. The association between COVID-related stress with GAD and MDD was signif cantly moderated by pre-pandemic mental disorders, except for comorbid GAD + MDD. Higher levels of social support were linked to better mental health. Only the association between social support and GAD was signif cantly moderated by pre-pandemic mental disorders. That is, for those without pre-pandemic mental disorders, higher levels of social support decreased the odds of GAD, while minor decreases were observed in those with pre-pandemic mental disorders.

Conclusions: The impact of COVID-related stress and social support on specif c indicators of mental health may vary depending on the existence of a previous mental disorder.

Keywords: Af ective disorders, SARS-Cov2, Psychiatric disorders, COVID-stress syndrome, Social determinants

Background

While societies continue to struggle to slow down the transmission of the SARS-Cov-2 (severe acute respiratory syndrome coronavirus 2), the COVID-19 (coronavirus infectious disease 19) pandemic is expected to have profound and enduring ef ects on mental health. Evidence derived from the f rst wave of COVID-19 suggests

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that there is a widespread emotional distress linked to the COVID-19 pandemic [1–3].

The different epidemic control measures such as lockdown restrictions, schools and business closures, and social distancing have disrupted people's daily lives, and the uncertainties/fears associated with the epidemic and the exceptional control measures have been linked to increases in anxiety and depression, meeting in many cases the threshold for clinical relevance [4–7]. In addition, concerns about fear of infection with COVID-19, the consequences of infection for oneself or loved ones, and the financial instability have also contributed to the increase of anxiety and depressive symptoms [8]. Examining the impact of the pandemic on anxiety and depression is crucial since these disorders are accompanied by substantial disability and high recurrence rates [9–11]. Moreover, they often co-occur [12], and compared to having one disorder alone, this co-occurrence is associated with more severe psychopathology and a poorer clinical course [13, 14].

Previous evidence indicates that people with pre-pandemic mental disorders are more vulnerable to COVID-19-related stress (danger and contamination fears, fears about economic consequences, compulsive checking and reassurance seeking, traumatic stress symptoms about COVID-19) than the general population [15–18], and this may be linked to poorer coping abilities, disruptions to mental health care routines, jeopardizing of treatments, and the associated increases in the risk of relapse or exacerbation of symptoms [17, 19, 20].

On the other hand, social support is known to be a key protective factor for anxiety and depression [21, 22], and it may be particularly important to improve psychological wellbeing and to prevent mental disorders during times of crisis such as the COVID-19 pandemic [23]. For instance, a study with more than 700,000 college students showed that during the disease outbreak, individuals with low perceived social support were 4.8 and 6.0 times more likely to have anxiety and depressive symptoms, respectively, compared to individuals with high perceived social support [24]. Moreover, positive social support has shown to be protective against the risk for affective disorders by buffering the effects of stress and by enhancing coping strategies [25]. However, little is known regarding the moderating effects of pre-pandemic mental conditions on the association between social support and depression and anxiety in the context of COVID-19.

Therefore, the aim of this study is to identify the moderating effect of pre-pandemic mental disorders on the associations of COVID-related stress and social support with those screening positive for Generalized Anxiety Disorder (GAD) and Major Depressive Disorder (MDD), during the first wave of the COVID-19 pandemic. In addition, since anxiety and depression often co-occur [12], a secondary aim of the present study was to assess such associations in those screening positive for depression and anxiety (comorbid form).

Methods

Sample and study design

Data from a cross-sectional survey conducted in a nationally representative sample of the Spanish adult general population were analyzed. The eligible sample consisted of adults aged ≥ 18 years that had no language barriers to Spanish and had access to a mobile phone or landline telephone.

A bureau of professional interviewers conducted computer-assisted telephone interviews from June 1 to June 30, 2020. The sample was drawn using dual-frame random digit dialing, including both mobile (85%) and landline (15%) telephone numbers. First, a sample of Spanish mobile telephone numbers was generated via an automated system. Subsequently, landline numbers were selected from an internal database developed and maintained by the survey company to ensure that all Spanish geographical areas were adequately represented. Up to seven calls were attempted to each number. The sample distribution was planned according to quotas proportional to the Spanish population in terms of age groups, gender and region of residence (National Institute of Statistics in Spain, July 2019). A total of 138,656 numbers were sampled, with a final split of 71% mobile and 29% landline telephones. Of them, 45,002 were non-eligible (i.e., non-existing numbers, numbers of enterprises, numbers of people with Spanish language barriers, fax numbers and numbers belonging to quota that were already completed), and 72,428 had unknown eligibility (i.e., no contact was made after the seven attempted calls). Among the remaining 21.266 eligible numbers, 3500 agreed to participate in the interviews (cooperation rate of 16.5%).

Ethical approval was provided by the Fundació Sant Joan de Déu Ethics Committee, Barcelona, Spain (PIC 86-20) and by the Parc de Salut Mar Clinical Research Ethics Committee (2020/9203/I). Oral consent from all participants was obtained prior to proceeding with the interview.

Risk for screening positive for GAD, MDD and comorbid GAD + MDD (outcome variables)

The Spanish versions of the 7-item Generalized Anxiety Disorder Scale (GAD-7) [26, 27] and the 8-item Patient Health Questionnaire Depression Scale (PHQ-8) [28–30] were employed to screen for GAD (outcome 1) and MDD (outcome 2), respectively. Both scales showed good internal consistencies in our sample (Cronbach's $\alpha = 0.85$ and

0.83, respectively). The recommended cut-off point of ≥ 10 was applied as a diagnostic threshold of GAD and MDD in corresponding scales [26–29]. To address the secondary aim, a dichotomized variable that included those participants screening positive in both scales (GAD-7 and PHQ-8 ≥ 10), versus those who had only depression, only anxiety or none was also created.

COVID-related perceived stress and social support (predictors)

The COVID-related perceived stress was assessed with an adapted version of the Peri Life Events Scale [24, 25], that included 5 items "Concern about being probably infected by COVID-19", "Concern regarding my loved ones being infected by COVID-19", "Death of a loved one due to COVID-19", "Job loss or income reduction due to COVID-19" and "Alarming or negative media reporting about COVID-19". Each item was rated on a 5-point Likert scale ranging from ("none" to "very severe"). The total score was obtained by summing all responses, with higher scores reflecting greater levels of COVID-related perceived stress. (Cronbach's α in the current sample was = 0.76).

The Oslo Social Support Scale (OSSS-3) [32] was used to assess social support. It has 3 items: "How many people are you so close to that you can count on them if you have great personal problems?" ("more than 5", "from 3 to 5", "from 1 to 2", or "none"); "How much interest and concern do people show in what you do?" ("a lot", "some", "uncertain", "little", "none"), and "How easy is it to get practical help from neighbors if you should need it?" ("very easy", "easy", 3 "possible", "difficult", "very difficult"). The total score ranged from 3 to 14, with higher values representing higher levels of social support. (Cronbach's α in current sample = 0.50).

Pre-pandemic mental conditions

The presence of pre-pandemic lifetime mental disorders was assessed using a checklist based on the Composite International Diagnostic Interview (CIDI) that screens for self-reported lifetime depressive disorder, bipolar disorder, anxiety disorders, panic attacks, alcohol and drug use disorders, and "other" mental disorders [33]. A dichotomous variable (Y/N) was created (participants with ≥ 1 pre-pandemic, vs none).

Covariates

Sociodemographic characteristics included age, gender, highest level of education (≤ primary, secondary, ≥ tertiary education), marital status (single, married, divorced/separated, widowed), and employment status (employed, unemployed, student, retired/sick-paid). Also, the number of rooms per person living in the household was calculated by dividing the house size (number of rooms) by the number of people living in it. Health-related covariates included positive diagnosis of the COVID-19 (Y/N) and the presence of chronic physical conditions assessed using 7-item checklists that included diabetes, cancer, cardiovascular diseases, chronic hepatic diseases, immunological diseases, respiratory diseases not caused by COVID-19, and "other" [34]. The answers to these questions were summed and the variable was operationalized as none, 1, and ≥ 2.

Statistical analysis

To ensure sample representativeness and to compensate for potential survey non-response bias, all data were weighted with post-stratification weights to restore the distribution of the adult general population of Spain according to age groups, sex and geographic area. Missing survey data were minimal (median 0.17% [IQR 0.06–0.59%] across all survey variables) and addressed using fully conditional specification methods (FCS) [35]. Simulation studies provide evidence that FCS multiple imputation generally yields estimates that are unbiased and provide appropriate coverage, particularly under missing at random assumption [36]. Descriptive analyses were conducted to characterize the study sample. These analyses included unweighted frequencies and weighted proportions for categorical variables, and mean and standard deviations for continuous variables. The difference in sample characteristics by the three outcomes (GAD, MDD and comorbid GAD + MDD) was tested by Chi-squared tests for categorical variables and Student's t-tests for continuous variables. Cronbach alpha coefficients were computed to estimate the internal-consistency reliability of each scale score. Unadjusted logistic regressions were fitted to test the relationships between pre-pandemic mental disorders, COVID-related stress, social support, and the remaining covariates with MDD, GAD and the comorbid form. Those variables that predicted the outcome ($p < 0.20$) were included in multivariate logistic regression models as covariates [37]. Interactions of pre-pandemic mental disorders with social support and COVID-related stress were tested in separate multivariate logistic regression models for GAD, MDD and the comorbid form as outcomes. Statistically significant interactions ($p < 0.05$) were included in the final multivariate regression models. To clarify statistically significant interaction effects, estimated probabilities of GAD and MDD were calculated based on the adjusted logistic regression models through margins command [38] adjusting for covariates at mean, taking the real proportion in the sample into account.

Results from the regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed with Stata 14.1 (Stata Corp LP, College station, Texas).

Results

A total of 3500 participants aged ≥ 18 years were included in the analysis. The mean age was 49.25 (SD = 15.64) and 51.50% were females. The prevalence of screening positive for GAD, MDD and the comorbid form (GAD + MDD) were 10.9%, 11.3% and 6.63% respectively. Among those without any pre-pandemic mental disorders, the prevalence of GAD, MDD and the comorbid form were 5.6%, 5.9% and 2.96% Among those with pre-pandemic mental disorders the prevalence of screening positive for GAD, MDD and the comorbid form were 21%, 22%and 13.67% respectively. More information on the sample characteristics is provided in Table 1.

Bivariate logistic regression models showed that higher levels of COVID-related stress and having a pre-pandemic mental disorder were significantly associated with increased risk of screening positive for GAD, MDD and comorbid GAD + MDD (for COVID-related stress, OR ranging from 1.14 to1.18, $p < 0.001$; and OR ranging from 4.40 to 5.20, $p < 0.001$ for pre-pandemic mental disorders). Higher levels of social support were related to lower odds of screening positive for GAD, MDD and comorbid GAD + MDD (OR 0.81–0.85, $p < 0.001$). Additionally, being female, being unemployed or a student, and reporting ≥ 2 chronic somatic conditions were common significant risk factors. On the other hand, being older, a higher educational level, and being married were significantly associated with a lower risk of for screening positive on GAD, MDD and comorbid GAD + MDD (Table 2).

Results of the significant interaction effects between pre-pandemic mental disorders, COVID-related stress and social support for GAD, MDD and comorbid GAD + MDD are shown in Table 3. Pre-pandemic mental disorders significantly moderated the relationship with COVID-related stress for GAD and MDD, whereas pre-pandemic mental disorders significantly moderated the relationship between social support and GAD, but not MDD [OR 95%CI 1.00 (0.87–1.13)]. As for the secondary analysis, no significant interactions were found for comorbid GAD and MDD either for COVID-related stress or social support [OR 95%CI 0.95 (0.88–1.02); 1.09 (0.93–1.28), respectively].

Patterns of significant interactions between pre-pandemic mental disorders and COVID-related stress for both GAD and MDD indicated that higher COVID-related stress predicted increased risk of GAD and MDD in both groups (Fig. 1). The pattern of interaction between pre-pandemic mental disorders and social support for GAD showed that among those who had no pre-pandemic mental disorder, higher levels of social support decreased the probabilities of screening positive for GAD, while among those who had a pre-pandemic mental condition, higher levels of social support had very modest decreases in the risk of GAD (Fig. 2).

Discussion

Our study provides an extension of previous evidence by examining the link between COVID-19-related stress and social support with the risk of GAD, MDD and comorbid GAD + MDD. Furthermore, we provided evidence on the moderating effect of pre-pandemic mental conditions in the association between COVID-19-related stress and social support with GAD, MDD and comorbid GAD + MDD.

The present study found that higher COVID-related stress predicted increased risk of GAD, MDD and comorbid GAD + MDD, which is consistent with previous COVID-based evidence [15, 39]. While pre-pandemic mental disorders did not significantly moderated the relationship with COVID-related stress and comorbid GAD + MDD, significant interactions were found for only GAD and only MDD. Similar patterns according to pre-pandemic mental disorders were found, but those with pre-pandemic mental conditions have a higher risk and more steady increases in the odds of screening positive these affective disorders.

These findings are consistent with previous studies demonstrating that people with a pre-pandemic mental health disorder are more negatively impacted by COVID-related stress [15–17], which is correlated with an increased likelihood to be concurrently depressed or anxious [15]. The increased susceptibility of people with pre-pandemic mental disorders to COVID-related stressors might be caused by different factors including the disruption of daily routines and mental health care caused by lockdown and mobility restrictions [19, 20], and a higher difficulty to cope with the COVID-19 pandemic [17]. However, there is conflicting evidence regarding whether there has been an increase in symptoms during the pandemic. For instance, a recent systematic review shows that people with pre-pandemic mental disorders have significantly higher psychiatric symptoms, anxiety symptoms and depressive symptoms compared to controls during a pandemic [40], while others do not report such increases [17]. Future research is warranted to examine the mental health impact and coping mechanisms of those with and without pre-pandemic mental conditions during the COVID-19 pandemic in the medium and long term.

Table 1 Sample characteristics

	Overall (n = 3500)	Outcome 1 GAD yes (n = 395)	Outcome 2 MDD yes (n = 407)	Outcome 3 GAD + MDD yes (n = 242)
Age (years), *n (%)*				
18–34	697 (22.10)	111 (28.10)***	116 (16.18)***	62 (8.53)**
35–54	1501 (38.27)	180 (11.78)	177 (11.55)	112 (7.39)
55–64	680 (15.94)	63 (8.77)	71 (10.09)	43 (6.06)
+ 65	622 (23.68)	41 (6.62)	43 (6.93)	25 (4.02)
Gender, *n (%)*				
Male	1538 (48.50)	119 (7.88)	126 (8.35)	79 (5.15)
Female	1962 (51.50)	276 (13.75)***	281 (13.98)***	163 (8.04)***
Highest level of education, *n (%)*				
≤ Primary	237 (7.65)	40 (15.40)***	40 (15.91)***	27 (10.37)***
Secondary	1856 (52.7)	225 (11.78)	243 (12.52)	145 (7.44)
≥ Tertiary	1407 (39.5)	130 (8.87)	124 (8.65)	70 (4.84)
Marital status, *n (%)*				
Single	1180 (35.3)	161 (13.49)**	174 (14.51)***	99 (8.17)**
Married	1806 (49.7)	175 (9.08)	161 (8.40)	99 (5.14)
Divorced/separated	319 (8.2)	41 (11.86)	51 (14.96)	31 (9.02)
Widowed	195 (6.72)	18 (9.59)	21 (10.61)	13 (6.77)
Employment status, *n (%)*				
Employed	1788 (48.61)	187 (10.42)***	177 (9.89)***	98 (5.44)***
Unemployed	784 (21.67)	116 (14.34)	124 (15.41)	82 (10.20)
Student	131 (4.60)	22 (16.47)	24 (17.79)	13 (9.60)
Retired/sick-paid	719 (25.13)	58 (7.42)	63 (7.88)	39 (4.75)
Number of rooms per person, mean (SD)				
Per unit increase	1.38 (0.83)	1.24 (0.70)***	1.30 (0.79)	1.31 (0.75)
Infection status, *n (%)*				
Negative	3406 (94.46)	381 (10.83)	392 (11.14)	238 (6.72)
Positive	94 (2.54)	14 (13.62)	15 (15.41)	4 (3.34)
N. chronic physical conditions, *n (%)*				
None	2119 (60.30)	208 (9.55)***	208 (9.61)***	123 (5.66)***
1	997 (28.60)	110 (10.49)	122 (11.68)	64 (6.03)
>1	384 (11.10)	77 (19.31)	77 (19.06)	55 (13.49)
Social support[a], mean (SD)				
Per unit increase	11.13 (1.89)	10.57 (2.33)***	10.43 (2.39)***	10.35 (2.45)***
COVID-related perceived stress[b], mean (SD)				
Per unit increase	13.19 (4.91)	16.38 (4.8)***	15.93 (4.88)***	16.68 (4.89)***
Pre-pandemic mental disorder, *n (%)*				
No	2274 (65.65)	134 (5.59)***	136 (5.87)***	70 (2.95)***
Yes	1226 (34.35)	261 (21.06)	271 (21.52)	172 (13.67)

Unweighted frequencies and weighted proportions are displayed for categorical variables. Mean and standard deviation (SD) are shown for continuous variables. Percentages in the overall column show the distribution of the sample, while GAD, MDD and GAD+MDD columns show proportion by sample characteristics. Asterisks ref ect dif erence in sample characteristics by GAD, MDD and GAD+MDD (yes vs no) as indicated by Chi- and Student's *t*-tests. **$p < 0.01$, ***$p < 0.001$

GAD generalized anxiety disorder, *MDD* major depressive disorder, *COVID* coronavirus infectious disease

[a] Scores ranged from 3 to 14 with higher scores representing higher levels of social support

[b] Scores ranged from 5 to 25 with higher scores representing higher levels of perceived stress

With regard to social support, we found that higher levels of social support were related to lower risk of GAD, MDD and the comorbid form, which is consistent with previous evidence conducted in the general population during the f rst wave of the COVID-19 [41–43]. Social support contributes to coping with traumatic

Table 2 Unadjusted logistic regression models of factors related to GAD, MDD and the comorbid form

Characteristic	Outcome 1 GAD	(95%CI)	Outcome 2 MDD	(95%CI)	Outcome 3 GAD + MDD	
	OR		OR		OR	(95%CI)
Age						
18–34	Ref		Ref		Ref	
35–54	0.73*	(0.56, 0.94)	0.68**	(0.52, 0.87)	0.86	(0.61, 1.19)
55–64	0.52***	(0.38, 0.73)	0.58**	(0.42, 0.80)	0.69	(0.46, 1.04)
+ 65	0.39***	(0.26, 0.56)	0.39***	(0.27, 0.56)	0.50**	(0.28, 0.73)
Gender						
Female vs male	1.84***	(1.48, 2.35)	1.78***	(1.42, 2.24)	1.61**	(1.21, 2.13)
Highest level of education						
≤ Primary	Ref		Ref		Ref	
Secondary	0.73	(0.50, 1.07)	0.76	(0.51, 1.11)	0.69	(0.44, 1.09)
≥ Tertiary	0.53**	(0.36, 0.80)	0.50**	(0.34, 0.75)	0.44**	(0.27, 0.71)
Marital status						
Single	Ref		Ref		Ref	
Married	0.64***	(0.51, 0.81)	0.54***	(0.43, 0.68)	0.61**	(0.45, 0.82)
Divorced/separated	0.86	(0.59, 1.26)	1.04	(0.73, 1.50)	1.11	(0.72, 1.72)
Widowed	0.68	(0.41, 1.14)	0.70	(0.43, 1.14)	0.82	(0.44, 1.50)
Employment status						
Employed	Ref		Ref		Ref	
Unemployed	1.43**	(1.12, 1.86)	1.66***	(1.29, 2.14)	1.97***	(1.44, 2.70)
Student	1.70*	(1.04, 2.76)	1.97**	(1.22, 3.17)	1.84	(1.00, 3.42)
Retired/sick-paid	0.69*	(0.50, 0.95)	0.78	(0.57, 1.06)	0.87	(0.58, 1.29)
Number of rooms per person						
Per unit increase	0.77**	(0.65, 0.91)	0.87	(0.75, 1.01)	0.89	(0.74, 1.06)
Infection status						
Positive vs negative	1.30	(0.72, 2.35)	1.45	(0.81, 2.60)	0.49	(0.18, 1.35)
N. of chronic physical conditions						
None	Ref		Ref		Ref	
1	1.11	(0.86, 1.43)	1.24	(0.97, 1.59)	1.07	(0.78, 1.47)
>1	2.27***	(1.68, 3.05)	2.22***	(1.64, 2.98)	2.60***	(1.83, 3.68)
Social support						
Per unit increase	0.85***	(0.80, 0.90)	0.81***	(0.77, 0.86)	0.81***	(0.75, 0.87)
COVID-related perceived stress						
Per unit increase	1.17***	(1.14, 1.20)	1.14***	(1.12, 1.17)	1.18***	(1.14, 1.21)
Pre-pandemic mental disorder						
Yes vs no	4.51***	(3.59, 5.67)	4.40***	(3.51, 5.51)	5.20***	(3.87, 6.99)

GAD generalized anxiety disorder, *MDD* major depressive disorder, *OR* odds ratio, *COVID* coronavirus infectious disease, *CI* confidence interval

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

experiences and it is important for buffering individual psychological responses to life crises [44, 45]. Although the exact pathways through which perceived social support operates to reduce the risk of mental disorders are unclear, several mechanisms have been suggested. First, social support acts as a buffer against the negative impact of COVID-related stressors [39], possibly through the promotion of feelings of security and sense of control over the situation, which may enhance self-esteem and therefore reduce the impact of stress on the psychological adjustment [46, 47]. Additionally, social support may provide protection form stressful events and reduce the affective reaction by attenuating or preventing a stress appraisal [48], by providing distraction from the problem, preventing maladaptive behavioral responses [49] and facilitating health promotion behaviors, factors that may ultimately act on regulating physiological processes [25].

Table 3 Adjusted logistic regression models of factors related to the three outcomes (GAD, MDD and the comorbid form)

	(Model 1) GAD OR (95%CI)	(Model 2) MDD OR (95%CI)	(Model 3) GAD + MDD OR (95%CI)
Social support	0.80 (0.72, 0.88)***	0.84 (0.79, 0.89)***	0.85 (0.79, 0.91)***
COVID-related stress	1.18 (1.13, 1.23)***	1.16 (1.11, 1.20)***	1.15 (1.11, 1.19)***
Pre-pandemic mental disorder	1.59 (0.31, 8.29)	9.65 (4.15, 22.41)***	3.47 (2.52, 4.79)***
Interactions			
Social support * pre-pandemic mental disorder	1.18 (1.04, 1.34)*	–	–
COVID-related stress * pre-pandemic mental disorder	0.94 (0.89, 0.99)*	0.93 (0.88, 0.97)**	–

Models included all variables, significant interaction terms shown in the table and age, gender, highest level of education, marital status, employment status, number of rooms per person, and number of chronic physical conditions.

COVID coronavirus infectious disease, *CI* confidence interval, *GAD* generalized anxiety disorder, *MDD* major depressive disorder

*$p < 0.05$, **$p < 0.01$, ***$p \leq 0.001$

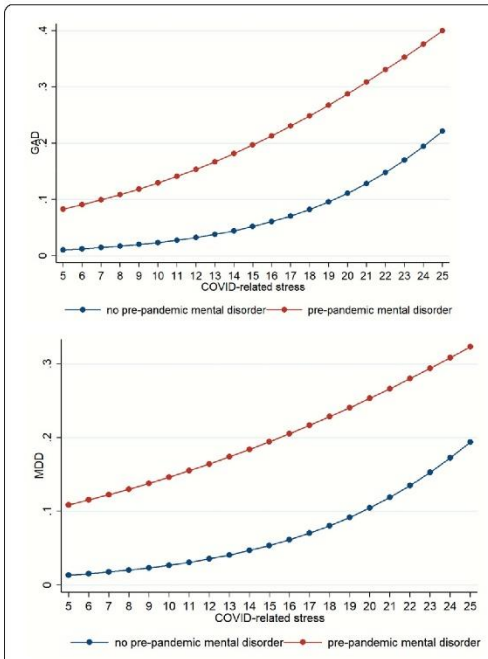

Fig. 1 Probabilities for GAD and MDD according to pre-pandemic mental disorders and COVID-related stress. Estimated probabilities of GAD and MDD were calculated based on the adjusted logistic regression models through margins command [38] adjusting for covariates at mean, taking into account the real proportion in the sample. GAD: generalized anxiety disorder; MDD: major depression disorder, COVID: coronavirus infectious disease

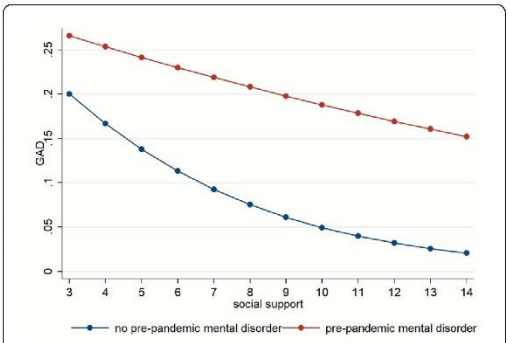

Fig. 2 Probabilities for GAD by pre-pandemic mental disorders and social support according to logistic regression model. Estimated probabilities of GAD and MDD were calculated based on the adjusted logistic regression models through margins command [38] adjusting for covariates at mean, taking the real proportion in the sample into account. GAD: generalized anxiety disorder; MDD: major depression disorder

The presence of pre-pandemic mental disorders did not moderate the relationship between social support and MDD and comorbid GAD + MMD, but a significant interaction was found for GAD. That is, higher social support levels were a protective factor for those with and without pre-pandemic mental condition, but for those with a pre-pandemic mental condition, higher levels of social support were related to very modest decreases in the risk of GAD. It is possible that for those with pre-pandemic mental conditions, other protective/risk factors may be more relevant for preventing the risk of GAD during the COVID-19 outbreak or that they need first to manage their distress or symptomatology before being able to benefit from social support. It is also possible that for people with pre-pandemic disorders it may be more difficult to draw support from their social circles [50] and to socially withdraw, which may ultimately enhance the feelings of loneliness and

subsequently the risk for current GAD. Further longitudinal research is needed in order to better understand the role of pre-pandemic mental conditions in the association between social support and affective disorders in the context of a health crisis. Additionally, digital interventions for vulnerable population groups at risk of worse mental health linked to the COVID-19 are increasing (e.g., those under being infected, and under quarantine) [51, 52], and telehealth and digital interventions could be a useful tool to improve social support and to guarantee that people with pre-pandemic mental disorders have access to their psychological interventions and treatment during a pandemic such as COVID-19 or when social distancing measures are established [53].

The study results should be interpreted in light of several limitations. First, the cross-sectional nature of the study does not allow to infer causal conclusions. Also, given that the course of the pandemic is uncertain, longitudinal evidence assessing multiple time points is warranted to better understand the impact of COVID-19 in population's mental health, and to disentangle the exact contribution of correlates of risk and protection. Second, while the sample is representative of the general population, present findings cannot be generalized to other institutionalized populations as well as other hard to reach groups. Third, the assessment of mental disorders was based on self-reported screening scales (GAD and MDD) and a CIDI checklist (pre-pandemic lifetime disorders), but these assessments are inferior to face-to-face clinical assessments. Forth, in our sample, the OSSS-3 had a lower internal consistency coefficient compared to previous studies (*Cronbach's α* = 0.50 versus 0.64) [32]. A possible reason for this lower value might be due to the use of this scale in the context of COVID-19, in which social relationships were directly affected and for which the scale had not been previously validated. Finally, given the relatively modest sample size of the comorbid MDD + GAD group, it is possible that null results in the interaction analysis for those scoring positive on comorbid GAD + MDD might be underpowered due to the small sample size.

Conclusions

In conclusion, current findings suggest that higher COVID-related stress predicted increased risk of GAD, MDD and comorbid GAD + MDD, with potential greater adverse consequences for those with pre-pandemic mental disorders. In addition, interventions focused on increasing social support to manage psychological distress may be effective in reducing affective disorders, independently of the presence of a pre-pandemic disorder.

Abbreviations

SARS-Cov-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus infectious disease 19; GAD: Generalized anxiety disorder; MDD: Major depressive disorder; GAD-7: 7-Item Generalized Anxiety Disorder Scale; PHQ-8: 8-Item Patient Health Questionnaire Depression Scale; OSSS-3: 3-Item Oslo Social Support Scale; CIDI: Composite International Diagnostic Interview; FCS: Fully conditional specification methods; OR: Odds ratio; CI: Confidence interval.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by PM, GV, MF and JA. Statistical analyses were performed by MFN and JDA. The first draft of the manuscript was written by AMM, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The de-identified participant data as well as the study protocol, statistical analysis plan, and data dictionaries used for this study are available as from publication and upon reasonable request from the corresponding author as long as the main objective of the data sharing request is replicating the analysis and findings as reported in this paper (without investigator support), after approval of a proposal, and with a signed data access agreement.

Declarations

Ethics approval and consent to participate

Ethical approval was provided by the Fundació Sant Joan de Déu Ethics Committee, Barcelona, Spain (PIC 86-20) and by the Parc de Salut Mar Clinical Research Ethics Committee (2020/9203/I) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Oral consent from all participants was obtained prior to proceeding with the interview.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

STUDY IV

Mental health symptoms 1 year after the COVID-19 outbreak in Spain: The role of pre-existing mental disorders and their type

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Mental health symptoms 1 year after the COVID-19 outbreak in Spain: The role of pre-existing mental disorders and their type

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ABSTRACT

Background: The type of pre-existing disorder might determine changes in mental health symptoms (i.e., anxiety, depression) during the COVID-19 pandemic and inf uence the effect of psychological factors (e.g., social support, resilience, stress) on such symptoms.
Methods: Longitudinal data from two assessments (June-2020 and February/March-2021) collected through telephone interviews (Spanish general population) were analysed. Outcome variables included anxiety (GAD-7) and depressive symptoms (PHQ-8). Psychological factors included COVID-perceived stress (adapted COVID-perceived risk scale), social support (OSSS-3), and resilience (CD-RISC). Pre-existing mental conditions (3 groups: mood, anxiety, and comorbid depression+anxiety) were assessed using the CIDI checklist. Changes in anxiety and depressive symptoms between baseline and follow-up were assessed with the paired samples Wilcoxon test. Tobit regression and interaction models were conducted to test associations between psychological factors and these symptoms in follow-up.
Results: Final sample included 1942 participants (mean age 49.6 yrs., ±16.7; 51.7 %females). Anxiety symptoms increased in all groups except for those with pre-existing mood conditions. Depressive symptoms only increased in those without pre-existing mental disorders and in those with pre-existing anxiety. Higher baseline resilience, increases in social support, and decreases in COVID-perceived stress were associated with lower anxiety and depressive symptoms. The type of pre-existing mental disorder did not modify these associations.
Limitations: Lack of pre-pandemic data and the limited number of pre-existing mental conditions.
Conclusions: Having pre-pandemic mental disorders is associated with different patterns of anxiety and depressive symptoms during the pandemic. COVID-related stress, social support, and resilience are key factors in improving mental health regardless of the mental diagnosis.

1. Introduction

In addition to being a public health emergency, COVID-19 has also had a detrimental impact on global mental health (González-Sanguino et al., 2020; Vindegaard and Benros, 2020; Wang et al., 2020; Wu et al., 2021). In general, the evidence indicates that compared to pre-pandemic data, a notable increase in the prevalence of mental health symptoms was observed during the early phase of the global pandemic

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(March–July 2020) (Cénat et al., 2021; Schafer et al., 2022; Wu et al., 2021). Nonetheless, according to a recent meta-analysis of longitudinal cohort studies (n = 65 studies), this increase was short-lived and by mid-2020 mental distress decreased to pre-pandemic levels for most symptom types (anxiety symptoms and general mental health, but not for depressive symptoms) (Robinson et al., 2022).

People with pre-existing mental disorders are not only at increased risk for COVID-19 infection (Taquet et al., 2021), but are also particularly vulnerable to the mental health threat of the pandemic (Moreno et al., 2020). Indeed, several studies conducted during the COVID-19 pandemic outbreak stated that having a pre-existing mental disorder was a risk factor for increased levels of anxiety and depression (Fancourt et al., 2021; Vindegaard and Benros, 2020; Xiong et al., 2020) and that there might be a differential mental health impact across types of pre-existing mental problems (Tamsyn et al., 2020). In addition, there is some longitudinal evidence suggesting that the type of pre-existing mental disorder could predict different levels or changes of anxiety and depressive symptoms over the course of the pandemic. For instance, a study conducted in Germany in March–June 2020 (n = 2376) found that depressive and anxiety symptoms were greater in individuals with comorbid depression and anxiety (D + A) than in individuals with pure anxiety or depression (Bendau et al., 2021). However, most of the evidence is based on the f rst phase of the pandemic, and longer longitudinal studies are needed to determine the middle-term implications of the COVID-19 pandemic on the population's mental health and, particularly, on those with pre-existing mental health conditions.

Previous studies have identif ed a variety of psychological factors that may be key determinants for maintaining psychological health during the COVID-19 pandemic such as lower levels of COVID-19 stressors (Abdalla et al., 2021), and greater social support and resilience (Chen et al., 2021; Guo et al., 2021; Liu et al., 2020). Nevertheless, while the signif cance of these psychological factors during the COVID-19 pandemic is well established for the general population (Seraf ni et al., 2020), relatively little is known about their clinical signif cance in patients with pre-existing disorders, and how these may differ according to psychiatric diagnosis. For instance, one study reported that people with pre-existing anxiety-related disorders had higher COVID-related stress than those with mood disorders and no mental disorders during the COVID-19 outbreak (Asmundson et al., 2020). However, it is not well understood whether the type of pre-existing disorder may inf uence the association between psychological factors and mental health outcomes (i.e., anxiety and depressive symptoms). These are important research gaps, since the identif cation of these factors is essential to the design of transdiagnostic or disorder-specif c intervention strategies.

In this context, the aim of this study was to examine whether the type of pre-existing mental disorder moderated changes and levels of anxiety and depressive symptoms from June 2020 (baseline) to February–March 2021 (follow-up). In addition, we aimed to determine whether the type of pre-existing mental disorder inf uenced the associations between the aforementioned psychological factors (COVID-related stress, social support, resilience), and anxiety and depression at follow-up.

2. Methods

2.1. Study design and population

The MINDCOVID research project includes a population-based survey of adults residing in Spain; it aims to study the impact of the COVID-19 pandemic on mental health ("MINDCOVID project", 2020). The current analysis was based on two consecutive assessments: baseline (June 1–30, 2020) and follow-up (February 18–March 12, 2021). The f rst assessment took place at the end of lockdown in Spain, when COVID-19 infection and mortality rates were low and most of the restrictions had been lifted. Conversely, the second assessment took place at the end of the third wave of infection in Spain. In that period, people had experienced two waves of high infection and mortality rates, tight restrictions were still on (e.g., curfew and limited geographical mobility), and the vaccination campaign had started. Full details of the surveys and their sampling procedure have been described elsewhere (Domènech-Abella et al., 2021; Mortier et al., 2021). In brief, the eligible sample consisted of non-institutionalized adults aged ≥18 that had no language barriers to Spanish and had access to a mobile phone or landline telephone. Baseline assessment and follow-up were conducted by professional interviewers via computer-assisted telephone. For baseline, the sample was drawn using dual-frame random digit dialling including mobile and landline. The sample distribution was planned according to quotas proportional to the Spanish population in terms of age group, gender, and region of residence, with all regions represented (National Institute of Statistics in Spain, July 2019). The cooperation rate (i.e., the proportion of individuals interviewed among all eligible callers) was 16.5 %. Of those who took part at baseline (n = 3500), 57 % completed the follow-up survey (n = 2000). Ethical approval was obtained from corresponding research committees, and oral consent was obtained from all participants.

2.2. Depressive and anxiety symptoms (outcome variables)

The Spanish version of the 7-item Generalized Anxiety Disorder Scale (GAD-7) (García-Campayo et al., 2010; Spitzer et al., 2006) was employed to screen for anxiety. GAD-7 scores range from 0 to 21, with higher scores indicating higher levels of anxiety symptoms. The Spanish version of the Patient Health Questionnaire Depression Scale (PHQ-8) (Kroenke et al., 2009; Muñoz-Navarro et al., 2017) was used to assess depressive symptoms, with higher scores indicating greater depressive symptoms (range 0–24). Anxiety and depressive symptoms were measured both at baseline and in follow-up.

2.3. Pre-existing mental health conditions

The presence of pre-existing mental disorders was assessed using a checklist based on the Composite International Diagnostic Interview (CIDI) (Kessler and Üstün, 2004), which screens for self-reported lifetime depressive disorder, bipolar disorder, anxiety disorders, panic attacks, alcohol and drug use disorders, and other mental disorders. A 4-level variable was created for the type of pre-existing disorder: no disorder, only mood disorders (depressive and/or bipolar disorders), only anxiety disorders (including crisis and/or panic attacks), and comorbid D + A (depressive and anxiety disorders). Those with pre-existing substance abuse disorders, comorbid bipolar and anxiety disorders, and other mental disorders were excluded from the current study due to the small sample size (n = 36, n = 8 and n = 14, respectively).

2.4. Psychological factors and covariates

COVID-perceived stress was assessed at baseline and in follow-up using an adapted version of the COVID-19 perceived risk scale (Wu et al., 2009), which included 4 items related to concerns about being infected, infecting loved ones, dying due to COVID-19, and loved ones' concerns about infecting them. Each item was rated on a 5-level scale ranging from very intense to no stress. The total score was obtained by adding all responses (0–16), with higher scores ref ecting greater levels of COVID-perceived stress. Social support was also assessed both at baseline and in follow-up, using the 3-item Oslo Social Support Scale (OSSS-3) (Kocalevent et al., 2018) (range 0—11), with higher scores representing higher levels of social support. Lastly, resilience was evaluated only at baseline using the 10-item Connor-Davidson Resilience Scale (CD-RISC), in which higher scores represent greater resilience (range 0–40). The authors describe resilience as personal qualities that enable a person to thrive in the face of adversity (Connor and Davidson, 2003).

To account for changes in the COVID-perceived stress and the social support between the two time points, the variables "change in COVID-

perceived stress" and "change in social support" were calculated as the difference between the levels of COVID-perceived stress in follow-up and at baseline, and the levels of social support in follow-up and at baseline, respectively. Thus, positive values for these variables indicate increases in COVID-perceived stress and social support, respectively. The included covariates were age at baseline and gender.

2.5. Statistical analysis

To compensate for potential survey non-response bias in follow-up and ensure sample representativeness, data were weighted with inverse probability weights (IPW) (Seaman and White, 2013), obtained as the inverse of the probability of completing the follow-up survey on observed related baseline covariates, estimated using a logistic regression model, and with post-stratif cation weights to restore the distribution of the adult general population of Spain according to age groups, sex and geographic area. Missing item-level data were minimal (6.5 %) and were addressed using multivariate fully conditional specif cation methods, where imputations for each variable were created by drawing from iterated conditional models (van Buuren, 2018). No signif cant differences in demographic characteristics were observed between participants with complete data and those excluded because of missing data.

Descriptive analyses were conducted to characterize the study sample. These analyses included unweighted frequencies, weighted proportions, and weighted mean age and standard deviation. The paired samples Wilcoxon test was used to determine whether there were signif cant differences in anxiety, depressive, COVID-perceived stress, and social support levels between the two waves of data collection.

Tobit models are suitable to test for dependent variables which are not normally distributed, and a large number of responses are piled up at the lowest or highest values due to insuff cient range of measurement of the given instrument (McBee, 2010). The model yields theoretically continuous values normally distributed through maximum likelihood estimates for censored values while using a standard linear model for the remaining values (Long, 1997). In our case, the Tobit approach assumes that several responses are censored at the lowest value because the measured categories are not suff ciently detailed to detect latent values in anxiety and depression scales. Approximately 17.2 % of our sample accumulated at the lowest score of anxiety or depression (0), and around 41.8 % among the three lowest values (0, 1 and 2). The rest of the sample was distributed among the remaining values, and the frequencies gradually decreased towards the highest values (21 for GAD-7 and 24 for PHQ-8).

First, univariate Tobit regression models were performed to analyse the unadjusted associations between the two outcomes (anxiety and depressive symptoms at follow-up) and the following variables: age, gender, type of pre-existing mental disorder, change in COVID-perceived stress, and change in social support and resilience (all of them adjusted by outcomes at baseline). Then, to analyse the inf uence of the type of pre-existing mental disorder on the outcomes, multivariate Tobit regression models were run adjusting for age, gender, and baseline levels of anxiety and depressive symptoms.

Finally, to determine whether the type of pre-existing mental disorder modif ed the association between the psychological factors and anxiety and depressive symptoms in follow-up, several interactional models were run for depressive and anxiety symptoms separately, as follows: resilience*pre-existing mental disorder, change in social support*pre-existing mental disorder, and change in COVID-perceived stress*pre-existing mental disorder. Models for change in COVID-perceived stress and change in social support were also adjusted for baseline COVID-perceived stress and baseline social support, respectively. Results from Tobit regression models are presented as unstandardized coeff cients and standard errors (SE).

The level of statistical signif cance was set at $p < 0.05$. Statistical analyses were performed with Stata 14.1 (Stata Corp LP, College Station, Texas) and R (version 4.1.0).

3. Results

The f nal sample included 1942 participants who completed both assessments. The socio-demographic characteristics of the study sample are shown in Table 1. 67 % of individuals reported no pre-existing mental disorders, 3.6 % reported having pre-existing mood disorders, 20.4 % pre-existing anxiety, and 9 % comorbid D + A. Mean age was 49.6 years (SD: 16.7), and 51.7 % were female.

Anxiety and depressive symptoms signif cantly increased from baseline to follow-up. Nevertheless, as illustrated in Fig. 1, after stratifying for each type of pre-existing mental disorder we observed that not all the subgroups experienced an increase in symptoms. A statistically signif cant increase in anxiety levels was observed for those with anxiety disorders, comorbid D + A, and no pre-existing mental disorder, but not for those with mood disorders. Regarding depressive symptoms, only those with no pre-existing disorder and pre-existing anxiety experienced a signif cant increase in symptomatology. Median difference of anxiety and depressive symptoms between baseline and follow-up for each type of pre-existing disorder is also represented in Supplementary Fig. 1.

Results of univariate analysis are presented in Supplementary table 1. Table 2 presents multivariate models of the associations between type of pre-existing mental disorder, and anxiety and depressive symptoms at follow-up, adjusting for covariates. Compared to those with no pre-existing mental conditions, having pre-existing anxiety disorders and pre-existing comorbid D + A were factors signif cantly associated with higher levels of anxiety symptoms. Having a pre-existing mood disorder was not signif cantly associated with anxiety. Furthermore, all types of pre-existing mental disorders were signif cantly associated with higher levels of depressive symptoms, compared to those with no pre-existing mental disorder. For both outcomes, those with comorbid D + A were the group with the strongest associations.

The multivariate models including the psychological factors are presented in Table 3. We found that increases in COVID-perceived stress (from baseline to follow-up) (model A) were associated with higher anxiety and depressive symptoms at follow-up. Similarly, decreases in social support between baseline and follow-up (model B) were associated with higher anxiety and depressive symptoms at follow-up. The interactions between these factors and the type of pre-existing mental disorders for anxiety and depressive symptoms were not signif cant (Supplementary table 2). Furthermore, we found that greater resilience (at baseline) was negatively associated with higher anxiety and depressive symptoms at follow-up (model C). An interaction tendency was found towards a different effect of resilience in anxiety symptoms for those with pre-existing mood disorders (Supplementary table 2). No signif cant interactions were found between resilience and the type of pre-existing mental disorders for depressive symptoms.

4. Discussion

This longitudinal study expands upon previous evidence by assessing levels of and changes in current anxiety and depressive symptoms according to the type of pre-existing mental disorder, a year after the COVID-19 outbreak in Spain. Furthermore, we provided evidence regarding the role of COVID-perceived stress, social support, and resilience on anxiety and depressive symptoms, according to the type of pre-existing mental disorder.

4.1. Changes in anxiety and depressive symptoms by type of pre-existing mental condition

Our results show that levels of anxiety and depressive symptoms signif cantly increased from baseline (June 2020) to follow-up (February–March 2021) for the overall sample. After stratifying by type of pre-existing mental disorder, all groups showed increased levels of anxiety

Table 1
Characteristics of study population.

		Overall (*n* = 1942)	No disorder (*n* = 1303)	Pre-existing anxiety (*n* = 397)	Pre-existing mood disorders (*n* = 70)	Pre-existing D + A (*n* = 172)
Age, *mean* (SD)		49.5 (16.70)	50.78 (16.85)	43.67 (15.83)	56.33 (13.98)	51.05 (15.28)
Gender, *n* (%)	Male	861 (48.30)	629 (48.27)	149 (42.47)	30 (47.19)	53 (33.96)
	Female	1081 (51.70)	674 (51.72)	248 (57.53)	40 (52.81)	119 (66.04)
COVID-perceived stress, *mean* (SD)	Baseline	5.02 (3.64)	4.8 (3.63)	5.7 (3.57)	4.49 (3.62)	5.37 (3.60)
	Follow-up	4.52 (3.47)***	4.28 (3.39)***	5.16 (3.51)*	4.29 (3.6)	4.94 (3.73)
Social support, *mean* (SD)	Baseline	8.13 (1.86)	8.28 (1.76)	7.93 (1.99)	7.92 (1.77)	7.58 (2.12)
	Follow-up	7.97 (1.96)***	8.12 (1.90)***	7.85 (1.84)	7.61 (2.33)	7.28 (2.31)
Resilience, *mean* (SD)	Baseline	33 (6.00)	33.79 (5.72)	31.91 (5.66)	32.32 (5.80)	29.95 (7.33)
Outcomes						
Anxiety symptoms, *mean* (SD)	Baseline	3.45 (4.07)	2.62 (3.44)	4.76 (4.20)	4.24 (4.40)	6.38 (5.52)
	Follow-up	4.12 (4.46)***	3.33 (3.96)***	5.27 (4.60)*	4.78 (4.99)	7.15 (5.50)*
Depressive symptoms, *mean* (SD)	Baseline	3.79 (4.44)	2.86 (3.79)	4.94 (4.20)	5.18 (4.91)	7.59 (6.24)
	Follow-up	4.34 (4.71)***	3.47 (4.21)***	5.44 (4.72)*	5.84 (4.95)	7.64 (5.86)

Unweighted frequencies and weighted proportions are displayed for categorical variables. Weighted mean and standard deviation (SD) are shown for continuous variables. Differences between baseline and follow-up variables (*p* values) were obtained with the paired samples Wilcoxon test. D + A: Depression and anxiety.

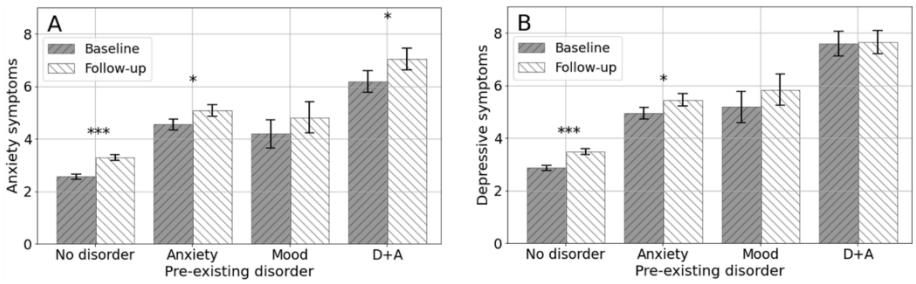

Fig. 1. Mean anxiety symptoms (A) and mean depressive symptoms (B) in the two waves of data collection by type of pre-existing mental disorder. Error bars show standard errors of the means. *P*-values were obtained with the paired samples Wilcoxon test, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Anxiety symptoms were measured with GAD-7; depressive symptoms were measured with PHQ-8. D + A: depression and anxiety.

Table 2
Adjusted Tobit regression models of the associations between type of pre-existing mental disorder, and anxiety and depressive symptoms.

	Anxiety symptoms Coef (SE)	p-Value	Depressive symptoms Coef (SE)	p-Value
Type of pre-existing mental disorder				
No disorder	Ref		Ref	
Anxiety	0.70 (0.27)	0.009	0.94 (0.28)	0.001
Mood disorders	1.01 (0.55)	0.067	1.60 (0.59)	0.007
Comorbid D + A	2.00 (0.37)	<0.001	1.89 (0.40)	<0.001

Unstandardized coeff cients with the Standard Errors (SE) are displayed. Analyses were adjusted for age, gender, and baseline levels of anxiety and depression, respectively. D + A: Depression and anxiety.

and depressive symptoms, but the increases did not reach statistical signif cance for all groups. Those with no pre-existing mental disorders and those with pre-existing anxiety showed signif cant increases in both anxiety and depressive symptoms. Those with pre-existing comorbid D + A had signif cantly increased anxiety symptoms only, while those with pre-existing mood disorders did not show signif cant increases either in anxiety or depressive symptoms.

These results contradict the f ndings of prior studies reporting a progressive decrease in mental health symptoms over the course of the pandemic in people with pre-existing affective disorders (Bartels et al., 2022; Bendau et al., 2021). One way to explain these divergent f ndings is related to the timing of data collection points and the associated evolution of the pandemic. Some authors have suggested that mental health symptoms might f uctuate following the COVID-19 pandemic waves (i.e., infection and mortality rates) (Santomauro et al., 2021), and associations between periods of tighter containment measures and worsening of mental health symptoms have been reported (Pedersen et al., 2022). In this study, baseline data collection occurred after the devastating f rst wave of infection, at the end of the lockdown in Spain. During this period, infection and mortality rates were much lower compared to the outbreak (140 vs 5300 mean weekly conf rmed deaths) (Spain - WHO Coronavirus (COVID-19) Dashboard, 2022), an easing of restrictive control measures was occurring, and there was a general optimistic thinking concerning the pandemic. Follow-up data were collected at the end of the third COVID-19 wave in Spain. In this period people had experienced two waves of high infection and mortality rates, which were still quite high at the time of data collection (1260 mean weekly conf rmed deaths) (Spain - WHO Coronavirus (COVID-19) Dashboard, 2022). Furthermore, tight restrictions were still on (e.g., curfew and limited geographical mobility), and the vaccination campaign had started. Therefore, the observed increase in mental health symptoms in most groups might be explained by the worsening of the epidemiological situation that occurred during the specif c data collection periods.

Beyond potential explanations linked to data collection points, those with pre-existing anxiety might experience increased mental health symptoms (i.e., anxiety and depressive symptoms) for several reasons. First, their elevated tendency to overestimate threat (Abramowitz and Blakey, 2020) and their lower tolerance of uncertainty (Carleton et al., 2012; Gu et al., 2020) could be key contributing factors in explaining

Table 3
Adjusted Tobit regression models for each psychological factor between these factors and the type of pre-existing disorder for anxiety and depressive symptoms.

		Anxiety symptoms Coef (SE)	*p* value	Depressive symptoms Coef (SE)	*p* value
Model A					
Change in COVID-perceived stress		0.43 (0.03)	<0.001	0.37 (0.03)	<0.001
Pre-existing mental disorder	No disorder	Ref		Ref	
	Anxiety	0.61 (0.25)	0.015	0.81 (0.27)	0.003
	Mood disorders	1.12 (0.52)	0.033	1.69 (0.57)	0.003
	Comorbid D + A	2.07 (0.35)	<0.001	1.92 (0.39)	<0.001
Model B					
Change in social support		−0.20 (0.07)	0.002	−0.24 (0.07)	0.001
Pre-existing mental disorder	No disorder	Ref		Ref	
	Anxiety	0.65 (0.26)	0.015	0.92 (0.28)	0.001
	Mood disorders	0.89 (0.55)	0.106	1.53 (0.59)	0.010
	Comorbid D + A	1.83 (0.37)	<0.001	1.79 (0.40)	<0.001
Model C					
Resilience		−0.07 (0.02)	<0.001	−0.11 (0.02)	<0.001
Pre-existing mental disorder	No disorder	Ref		Ref	
	Anxiety	−0.27 (1.49)	0.854	0.85 (1.59)	0.594
	Mood disorders	−5.41 (3.17)	0.088	−3.13 (3.32)	0.346
	Comorbid D + A	−0.92 (1.60)	0.565	−1.35 (1.71)	0.430

Unstandardized coeff cients with Standard Errors (SE) and p-values are displayed. Analyses were made separately for each psychological factor and adjusted for age, gender, type of disorder, and baseline anxiety or depressive symptoms. COVID-perceived stress and change in social support regression models were also adjusted for baseline COVID-perceived stress and baseline social support, respectively. D + A: depression and anxiety.

increases in their symptomatology during periods of high COVID-19 incidence and restrictive measures (i.e. follow-up). Related to this, one study conducted at the beginning of the pandemic suggested that those with pre-existing anxiety were more likely to make efforts to cope with the COVID-19 stressors (Asmundson et al., 2020). However, it is possible that these efforts were directed towards maladaptive coping strategies (Penley et al., 2020), or that, due to pandemic stressors becoming chronic over time, coping mechanisms that were effective at baseline were no longer effective in follow-up, which may ultimately have led to a worsening of mental distress symptoms.

We found that those with pre-existing mood disorders did not show signif cantly increased mental health symptoms. This is seemingly the result of the limited sample size of this group (n = 70) as similar increases in both anxiety and depressive symptoms between baseline and follow-up were statistically signif cant for those with no disorder and the group with pre-existing anxiety.

Finally, those with pre-existing comorbid D + A showed increases in anxiety symptoms, but depressive symptoms remained high and stable. When depression and anxiety symptoms occur together, the severity and the chronicity of each disorder increases, recovery slows, and the likelihood of recurrence increases (Choi et al., 2020; Hirschfeld, 2001). This suggests that people with pre-existing comorbid D + A are at a greater risk of suffering the mental health impact of the pandemic. Their increased vulnerability, together with a worse response to psychosocial and pharmacological treatments (Coplan et al., 2015), greater utilization of medical services, and higher treatment costs (McLaughlin et al., 2006), all suggest that people with comorbid D + A require special attention during a prolonged stressful situation such as a pandemic.

While our results provide evidence regarding the middle-term impact of the COVID-19 pandemic on those with pre-existing mental disorders, further research is needed to elucidate the complete courses of mental health symptoms during the entire duration of the COVID-19 pandemic in relation to pre-existing mental conditions.

4.2. Psychological factors related to changes in mental health over time

As for psychological factors, we observed that after adjusting for confounders and type of pre-existing disorder, COVID-perceived stress predicted higher levels of anxiety and depressive symptoms, while resilience and social support were protective factors. This is in line with previous evidence from studies of the general population (Coiro et al., 2021; Grey et al., 2020; Haliwa et al., 2021; Ran et al., 2020), and it suggests that clinical interventions aimed at reducing pandemic-related stress and boosting social support and resilience could be effective in reducing mental health symptoms. Indeed, one randomized controlled trial reported the effectiveness of an online intervention aimed at reducing mental health symptoms in a sample of distressed adults that included strategies for the management of pandemic-related worries and for accessing social support during lockdown (Bryant et al., 2022). Furthermore, the f nding that the type of pre-existing mental disorder did not moderate the relationships between psychological factors and mental health outcomes suggests that these psychological variables are risk and protective factors independently of the type of pre-existing disorder and can be considered in transdiagnostic approaches.

4.3. Limitations

This study should be considered in light of several limitations. First, while this study included two waves of data, future longitudinal evidence assessing multiple time points is warranted to better understand the mental impact dynamics of the COVID-19 pandemic. In addition, other factors not assessed in the current study may be also important to understand the impact of the pandemic on people with pre-existing mental disorders (e.g., whether participants were receiving mental health treatment, etc....). Second, since we lacked pre-pandemic data, assessment of the pre-existing mental conditions was based on a CIDI checklist, which includes lifetime-based items. Moreover, current mental health symptoms were based on self-reported screening scales, which are inferior to face-to-face clinical diagnostic interviews. Third, while the sample is representative of the general population, present f ndings cannot be generalized to other institutionalized populations or other hard-to-reach groups. Fourth, the loss of follow-up was considerable (43 %), which might reduce the generalizability and comparability of the results. However, no signif cant differences in demographic characteristics were observed between participants with complete data and those excluded because of missing data, and weights were used to restore representativeness. Finally, the sample size for the group of people with pre-existing mood disorders was limited (n = 70), so the results obtained in this group might be underpowered.

5. Conclusions

Notwithstanding the above limitations, current f ndings suggest that people with distinct pre-existing mental disorders have experienced different patterns of anxiety and depressive symptoms during the middle phase of the COVID-19 pandemic in Spain. Furthermore, we found COVID-perceived stress to be a risk factor for increased anxiety and depressive symptoms, while resilience and social support were

protective factors. Thus, efforts should be made to implement interventions focused on reducing pandemic-related stress and increasing social support and resilience. Such efforts could be effective transdiagnostic approaches regardless of the pre-existing mental diagnosis.

Ethical approval

Ethical approval was provided by the Fundació Sant Joan de Déu Ethics Committee, Barcelona, Spain (PIC 86-20) and by the Parc de Salut Mar Clinical Research Ethics Committee (2020/9203/I) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Oral consent from all participants was obtained prior to proceeding with the interview.

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CRediT authorship contribution statement

AMM and MFN conceptualized the study. Material preparation and data collection were performed by PM, GV, JA and JMH. Statistical analysis were performed by MVM, EC, MFN and AMM. The f rst draft of the manuscript was written by AMM, and all authors commented on previous versions of the manuscript. All authors read and approved the f nal manuscript.

Availability of data and materials

The de-identif ed participant data is available as from publication and upon reasonable request from the corresponding author as long as the main objective of the data sharing request is replicating the analysis and f ndings as reported in this paper (without investigator support), after approval of a proposal, and with a signed data access agreement.

Conf ict of Interest

The authors declare that there is no conf ict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.08.127.

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STUDY V

The effect of polygenic liability to mental disorders on COVID-19 outcomes in people with depression: the mediating role of anxiety

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The effect of polygenic liability to mental disorders on COVID-19 outcomes in people with depression: the mediating role of anxiety

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ABSTRACT

Background. Genetic vulnerability to mental disorders has been associated with COVID-19 outcomes. We explored whether polygenic risk scores (PRS) for several mental disorders predicted poorer clinical and psychological COVID-19 outcomes in people with pre-existing depression.

Methods. Data from three assessments of the Australian Genetics of Depression Study (N = 4,405; 52.2 years ±14.9; 76.2% females) were analysed. Outcomes included COVID-19 clinical outcomes (SARS-CoV-2 infection and long COVID, noting the low incidence of COVID-19 cases in Australia at that time) and COVID-19 psychological outcomes (COVID-related stress and COVID-19 burnout). Predictors included PRS for depression, bipolar disorder (BD), schizophrenia and anxiety. The associations between these PRS and the outcomes were assessed with adjusted linear/logistic/multinomial regressions. Mediation (N = 4,338) and moderation (N = 3,326) analyses were performed to explore the potential influence of anxiety symptoms and resilience on the identified associations between the PRSs and COVID-19 psychological outcomes.

Results. None of the selected PRS predicted SARS-CoV-2 infection or long COVID. In contrast, the depression PRS predicted higher levels of COVID-19 burnout. Anxiety symptoms fully mediated the association between the depression PRS and COVID-19 burnout. Resilience did not moderate this association.

Conclusions. A higher genetic risk for depression predicted higher COVID-19 burnout and this association was fully mediated by anxiety symptoms. Interventions targeting anxiety symptoms may be effective in mitigating the psychological effects of a pandemic among people with depression.

1. INTRODUCTION

The emergence of the coronavirus disease-19 (COVID-19), caused by the SARS-CoV-2 virus, became a global health crisis of unparalleled magnitude, first, due to the rapid spread of the virus and the high mortality rates of the disease, and second, due to the existence of a persistent form of COVID-19, known as long COVID, in which symptoms last for several months after the infection (World Health Organization, 2022). Such prolonged syndromes characterized by physical,

cognitive, and affective symptoms have been reported previously, and followed longitudinally, after other severe infective disorders (Hickie et al., 2006). A range of concurrent mood and individual psychological traits appear to predict such prolonged illness experiences (Cvejic et al., 2019). Among these, depression, the most common mental health disorder and the largest contributor to global disability (König, König, & Konnopka, 2019), is of particular concern. Results from a recent meta-analysis suggest that individuals with depression present increased risks of severe COVID-19 and mortality than the general population (Molero et al., 2023). Moreover, this population has been reported to have an increased risk of long COVID (Wang et al., 2022), making them particularly vulnerable to COVID-19.

Prior studies suggest a potential role of genetic factors underlying the phenotypic association between mental disorders, including depression, and COVID-19 (Moni, Lin, Quinn, & Eapen, 2021; Nudel et al., 2019). However, current evidence as to whether a genetic predisposition to mental disorders are associated with the risk of COVID-19, or its long-term consequences, is inconsistent. For instance, one study of more than 140,000 adults (+50 years at the time of COVID-19), found that a higher genetic predisposition to depression, anxiety, and substance use disorder, but not to psychotic disorders, increased the risk of SARS-CoV-2 infection and severe COVID-19 (W. Chen et al., 2022). Conversely, another study of 15,000 participants reported that the genetic risk for schizophrenia, but not depression or bipolar disorder, predicted a higher risk of severe COVID-19 (Alemany-Navarro et al., 2023). However, none of the studies examining the influence of psychiatric PRSs on COVID-19 outcomes have focused on cohorts of individuals with a mental health diagnosis.

Individuals with depression are especially susceptible to stressors associated to the pandemic, such as disrupted access to mental health services and reducing social networks, thereby increasing their risk of relapse or worsening of existing mental health conditions (Yao, Chen, & Xu, 2020). Indeed, these individuals were shown to have experienced higher levels of COVID-related stress, burnout, and mental health symptoms than the general population (Asmundson et al., 2020; Pan et al., 2021). Additionally, the impact of the COVID-19 pandemic on the levels of psychological distress might also vary depending on the strength of the genetic load of depression and other mental disorders. Certainly, one study assessing mental health trajectories during the COVID-19 pandemic in the general population reported that a general PRS psychopathology factor based on the aggregation of 12 PRSs for mental disorders predicted being assigned to an acute dysfunction group (those showing an increase in mental health symptoms during lockdown but a decrease in symptoms once lockdown ended) rather than a resilient group (those not presenting alterations in mental health symptoms during the COVID-19 pandemic) (Ahrens et al., 2022). Nevertheless, to the best of our knowledge, no study has assessed yet whether the genetic predisposition to different mental disorders can predict levels of stress and burnout related to the COVID-19 pandemic in a cohort of individuals with depression.

Anxiety symptoms are commonly present in individuals with depression (Kessler et al., 2015). The presence of anxiety can exacerbate the emotional and psychological toll of the pandemic, leading to increased levels of worry, fear, and uncertainty. Indeed, anxiety symptoms have been associated with increased COVID-related stress (Monistrol-Mula et al., 2022). On the other hand, studies have shown that individuals with higher levels of resilience are better equipped to cope with the challenges posed by the pandemic, experiencing less stress and burnout associated with the COVID-19 pandemic (Armstrong, Porter, Larkins, & Mesagno, 2022) and prior viral epidemics (Bonanno et al., 2008).

The COVID-19 pandemic is a universal environmental stressor. The aims of the current study were to investigate, in a cohort of people with history of depression, whether 1) PRSs for depression, bipolar disorder, schizophrenia and anxiety, used as proxies for a genetic predisposition to these disorders, predicted susceptibility to COVID-19 disease outcomes (SARS-CoV-2 infection and long COVID), as well as to COVID-19 psychological outcomes (COVID-related stress and COVID-19 burnout); 2) anxiety

symptoms mediate the relationship between a genetic predisposition to these disorders and psychological outcomes; and 3) resilience moderates the associations between a genetic predisposition to the mental disorders of interest and COVID-19 psychological outcomes. Importantly, COVID-19 remains a critical health concern, so results from this study might offer valuable insights for shaping effective public health policies and strategies aimed at protecting vulnerable populations and promoting mental well-being in the ongoing COVID-19 pandemic and potential future epidemics.

2. METHODS

2.1 Australian Genetics of Depression Study (AGDS)

The Australian Genetics of Depression Study (AGDS) was established to identify the genetic risk factors associated with clinical depression and response to treatment. Full details regarding the AGDS recruitment strategy, sample collection, and measures have been described elsewhere (Byrne et al., 2020). In brief, the study comprises more than 22,000 Australian adults aged 18 and over (15,792 of whom have been genotyped) of European ancestry who have received treatment for clinical depression. Participants were recruited through two distinct approaches: by identifying individuals with a nationwide antidepressant prescription history over the past 4.5 years, and through a media campaign across Australia. Once recruited, participants completed an online baseline questionnaire that included a mandatory core module that focussed on depression. Participants could then chose to complete satellite modules focusing on other aspects of mental health, physical health and lifestyle. Following the baseline questionnaire (2017), participants were invited to complete three follow-up surveys during the COVID-19 pandemic (2020, 2021 and 2022), which included questions regarding the impact of the COVID-19 pandemic on both their mental and physical health. The current study was based on data collected in three surveys: the baseline questionnaire and the COVID-19 focused follow-ups conducted in 2021 and 2022. Of those who took part in the baseline survey and did not have missing age (n = 22,289), 25.6% (n = 5,701) also participated in the 2022 COVID-19 survey, which included the main outcomes analysed in this study. Of these, 87.1% (n = 4,969) had been genotyped, and 77.3% (n = 4,405) had no missing outcome variables. Finally, 58.3% (n = 3,326) completed both the 2021 and 2022 COVID-19 surveys, where resilience data was collected.

2.2 Polygenic risk scores for mental disorders

PRSs were calculated using the summary statistics from the most recent genome-wide association studies (GWAS) of depression (246,363 cases and 561,190 controls) (Howard et al., 2019), bipolar disorder (41,917 cases and 371,549 controls) (Mullins et al., 2021), schizophrenia (76,755 cases and 243,649 controls) (Trubetskoy et al., 2022) and anxiety (25,453 cases and 58,113 controls). (Purves et al., 2020) We used SBayesR v2.03 to generate the PRSs, which has been shown to outperform classic PRS calculation methods in the prediction of complex traits (Lloyd-Jones et al., 2019). SBayesR is a Bayesian method that re-scales the GWAS SNP effects with SNPs presumed to have an effect size of zero. For the LD reference, we used one LD matrix based on the HapMap3 SNPs of 50,000 unrelated individuals randomly selected from the UK Biobank (Lloyd-Jones et al., 2019). The posterior SNP effects estimated by SBayesR were used to generate PRSs for each individual using the --score function in PLINK.

2.3 Outcome variables

2.3.1 COVID-19 disease outcomes

Disease outcomes were assessed in the 2022 COVID follow-up questionnaire (completed between May and June) and included SARS-CoV-2 infection and long COVID. SARS-CoV-2 infection was based on the number of self-reported COVID-19 diagnoses. Only those infections diagnosed with a PCR, a rapid antigen test or by a doctor were considered as positive diagnosis of COVID-19. Likewise, only those reporting never being diagnosed with COVID-19 were considered as negative cases. Participants who reported a probable diagnosis of COVID-19 (having potential symptoms but not getting tested) (n=127) were excluded. One participant who reported an implausible number of infections (n = 18) was also excluded. A 3-level variable was created for SARS-CoV-2 infection: never had COVID-19, had COVID-

19 once and had COVID-19 twice. Importantly, at the time of this study the population incidence of confirmed COVID-19 infections in Australia was low compared with many other countries. Participants were considered to have long COVID if they reported having COVID-19 at least 3 months ago and reported experiencing fatigue, shortness of breath, and/or brain fog for at least 2 months following the COVID-19 diagnosis. A dichotomous variable was created for long COVID (yes/no).

2.3.2 COVID-19 psychological outcomes

Psychological outcomes of the COVID-19 pandemic were assessed in the 2022 COVID-19 follow-up questionnaire and included COVID-related stress and COVID-19 burnout. COVID-related stress refers to the psychological and emotional strain experienced by individuals in response to the COVID-19 pandemic (Taylor, 2021). COVID-related stress was assessed with 6 items evaluating how much stress the following situations caused in the prior two weeks: you or others catching COVID-19, the impact of COVID-19 on your physical/mental health, being lonely during the pandemic and following social distancing recommendations (some items were based on the COVID Worries domain of the CRISIS questionnaire) (Nikolaidis et al., 2021). Each item was rated on a 5-level scale ranging from not at all (0) to extremely worried (4). The total score was obtained by adding all responses (0-24), where higher scores reflected higher levels of COVID-related stress.

COVID-19 burnout refers to a state of physical, emotional, and mental exhaustion experienced by people as a result of the prolonged exposure to the COVID-19 pandemic stressors (Queen & Harding, 2020). COVID-19 burnout was evaluated using an adapted version of the COVID-19 Burnout Scale (Yildirim & Solmaz, 2020) (the item When you think about COVID-19 overall, how often do you feel "I've had it"? was excluded). The resulting 9-item questionnaire assessed how frequently you experienced tiredness, disappointment, depression, hopelessness, helplessness, physical weakness or sickness, feeling trapped, worthlessness and sleep difficulties when thinking about COVID-19. Each item was rated from never (0) to always (4), with a total score ranging from 0-36.

2.4 Anxiety symptoms (mediator) and resilience (moderator)

We used the 7-item Generalized Anxiety Disorder Scale (GAD-7) in the COVID-19 follow-up to screen for anxiety symptoms, with items describing problems related to anxiety and participants responding how often they have been bothered by them, with answers ranging from 0 (not at all) to 3 (nearly every day). The total sum scores range from 0 to 21, with higher scores showing higher levels of anxiety symptoms (Spitzer, Kroenke, Williams, & Löwe, 2006). We used the 6-item Brief Resilience Scale (BRS) in the 2021 COVID-19 follow-up to screen for resilience. The authors of this scale define resilience as "the ability to bounce back or recover from stress" (Smith et al., 2008). Thus, the 6 items from the BRS assess your agreement with statements related to your ability to recover after hard times, how fast you recover from stressful events, and how you unfold through stressful situations, with responses varying from 1 (strongly disagree) to 5 (strongly agree). The item average divided by the total number of items results in scores ranging from 1 to 5, with higher scores showing higher resilience symptoms.

2.5 Covariates

Covariates used in all statistical analysis were 8 genetic principal components, sex, severity of depression history, and age from the 2022 COVID-19 survey. Severity of depression history was assessed in the baseline questionnaire and was based on the number of self-reported lifetime depressive episodes lasting at least two weeks (1-13+). Self-reported smoking, comorbid mental disorders (including bipolar disorder, schizophrenia, anorexia nervosa/bulimia, attention-deficit/hyperactivity disorder, autism spectrum disorder, Tourette's disorder, anxiety disorder, panic disorder, obsessive compulsive disorder, hoarding disorder, posttraumatic stress disorder, phobias, seasonal affective disorder, premenstrual dysphoric mood disorder, personality disorder and substance use disorder) and physical diseases (including cancer, diabetes, hypertension, renal disease, lung disease and heart disease) were also tested as covariates in our analyses, but given that these variables did not contribute to any of the regression models, they were not included in the final analyses.

2.6 Statistical analysis

The association between each PRS (depression, bipolar disorder, schizophrenia, and anxiety) and our outcome variables was estimated using linear regression for continuous variables (COVID-related stress and COVID-19 burnout), logistic regression for the binary long COVID variable, and multinomial regression for the categorical SARS-CoV-2 infection variable. All PRSs were standardized to a normal distribution, so each unit increase corresponded to one standard deviation increase in genetic predisposition. All previously described confounders were included in each analysis. Models with all PRS predicting each outcome were also fitted. Odds ratios (OR), relative risk ratios (RRR), and 95% confidence intervals (CI) were calculated where appropriate. Sex-stratified analyses were conducted. Differences in mean PRS among SARS-CoV-2 infection levels were assessed using ANOVA. Participants were divided by PRS deciles, and results were plotted to show the log OR of COVID-related stress and COVID-19 burnout for each PRS decile relative to the lowest decile.

To understand the potential mediating role of anxiety symptoms on the identified associations between the psychiatric PRSs and COVID-19 psychological outcomes, we performed a mediation analysis. This method decomposes the full effect of a variable into direct effects, this is, the effect of psychiatric PRSs (independent variable) on COVID-19 psychological outcomes (outcome), without considering the anxiety symptoms (mediator), and indirect effects (the effect of anxiety symptoms on COVID-19 psychological outcomes due to the psychiatric PRS). We then quantified the percentage of mediation explained by anxiety symptoms on our main association through non-parametric bootstrap techniques with 5000 simulations (Alfons, Ateş, & Groenen, 2022). Bootstrap is superior to other methods to test the significance of indirect effects as it makes fewer assumptions (Alfons et al., 2022). Therefore, it is applicable in a wider variety of situations, providing generic ways to consistently build confidence intervals for indirect effects (Alfons et al., 2022).

Finally, we tested the potential moderating effect of resilience on the identified associations by adding the interaction term between resilience and the corresponding PRS, together with the first order interactions between covariates, in separate linear regression models predicting COVID-related stress and COVID-19 burnout where all variables had been centred.

To account for multiple testing we used Matrix Spectral Decomposition (MatSpD) for the correlation matrix of all the outcomes (Nyholt, 2004), and set the significance threshold to 0.013 for exploratory analysis. Statistical analyses were performed with R (version 4.2.0) and the R packages mediation and lmtest (Tingley, Yamamoto, Hirose, Keele, & Imai, 2014).

3. RESULTS

A total of 4,405 participants with a history of depression were included in the current study. The sample characteristics are shown in Table 1. The mean age was 52.2 years (SD: 14.9) and 76.2% were female. Nearly one quarter (22.7%) of participants reported being infected with SARS-CoV-2 once, while 0.7% had been infected twice at survey time. Approximately 3.8% reported suffering from long COVID.

3.1 PRS prediction of COVID-19 clinical outcomes

Using the PRS for depression, bipolar disorder, schizophrenia and anxiety as proxies for the genetic predisposition to the corresponding disorders, we analysed whether a higher genetic predisposition to these mental disorders predicted our COVID-19 clinical outcomes of interest. However, we did not observe that the genetic risk for any of the included mental disorders significantly increased the risk of SARS-Co-V-2 infection (Table 2). However, a non-significant shift towards an increased genetic risk of anxiety disorder was observed among those having two COVID-19 infections (Figure 1). Likewise, our results did not show an association between an increased genetic predisposition to the four mental disorders and long-COVID (Table 2). These results were maintained when models were fitted including all four PRS (Annex 1), when models were adjusted for all covariates (Annex 2), and in sex-stratified models (Annex 3).

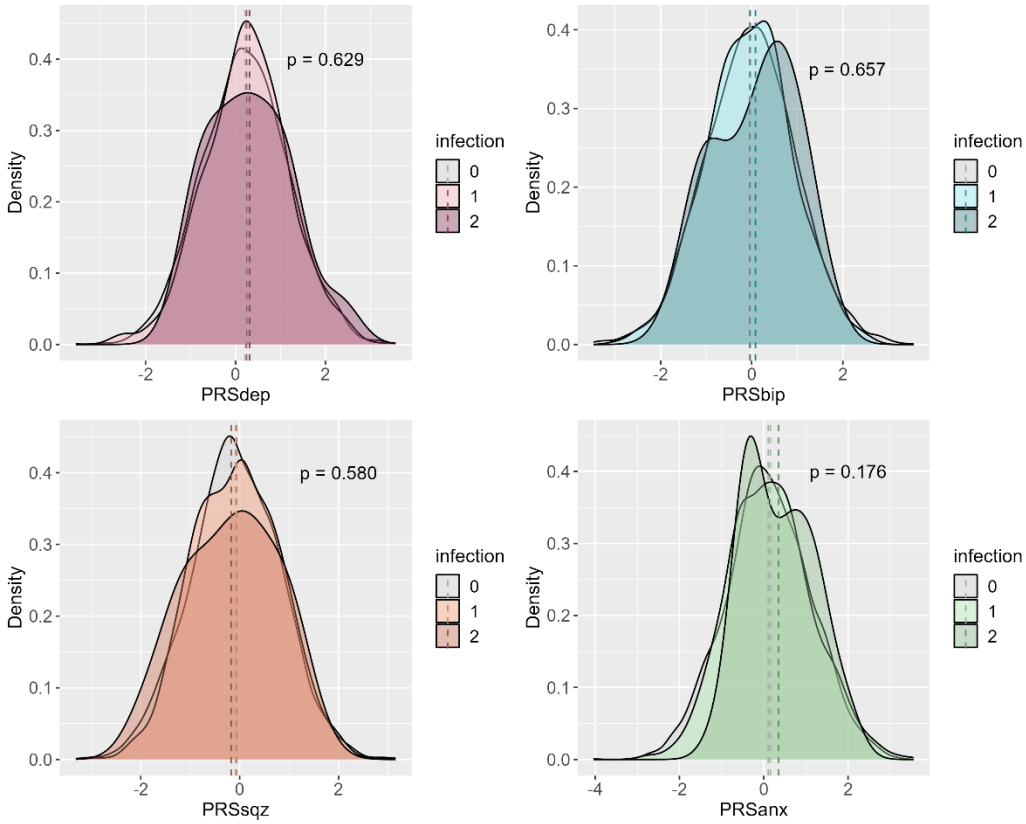

Figure 1. Polygenic Risk Score (PRS) prediction of SARS-CoV-2 infection. P-values were obtained using an ANOVA test facing PRS mean and SARS-CoV-2 infection. PRSdep: PRS for depression, PRSbip: PRS for bipolar disorder, PRSsqz: PRS for schizophrenia, PRSanx: PRS for anxiety.

3.2 PRS prediction of COVID-19 psychological outcomes

We also analysed whether a higher genetic predisposition to depression, bipolar disorder, schizophrenia and anxiety predicted the COVID-19 psychological outcomes of interest. A higher genetic risk of depression predicted higher COVID-related stress and COVID-19 burnout, although the former did not survive multiple testing correction (Table 2). Individuals in the top 10% of genetic risk for depression were 1.87 (95% CI 0.96-3.63) times more likely to report higher COVID-related stress, and 4.17 (95% CI 1.47-11.86) times more likely to report higher COVID-19 burnout than individuals in the lowest 10% of genetic risk (Figure 2). A higher genetic predisposition to bipolar disorder was nominally associated with lower COVID-19 burnout. Individuals in the top 10% of genetic risk for bipolar disorder were 0.27 (95%CI 0.09-0.76) times less likely to report higher COVID-19 burnout than individuals in the lowest 10% of genetic risk (Figure 2). A genetic predisposition to schizophrenia and anxiety did not predict either psychological outcome (Table 2). These results were also maintained when all PRS were included in the same model (see Annex 1), and when models were adjusted for all covariates (see Annex 2). When stratifying by sex, the observed associations were maintained in females, although only nominally, but not in males (Annex 3).

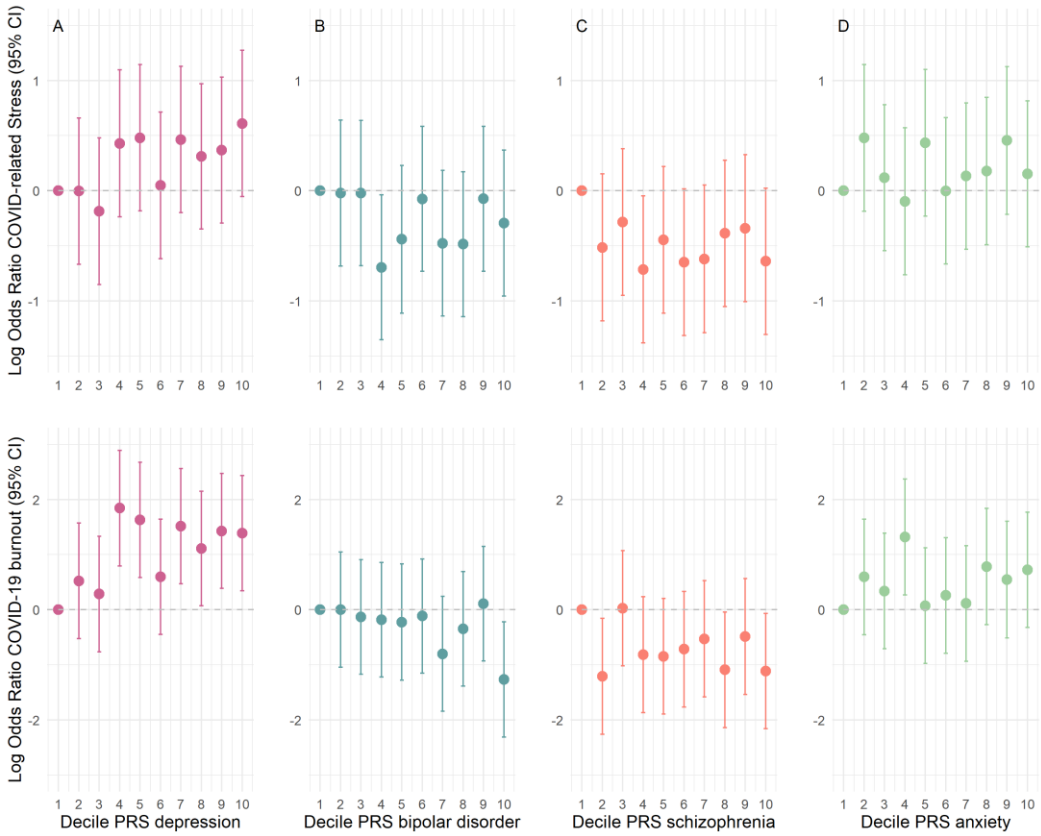

Figure 2. Log Odds Ratio of COVID-related stress and COVID-19 burnout within each polygenic risk score (PRS) decile for depression (A), bipolar disorder (B), schizophrenia (C), and anxiety (D) relative to those in the lowest decile in the Australian Genetics and Depression Study

3.3 Mediation and moderation analysis

We analysed the potential mediator role of anxiety symptoms on the significant association between the PRS for depression and COVID-19 burnout (N = 4,338). We found that anxiety symptoms significantly mediated the association, with a proportion of mediation of 78.0% (p = 0.003). Once the model included anxiety symptoms as the mediator, the direct effect of the genetic risk on COVID-19 burnout disappeared (full mediation) (Figure 3A). Lastly, we analysed whether resilience moderated the association between PRS for depression and COVID-19 burnout (N = 3,326). While resilience predicted lower COVID-19 burnout, it did not significantly moderate the association between PRS for depression and COVID-19 burnout (Figure 3B and Annex 4).

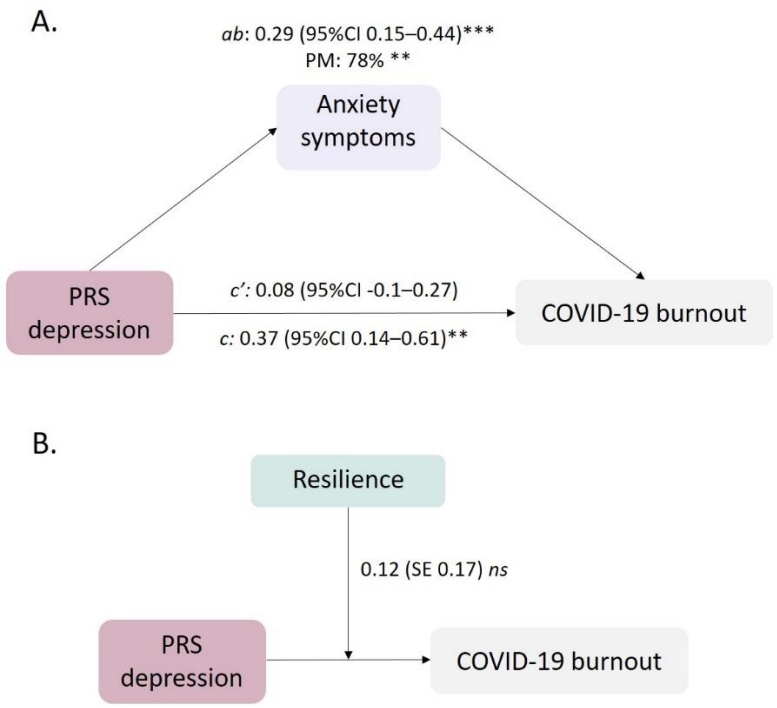

Figure 3. (A) Unstandardized coefficients and confidence intervals for the mediation model. The ab path coefficient represents the mediation effect of anxiety symptoms on the association between PRS depression and COVID-19 burnout. The c path coefficient represents the total effect of the PRS for depression on COVID-19 burnout. The c' coefficient represents the direct effect of the PRS for depression on COVID-19 burnout. (B) Standardized coefficients and standard error for the moderation effect of resilience on the association between PRS for depression and COVID-19 burnout. CI: confidence interval, SE: Standard error, PM: proportion mediated, ns: non-significant, *p<0.05, **p<0.01, *** p<0.001.

4. DISCUSSION

We examined whether genetic risk for depression, bipolar disorder, anxiety, and schizophrenia predicted COVID-19 disease and psychological outcomes in 4,405 AGDS participants who had a lifetime history of depression.

The genetic predisposition to these mental disorders did not significantly predict SARS-CoV-2, although a non-significant shift towards an increased genetic risk for anxiety was observed among who reported having had two SARS-CoV-2 infections. This is contrary to prior studies conducted in United Kingdom and Spain that have reported an association between a higher genetic risk for depression, anxiety (W. Chen et al., 2022), and schizophrenia (Alemany-Navarro et al., 2023), and higher risk of SARS-CoV-2 infection in the general population. The lack of significant association in our cohort might be explained by several factors. First, at the time of this study the population incidence of confirmed COVID-19 infections in Australia was low compared with many other countries. Australia was almost free of COVID-19 until early 2022 (World Health Organization (WHO), 2023), when over 93% of the population older than 16 years old had been fully vaccinated (Australian Government, 2022). Therefore, the vast majority of AGDS participants who became infected were vaccinated unlike participants from the previously mentioned studies, who became infected when unvaccinated. Given that vaccines significantly reduce the risk of infection and reinfection (Flacco et al., 2022; Zheng et al., 2022), our results might be influenced by a vaccination effect. Second, unlike prior studies, our study was conducted in a cohort of people with a history of depression. Current evidence is

inconclusive regarding whether people with depression have an increased risk of SARS-CoV-2 infection compared to people without depression (Bertolini et al., 2023) with some studies suggesting that commonly used antidepressants such as fluoxetine or sertraline could prevent viral infection by SARS-CoV-2 (Y. Chen et al., 2022; Clelland, Ramiah, Steinberg, & Clelland, 2021; Fred et al., 2022). Therefore, the potential increased use of antidepressants in our cohort might act as a confounding factor, as antidepressants might reduce the susceptibility to SARS-CoV-2 infection, thus masking the effect of the psychiatric genetic risk scores on infection rates. Finally, when restricting our sample to individuals with depression, we are capturing particularly those individuals with higher genetic risk for depression and other mental disorders than what population-based studies do. This phenomenon, known as Berkson's bias, could lead to an underestimation of the effect of the genetic risk for the tested mental disorders on SARS-CoV-2, potentially explaining the lack of association found in our results (Griffith et al., 2020; Lu, Gonsalves, & Westreich, 2024).

Prior studies of post-infective syndromes highlight that concurrent mood disorders, and other individual behavioural traits, predict ongoing ill-health (Cvejic et al., 2019). However, studies examining the link between the genetic risk for mental disorders (as distinct from phenotypic expressions) and long COVID, and other post-infective syndromes, is lacking. Nevertheless, epidemiological studies have reported an increased risk of long COVID among people with depression and other mental disorders, which could potentially be caused by the pro-inflammatory environment present in some mental disorders (Reme, Gjesvik, & & Magnusson, 2023; Wang et al., 2022). This suggests that genetic factors associated to these disorders might be contributing to the increased risk of long COVID. However, we did not find a significant association between the genetic predisposition to depression, bipolar disorder, anxiety and schizophrenia and a higher risk of developing long COVID, suggesting that the increased risk of long COVID reported in people with depression might not be driven by genetic factors associated with these disorders. Nevertheless, factors such as vaccination, which has been reported to reduce the risk of long COVID (Richard et al., 2023), might be influencing our results. Further studies involving larger and diverse cohorts, and accounting for vaccination status and use of psychiatric medications are needed to better understand the complex interplay between genetics, mental disorders, and SARS-CoV-2 infection and long COVID-19.

We explored whether a higher genetic risk for the selected mental disorders predicted greater levels of COVID-related stress and COVID-19 burnout. We found that a higher PRS for depression was linked to higher levels of COVID-related stress, although this association did not withstand multiple testing correction. However, the depression PRS significantly predicted higher COVID-19 burnout. A higher PRS for bipolar disorder predicted lower COVID-19 burnout, but only at a nominal level. In sex-stratified analysis these associations were maintained in women (although only nominally), while no significant results were obtained in men. Nevertheless, the lack of significant results in men might be explained by a reduced sample size, which was three times smaller than that of women. We hypothesized that anxiety symptoms might influence the identified association between genetic predisposition to depression and higher levels of COVID-19 burnout. Results from the mediation analysis showed that anxiety symptoms, conducted in a subset of the sample, explained a substantial portion of the association between genetic predisposition to depression and COVID-19 burnout (78%), to the extent that the direct effect of the genetic factors disappeared. This result suggests that the higher risk of COVID-19 burnout reported in people with depression is predominantly driven by anxiety symptoms. COVID-19 burnout can have a serious impact on both mental and physical wellbeing, affecting the individual's ability to function efficiently (World Health Organization. Regional Office for Europe, 2020). In addition, current evidence suggests that burnout can result in reluctance to adhere to anti-pandemic measures (Lilleholt, Zettler, Betsch, & Böhm, 2023). Hence, from a population-health perspective, the much wider promotion of specific cognitive or behavioural interventions that target anxiety symptoms (and that can be self-administered or facilitated by digital technologies) (Linardon et al., 2024) early during a pandemic, or

at other times of spikes in community-acquired viral infections, may well deliver significant mental health benefits. Such interventions focus on reduction in prolonged arousal, challenging irrational thoughts or fears and maintenance of regular 24 hour sleep-wake cycles. Most notably, those positive effects are largely likely to be derived in people with pre-existing depression, regardless of their genetic risk for the disorder.

Finally, we hypothesized that resilience could moderate the identified associations between the PRS for depression and COVID-19 burnout. However, although higher resilience predicted lower COVID-19 burnout, it did not moderate the association between genetic risk for depression and COVID-19 burnout. One potential reason for the absence of a moderating effect may be the relatively low levels of resilience within our population (mean BRS=2.8, SD=0.8) (Chmitorz et al., 2018; Soer et al., 2019), which could result in insufficient variation to detect a moderating effect in our analysis. Additionally, although resilience is a known protective factor for mental health, available evidence has not identified a moderation effect of resilience on the association between the genetic load for depression and the manifestation of depression (Navrady, Adams, Chan, Ritchie, & Mcintosh, 2018).

The results of our study should be considered in the context of some limitations. First, AGDS participants were predominantly women of European ancestry, so our findings may not be generalizable to other populations and studies. Second, our sample was significantly older and had a lower PRS for schizophrenia compared to those lost to follow-up. This may bias our findings towards older individuals and those with a lower genetic predisposition for schizophrenia, potentially limiting the generalizability of our results. Third, SARS-CoV-2 infection and long COVID were self-reported rather than clinically diagnosed. Nevertheless, self-reported SARS-CoV-2 infection and symptoms have been shown to be reliable indicators of SARS-CoV-2 infection (Adorni et al., 2020; McCarthy et al., 2022). Fourth, while evidence suggests a protective effect of antidepressants against SARS-CoV-2 infection (Fred et al., 2022; Lee et al., 2022), we lacked data on current antidepressant use in our sample. Therefore, antidepressants could confound the association between genetic risk for mental disorders and infection. Fifth, our sample size for individuals with two SARS-CoV-2 infections was limited (n = 29), which may have reduced our power to detect an association. Sixth, we focused on the association of genetic risk and our outcomes, and we did not consider specific genotype-environment interactions.

In conclusion, we found no evidence that the genetic risk for depression, bipolar disorder, schizophrenia or anxiety predicted susceptibility to SARS-CoV-2 infection and long COVID-19 in people with history of depression. However, these results could be influenced by the unique conditions of the pandemic in Australia. A greater genetic load for depression predicted higher COVID-19 burnout; this association was fully mediated by anxiety symptoms and resilience did not show a moderating effect. Thus, in the continuing COVID-19 pandemic and for future pandemics, efforts should be directed towards the implementation of interventions focused on reducing anxiety symptoms. This could be an effective approach for people with depression regardless of their genetic susceptibility to the disorder.

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7. ETHICAL STANDARDS

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

8. COMPETING INTERESTS

The authors declare no competing interests.

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4 Discussion

As your career grows, the list of things that makes you happy should not become smaller, it should become bigger

- Taylor Swift

4.1. SUMMARY AND INTERPRETATION OF FINDINGS

The present thesis expands current evidence concerning the link between infections, with a focus on the COVID-19 pandemic, and mental disorders. Using data from electronic health registries in Catalonia (Spain) from February to December 2020, Study I identified distinct patterns of SARS-CoV-2 infection and COVID-19 hospitalization among various mental health diagnoses. However, a consistently higher risk of COVID-19 death was found across almost all types of mental disorders, with the exception of PTSD and other stress-related disorders. Moreover, we utilized statistical genetics techniques to uncover shared altered biological pathways between mental disorders and COVID-19 infection and hospitalization (Study II). This approach also enabled us to identify causal genetic associations, reinforcing our findings on the increased vulnerability to COVID-19 among individuals with mental disorders. Multiple genomic regions were identified as shared across mental disorders, characterized by a general psychopathology factor (P-factor), and COVID-19 outcomes, as well as between specific mental health diagnoses and COVID-19 outcomes. Gene-based analysis within these regions indicated potential connections with immune-related pathways. Furthermore, compelling evidence was presented for causal associations between the P-factor and COVID-19 infection and hospitalization, as well as between specific diagnoses such as depression, ADHD, and PTSD, and these outcomes.

In Study III, we examined the impact of social support and COVID-related stress on the odds of screening positive for GAD and MDD during the early pandemic, and whether having a pre-existing mental disorder moderated these associations. Our results showed that higher levels of COVID-related stress and lower social support increased the odds of screening positive for GAD and MDD

during the early pandemic, with potentially greater adverse consequences for those with pre-existing mental disorders. Moreover, in Study IV we assessed changes in anxiety and depressive symptoms from the early to the mid-pandemic in Spain among individuals with different pre-existing mental disorders (anxiety, mood disorders, and comorbid depression and anxiety) and without any pre-existing mental disorder. We also explored how three psychological factors (COVID-related stress, social support, and resilience) influenced these patterns. Our findings indicated an increase in mental health symptoms in most groups, with those experiencing comorbid depression and anxiety showing the highest symptoms. Interestingly, our analysis revealed that the type of pre-existing mental disorder did not influence the effect of any of the three psychological factors.

Finally, in Study V we investigated whether the PRSs for depression, bipolar disorder, schizophrenia, and anxiety, used as proxies for genetic predisposition to these disorders, predicted COVID-19 disease outcomes (infection and long COVID) and COVID-19 psychological outcomes (COVID-related stress and COVID-19 burnout) in individuals with pre-existing depression from Australia. While none of the PRSs predicted infection or long COVID, PRS for depression predicted higher levels of COVID-19 burnout. Further investigation revealed that anxiety fully mediated this association, while resilience did not moderate it.

4.1.1. Risk of COVID-19 on individuals with pre-existing mental disorders

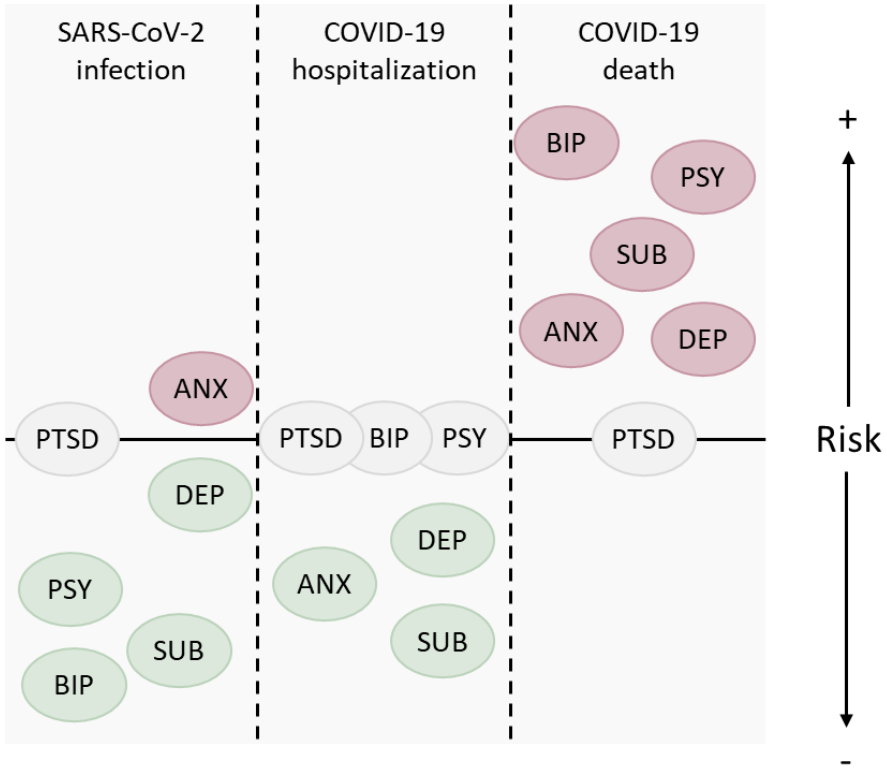
Risk of infection and severe COVID-19 outcomes across mental disorders

Results from Study I revealed a slightly higher risk of infection in individuals with anxiety and other neurotic/somatoform disorders, while a decreased risk of infection was found in those with depressive disorders, psychotic disorders,

bipolar disorder, and substance use disorders (Figure 7). The latest meta-analysis on this topic, including 81 studies from several countries, concluded that individuals with anxiety disorders, depressive disorder, bipolar disorder, psychotic disorders, neurodevelopmental disorders, and substance use disorders did not present increased risk of SARS-CoV-2 infection compared to individuals without mental disorders (212). However, there was significant variation in outcomes across studies.

Figure 7

Graphical representation of the identified risks of COVID-19 infection, hospitalization, and death across mental disorders compared to individuals without these mental health diagnoses



Note. Original figure. Green highlights indicate disorders associated with a decreased risk, grey represents non-significant results, and maroon indicates a higher risk. ANX: anxiety and other neurotic/somatoform disorders, PTSD: post-Traumatic Stress disorder

and other stress-related disorders, DEP: depressive disorder, PSY: non-affective psychotic disorders, SUB: substance use disorder, BIP: bipolar disorder.

Individuals with mental disorders, and particularly mood and psychotic disorders, have been reported to exhibit a biological vulnerability to infections (222–224). Furthermore, factors strongly associated to mental disorders, such as psychological stress or poor socioeconomic status have been reported to increase the susceptibility to infections (100,225). Therefore, we anticipated higher infection risks in those with mental disorders and especially severe mental disorders. However, the lower infection risks observed in these individuals, as well as in those with substance use disorders, might be explained by reduced exposure to the SARS-CoV-2 virus. For instance, individuals with mental disorders often undergo social withdrawal (226), which limits their interactions with people and exposure to crowded places, thereby reducing opportunities for virus transmission. Indeed, social deprivation was particularly heightened in this population during the COVID-19 pandemic (227). Thus, while social deprivation typically has negative consequences, during the pandemic, it might have inadvertently acted as a protective factor against infection. In addition, this lower risk of infection could also be attributed to a reduced access to diagnostic tests. In Spain, test availability was very limited during the early stages of the pandemic. Furthermore, several barriers to seek health screening have been identified in individuals with mental disorders, including cognitive dysfunction, low social support, unawareness of risk, and poverty (228). These factors might have contributed to a reduced access to COVID-19 testing, potentially resulting in late detection of the disease and therefore, a delayed medical care. Indeed, individuals with depression, anxiety and other neurotic/somatoform disorders, and substance use disorders exhibited a decreased risk of hospitalization but a higher risk of COVID-19-related death,

which could indicate lower access to healthcare in these populations. Those with psychotic and bipolar disorders also presented higher COVID-19 mortality. Conversely, individuals with PTSD and other stress-related disorders did not show increased risks of COVID-19 death. Schultebraucks *et al.,* reported that individuals with stress-related disorders showed decreased risk of COVID-19 death (229), which contradicts earlier literature suggesting an increased risk of life threatening infections in individuals with PTSD (87). However, literature on the risk of severe COVID-19 and mortality in this population is limited, so further studies are needed to elucidate the vulnerability of individuals with PTSD and other stress-related disorders to COVID-19 death.

Overall, our results indicate that once infected, individuals with most types of pre-existing mental disorders are disproportionately affected by COVID-19 compared to those without these mental disorders (Figure 7), which aligns with existing literature (212,229,230). Moreover, our results are in agreement with pre-COVID-19 studies reporting increased risks of life-threatening infections in individuals with different mental disorders (87,231,232). Beyond the potential explanations related to delays in treatment-seeking and reduced access to care, different factors – including a poor socioeconomic status (233), poor lifestyle habits (234,235), and biological factors related to their mental diseases (236) – also contribute to the heightened risks of severe infections and infection-related mortality.

Focusing on biological factors, the potential mechanisms linking COVID-19 and mental disorders are intricate and multifaceted. One key mechanism seems to involve a dysregulated pro-inflammatory immune status, where individuals with mental disorders often exhibit altered immune responses (99,237–239), including chronic inflammation and impaired immune function, making them more susceptible to COVID-19 and severe outcomes of the disease (235,240).

Moreover, in individuals with mental disorders, the hypothalamic-pituitary-adrenal (HPA) axis, which regulates stress responses, can become dysregulated, further contributing to inflammation (241). In addition, psychological distress can further compromise immune function, reducing the body's ability to fight off infections effectively (100). Indeed, psychological stress has been related to increased mortality caused by infections (242). Genetic factors can also play a role in this association. Genetic links between mental disorders and susceptibility to infection have been documented (90), and immunogenic variants associated with increased risk of mental disorders are related to increased vulnerability to infection and severe outcomes (223,243) via inflammatory dysfunction (244,245). However, the exact biological mechanisms involved in the interplay between COVID-19 and other infections and mental disorders remain unknown. Understanding these mechanisms would aid to develop tailored interventions to mitigate the impact of infections on individuals with mental disorders.

Genetic factors in the association between mental disorders and COVID-19

Study II aimed to uncover shared genetic alterations contributing to the heightened vulnerability to COVID-19 observed in individuals with most types of mental disorders. All previously mentioned mental health diagnoses, except for substance use disorders, were included in this study. In addition, we included ASD and ADHD, given that existing literature suggests increased vulnerability to COVID-19 in these populations (246–248). Moreover, considering the comorbidity and overlapping symptomatology among mental disorders, we constructed a general psychopathology factor (P-factor) derived from these seven mental disorders, which was intended to represent the overall genetic susceptibility to mental disorders (249).

Our results showed significant genetic correlations between the P-factor and both COVID-19 infection and hospitalization. This is in line with one study including data from more than 65,000 individuals, reporting positive genetic correlations between infection and mental disorders (90). Specifically, positive genetic correlations were identified between depression, ADHD, PTSD, and COVID-19 infection and hospitalization, as well as between anxiety and hospitalization. While previous studies had reported genetic correlations between depression and ADHD with COVID-19 outcomes (250,251), our study is the first to reveal genetic correlations between PTSD, anxiety, and COVID-19.

To further investigate the shared genetic architecture between our mental disorders of interest and COVID-19, we examined local genetic overlap at different regions across the genome. Shared genomic regions were found between at least one COVID-19 outcome and all mental health diagnoses, with the exception of ADHD and anxiety. Four genomic regions were found to be shared between at least two mental disorders, and COVID-19 infection or hospitalization: one in chromosome 4 (chr4q24) and the other three in chromosome 17 (17q12, 17q21.31-q21.32, and 17q24.2-q24.3). However, gene-based tests conducted on these regions revealed significant genes only in chromosome 17. For COVID-19 infection, we identified the *PSMD3* and the *THRA* genes. *PSMD3*, which encodes a proteasome subunit, was found to be shared among depression, bipolar disorder, and PTSD; while *THRA*, encoding a thyroid hormone receptor, was shared between depression and bipolar disorder. In the case of COVID-19 hospitalization, we discovered the *BPTF* gene and a cluster of nine genes which included the *CRHR1* gene. The *CRHR1* gene, which was significant for schizophrenia and ASD, codes for the corticotropin-releasing hormone receptor 1, which plays a pivotal role in activating the HPA axis. The *BPTF* gene, responsible for encoding the BPTF transcription factor, was found to

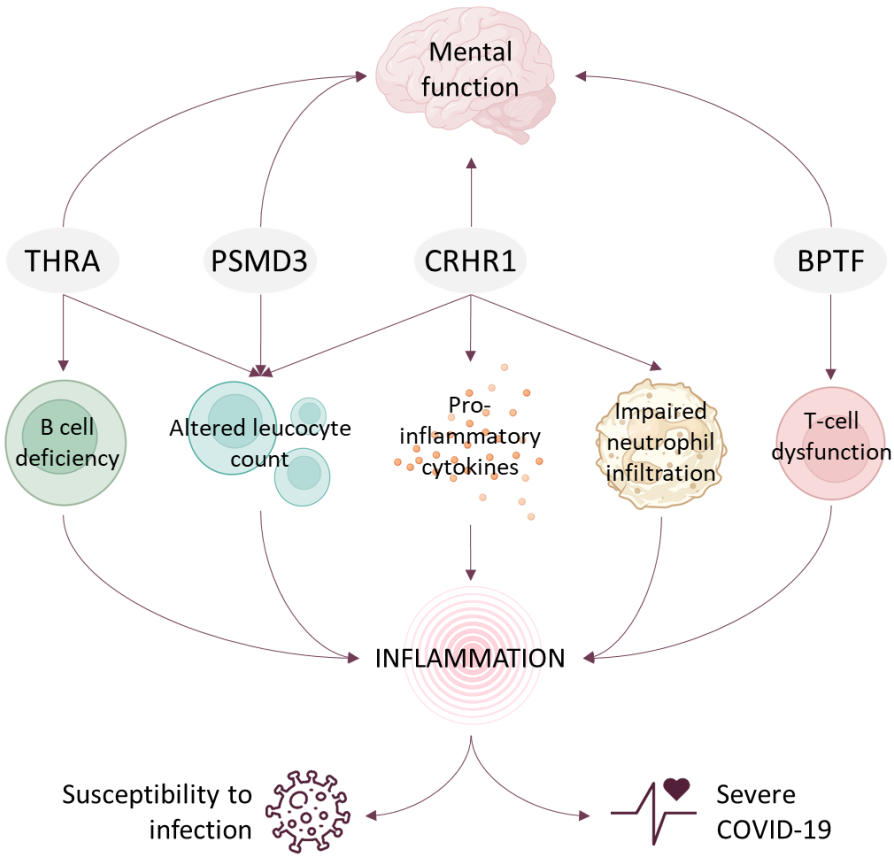
be shared among depression, PTSD, and ASD. Of the four identified genes, only *BPTF* was significant also for the P-factor. All the identified genes have been somehow related to mental function in previous studies (252–257), although literature on PSMD3 is limited. Interestingly, all these genes have connections to immune function (Figure 8). For instance, GWAS studies have identified mutations in *PSMD3, THRA,* and *CRHR1* associated with a reduced white cell count (258,259). Additionally, thyroid hormones play important roles in inflammation, and alterations in thyroid hormones or its receptors, such as THRA, can significantly affect the immune function (260). In mice, alterations in THRA have been associated to B cell deficiencies (261), while *in vitro* studies suggest that the absence of BPTF impairs T cell function (262). Moreover, blocking CRHR1 in mice infected with *Streptococcus pneumoniae* increased neutrophil infiltration in the lungs but did not confer resistance to infection (263). Moreover, CRHR1 exerts both indirect anti-inflammatory effects through the production of cortisol via HPA axis activation, which suppresses immune function, and direct pro-inflammatory effects on immune cells (264). Notably, alterations in *CRHR1* gene have been linked to increased levels of pro-inflammatory cytokines in individuals attempting suicide (265) and with suicidal behaviour in schizophrenia (266). Thus, while various potential genes have been identified across different mental disorders in relation to COVID-19 infection and hospitalization, existing literature suggests that altered immune responses might explain the increased vulnerability of people with mental disorders to COVID-19.

Prior studies have also linked mental disorders to higher levels of systemic inflammation and increased vulnerability to infections, including COVID-19 (221,267,268). Although the exact mechanisms connecting mental disorders and COVID-19 remain to be elucidated, some authors (212) have suggested that

altered T cell populations associated with these disorders could be a potential mechanism (269,270). An imbalance in T cell populations has been linked to higher mortality in COVID-19 patients, indicating a possible connection between T cell dysfunction and severe outcomes in this population (271). Notably, the chromosomal region 17q12-q21, where most of the identified genes are located, has been previously associated with antiviral responses and altered lymphocyte T activation (272–274).

Figure 8

Potential impact of alterations in the THRA, PSMD3, CRHR1, and BPTF genes on the relationship between mental disorders and COVID-19



Note. Original figure. THRA: thyroid hormone receptor alpha, PSMD3: proteasome 26S subunit, non-ATPase 3, CRHR1: corticotropin releasing hormone receptor 1, BPTF: bromodomain PHD finger transcription factor.

We further conducted Mendelian Randomization analyses to test the causality of the associations between various mental health diagnoses and increased vulnerability to COVID-19 identified in our previous study (see section 4.1.1.) and documented in the literature (212). Our findings suggested potential causal associations between the P-factor and increased risks of COVID-19 infection and hospitalization, indicating that having any pre-existing mental disorder might increase the likelihood of both contracting the virus and developing more severe forms of the disease. Specifically, putative causal associations were identified linking depression, PTSD, and ADHD with increased COVID-19 infection and hospitalization. Although no specific shared genomic regions were found between ADHD and COVID-19 infection or hospitalization, potential causal associations were identified, confirming prior results obtained in smaller samples (275). Demontis *et al.,* showed that nearly all genetic variants influencing ADHD also influenced smoking, with 79% of these variants showing concordant directions (30). Since smoking is a known risk factor for infection and severe COVID-19, (276) it is plausible that the causal associations identified between ADHD and COVID-19 are driven by smoking habits rather than by shared genetic causes.

Importantly, bidirectional causal associations were not identified between the P-factor and either COVID-19 infection or hospitalization, indicating that our results do not support a causal link between having COVID-19 or severe COVID-19 and the onset of mental conditions. This contradicts existing literature reporting higher rates of mental disorders following COVID-19 infection, particularly among those hospitalized for COVID-19 (277–279). Moreover, reverse causal associations were not found for any specific mental disorders except schizophrenia. We identified a potential reverse causality between SARS-CoV-2 infection and schizophrenia, a finding previously reported in the literature

(280). This suggests that the increase in the prevalence of psychotic disorders observed after COVID-19 might be driven by biological causes (279). This is supported by studies showing that the increased incidence of psychotic disorders after SARS-CoV-2 infection was persistent, unlike common disorders such as depression or anxiety, where the increased incidence was short-lived, indicating that the main driver of the increased incidence was the disease context and not the infection *per se* (143).

In summary, findings from Study II indicate that alterations in immune-related pathways may underlie the heightened COVID-19 risk of individuals with mental disorders. However, careful interpretation is warranted as our approach identified genomic regions and associated genes without fully accounting for biological pathways, gene-gene interactions, and regulatory mechanisms that could influence the interplay between mental disorders and COVID-19. Future research should include experimental validation to confirm the biological relevance and functional implications of these genetic associations.

4.1.2. Impact of the COVID-19 pandemic on mental health of individuals with pre-existing mental disorders

In addition to understanding the pathogenesis of COVID-19 in individuals with mental disorders, we were also interested in evaluating the pandemic's impact on mental health. We wanted to explore if the impact had been greater in individuals with pre-existing mental disorders, and the influence of several psychological factors.

Impact of pre-existing mental disorders on mental health during the COVID-19 pandemic

Results from Study III showed that having a pre-existing mental disorder was associated with increased risks of screening positive for GAD and MDD after the Spanish outbreak. Several studies conducted at the beginning of the pandemic indicated higher rates of mental health symptoms, and identified having a pre-existing mental disorder as a risk factor for such increases (281,282). However, most of these studies were cross-sectional and were conducted during the outbreak. Subsequent meta-analyses incorporating longitudinal studies with pre-pandemic data, concluded that mental health symptoms did not increase or increased only minimally in both the general population (193) and individuals with pre-existing mental disorders (283). However, almost all the included studies were conducted in 2020, providing no evidence on how mental health symptoms fluctuated in later stages of the pandemic, especially among individuals with different pre-existing mental disorders. Therefore, Study IV focused on analysing changes in anxiety and depressive symptoms in Spain from early to mid-pandemic across four population groups: individuals without any pre-existing disorders, individuals with pre-existing mood disorders (bipolar disorder and depression), individuals with pre-existing anxiety, and individuals with both pre-existing depression and anxiety. Our results revealed a general increase in anxiety and depressive symptoms from the early to mid-pandemic across groups of pre-existing mental disorders, although this increase did not reach statistical significance for mood disorders. In individuals with pre-existing comorbid depression and anxiety, depressive symptoms remained high and stable.

These findings were aligned with previous literature. For instance, a longitudinal Dutch study assessing mental health symptoms during the first year of the

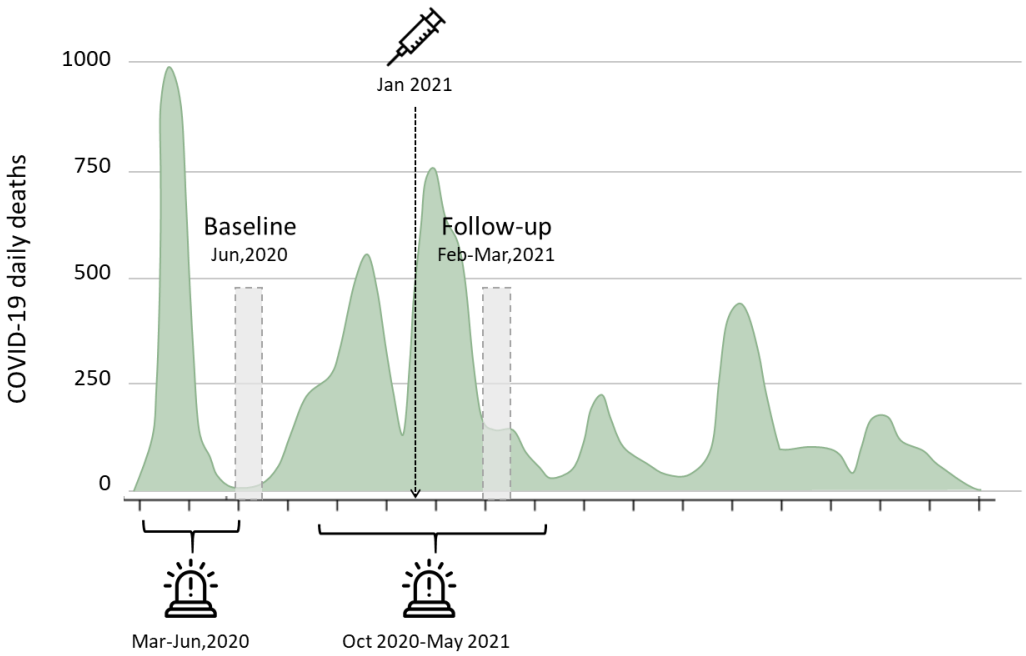
COVID-19 pandemic (March 2020-March 2021) reported that levels of depressive symptoms and worry remained higher than before the pandemic one year after the outbreak in healthy controls. Nevertheless, the authors found that this increase was not present in individuals with pre-existing mental disorders. Indeed, in those with high chronicity mental disorders, depressive symptoms improved (214). Conversely, subsequent studies evaluating the impact of the COVID-19 pandemic across two years reported overall stable trajectories of depressive and anxiety symptoms both in individuals with and without pre-existing mental disorders (284,285). Therefore, existing literature suggests that while mental health symptoms might have fluctuated at certain points during the COVID-19 pandemic, overall trajectories for those with pre-existing mental conditions have remained stable.

Punctual increases in mental health symptoms have been associated with the epidemiological situation of the pandemic, with increases in mental health symptoms following high infection and mortality rates (195,214) and strict containment measures (286). Hence, the overall increase in anxiety and depressive symptoms identified in our study across mental health groups might be influenced by the epidemiological situation. Baseline data collection occurred after the first wave of infection (June 2020), at the end of the first state of alarm in Spain, when infection and mortality rates were low, and restrictive control measures were easing, fostering an optimistic outlook on the pandemic (Figure 9). However, the follow-up (February-March 2021) occurred during the third COVID-19 wave in Spain, marked by high infection and mortality rates, along with stringent measures such as curfews and restricted geographical mobility (Figure 9). Moreover, by that time, the pandemic had persisted for a year, subjecting the population to prolonged exposure to emotionally demanding situations. This phenomenon, often referred to as COVID-19 burnout or

pandemic fatigue (189), has been linked to deteriorating mental health outcomes (287).

Figure 9

COVID-19 mortality waves in Spain from the pandemic outbreak in March 2020 to December 2022



Note. Original figure created using information from World Health Organization (WHO) (104), the Worldometer (165) and the CNE, ISCIII, Red Nacional de Vigilancia Epidemiológica, 2023 (288). The figure delineates the timeframes corresponding to the baseline and follow-up data collection points of the MINDCOVID study. Additionally, it denotes the two periods of the state of alarm, marked by restrictive measures aimed at curbing the spread of COVID-19, and the beginning of the vaccination campaign in Spain.

Interestingly, results from Study IV revealed a general increase in mental health symptoms, with those with comorbid depression and anxiety being the group with the highest anxiety and depressive symptoms (289). However, an increase in depressive symptoms was not observed in this group, likely due to ceiling effects. One study investigating the evolution of psychiatric symptoms during the COVID-19 pandemic (April-December 2020) also identified similar trends

across various diagnostic groups. However, unlike our findings, this study noted an improvement in symptoms over time in all groups but schizophrenia. Nevertheless, while individuals with mood disorders and neurotic/somatoform disorders experienced an improvement of symptoms over time, their overall psychological burden remained higher compared to other groups (290).

Influence of psychological factors on mental health during the COVID-19 pandemic

Study III revealed that higher levels of COVID-related stress and lower levels of social support in early pandemic were associated with higher odds of screening positive for GAD and MDD. Subsequent results from Study IV confirmed that increases in COVID-related stress and decreases in social support from the early to mid-pandemic were associated with higher levels of depressive and anxiety symptoms. We also found that higher levels of resilience at baseline predicted lower levels of depressive and anxiety symptoms. Further longitudinal studies support these findings (291–293). For instance, Graupensperger *et al.,* reported that COVID-related stressors had direct and time-varying associations with mental health and well-being (292). Furthermore, a study conducted from May to September 2020 including nearly 70,000 participants found that higher levels of social support predicted a lower risk of screening positive for MDD, as well as lower depressive symptoms (293).

We further examined whether having a pre-existing mental disorder moderated the associations between COVID-related stress and social support (Study III). Our findings revealed that individuals with pre-existing mental disorders exhibited a moderating effect on the association between COVID-related stress and both GAD and MDD. Although the association patterns were comparable between individuals with and without pre-existing mental disorders, the impact of COVID-

related stress on the likelihood of screening positive for these affective disorders was more pronounced among those with pre-existing mental disorders. This suggests that COVID-related stress may have disproportionately adverse effects on individuals with pre-existing mental disorders. Moreover, results from moderation analysis showed that having a pre-existing mental disorder influenced the association between social support and GAD, but not MDD. While higher levels of social support were associated with a protective effect against GAD in both groups, the impact was notably modest among individuals with pre-existing mental disorders. This observation suggests that individuals with pre-existing mental disorders may encounter challenges in deriving adequate support from their social networks (294). It is plausible that the type or quality of social support they receive may not be as effective or could even be counterproductive in mitigating the symptoms of GAD. Thus, results from Study III suggested a different impact of COVID-related stress and social support in MDD and GAD in those with pre-existing mental disorders compared to those without pre-existing mental disorders. In Study IV, we found that the type of pre-existing mental disorders did not modify the associations between changes in COVID-related stress, changes in social support, and resilience, and depressive and anxiety symptoms. Therefore, our findings emphasize the critical need for trans-diagnostic interventions designed specifically for individuals with pre-existing mental disorders during pandemics or similar crises. These interventions should address the unique challenges faced by this population in accessing and benefiting from social support, while also improving their resilience and coping skills in the face of unprecedented stressors. Notably, several randomized controlled trial (RCT) studies have reported the effectiveness of such interventions conducted during the COVID-19 pandemic in different populations (295–298).

4.1.3. Polygenic liability to mental disorders and risk of COVID-19 outcomes in individuals with pre-existing depression

Among the mental disorders included in the present thesis, depression emerges as particularly noteworthy due to its high prevalence and significant contribution to global disability (2). Consequently, understanding the impact of COVID-19 on individuals with pre-existing depression is of paramount concern. Our findings (see section 4.1.2.) suggest that potential genetic factors contributing to the risk for mental disorders might also contribute to COVID-19 risk, in agreement with current literature (221). Results from Study V indicated that none of the analysed psychiatric PRSs (depression, bipolar disorder, anxiety, and schizophrenia) predicted the risk of SARS-CoV-2 infection or reinfection. While current literature presents mixed findings regarding the risk of SARS-CoV-2 infection in individuals with depression (212), our results suggested a shared genetic vulnerability to depression and SARS-CoV-2 infection (see section 4.1.2.). Additionally, prior studies conducted in Europe had reported associations between these psychiatric PRSs and risk of SARS-CoV-2 infection in the general population (299,300). Therefore, we expected PRS for these mental disorders, especially depression, to predict risk of infection. However, it is important to note that our study was limited for the self-reported nature of SARS-CoV-2 infection data. Australia experienced minimal COVID-19 cases until early 2022 (301), by which time over 93% of the population older than 16 years old had been fully vaccinated (302). Vaccines significantly reduce the severity of infections, often making them asymptomatic (303), which suggests that many individuals may have been infected or reinfected without being aware. This underreporting likely affected our ability to detect associations between PRSs and infection risk. Furthermore, it is essential to note that the mentioned studies reporting associations between psychiatric PRSs and COVID-19 primarily focused

on the general population, so their findings may not directly translate to clinical populations, such as individuals with depression. Therefore, although our findings from Study V indicate that PRSs for these mental disorders do not predict a higher risk of infection or reinfection in individuals with depression, further studies are warranted. These studies should assess infection rates using clinical data rather than self-reported measures and take into account the individuals' vaccination status.

We also anticipated that a higher genetic load for mental disorders might explain the increased risk of long COVID reported in individuals with mood disorders (304,305). However, we did not find that PRSs for the mental disorders of interest predicted long COVID. The existing literature on the association between genetic factors linked to mental disorders and the risk of long COVID is limited, highlighting the need for further research on this topic. Nevertheless, our findings do not support the use of psychiatric PRSs as effective tools for predicting risk of post-COVID conditions in individuals with depression, highlighting the importance of identifying other potential risk factors, including environmental influences, behavioural patterns, or other biological mechanisms, that might better explain the vulnerability to long COVID in these individuals. This approach could provide a more comprehensive understanding of the interplay between mental health and long COVID, leading to better prevention and treatment strategies.

We hypothesized that levels of psychological distress caused by the pandemic may vary based on the genetic predisposition to depression and other mental disorders. Thus, we analysed the association between these psychiatric PRSs and COVID-related stress and COVID-19 burnout. We found that a higher genetic predisposition to depression predicted higher levels of COVID-19 burnout. Although prior studies have not directly assessed the association between

psychiatric PRSs and COVID-related stress or burnout, a previous study reported that the depression PRS was associated with higher COVID-19 risk perceptions (306). These findings may reflect maladaptive coping strategies among individuals with a high genetic predisposition to depression, potentially contributing to elevated levels of COVID-19 burnout (307). Results from mediation analyses suggested that this association was fully mediated by anxiety symptoms, indicating that in pandemic contexts or similar environmental stressors, targeting anxiety might be key to address burnout related to the stressor. Several studies have highlighted the significant amount of COVID-19 information in the news and media as a potential source of anxiety, due to both the volume of information and the prevalence of fake news (308–310). Reliable information programs from health agencies could help alleviate this anxiety, particularly if they target individuals with mental disorders. Notably, one study conducted in Iran found that increased health literacy was linked to decreased anxiety levels during the COVID-19 pandemic (311), suggesting a valuable focus for future interventions. Moreover, self-administered or digital psychosocial interventions focusing on reducing prolonged arousal, challenging irrational thoughts or fears, and maintenance of regular 24 hour sleep-wake cycles early during a pandemic, or at other times of spikes in community-acquired viral infections, may well significantly improve anxiety symptoms (312).

COVID-19 burnout can detrimentally impact both mental and physical well-being, while it can also result in reluctance to adhere to anti-pandemic measures (313,314). This underscores that addressing these mental health challenges is important not only for individual well-being, but also for public health efforts. Thus, by targeting anxiety symptoms, it might be possible to mitigate the effects of burnout on mental and physical health while also improving adherence to necessary health measures during such crises.

4.2. IMPLICATIONS AND INTERVENTIONS

The present thesis provides evidence of increased vulnerability of individuals with pre-existing mental disorders to COVID-19, which is consistent with findings related to other infections (67,87,90,222,231,232). Results from Study I indicate an increased risk of COVID-related death for individuals with most mental disorders, which further contributes to the morbidity and excess mortality observed in individuals with mental disorders, especially in those with severe mental disorders (13). While factors such as poor lifestyle habits and substance use contribute to this health burden, strong evidence supports the existence of inequalities in medical care that disadvantage individuals with mental disorders (315). People with mental disorders often receive less and lower quality preventive and screening services (316), and several studies assessing the risk of mortality due to different causes in patients with mental disorders have reported that deficits in quality of medical care explained a substantial part of the excess mortality (317,318). Thus, a critical step in addressing this excess of morbidity and mortality is to improve the access and the quality of the medical care.

For COVID-19 and other infectious diseases, prevention is paramount, so efforts should first focus on preventing infection. Targeted information campaigns aimed specifically at individuals with mental disorders could be useful in increasing awareness and adherence to preventive measures. One of the primary barriers to vaccination among individuals with mental disorders is a lack of understanding of the benefits of vaccines and a general lack of trust (209,211). Therefore, vaccination promotion strategies tailored to the psychiatric population would improve knowledge, address specific concerns, and subsequently enhance confidence in vaccines. A pre-pandemic study conducted

in the USA implemented a vaccination program at a non-traditional site to address these barriers and facilitate access for people with mental disorders. This approach improved the attitudes about the safety and efficacy of immunizations, with a significant increase in vaccination rates over baseline, ranging from 18% to 83% for individual vaccines (319).

Individuals with mental disorders could also benefit from systematic screening for common infectious diseases, including COVID-19. Existing evidence suggests that these screenings might work if they were nurse-led and implemented in mental health services (320), as one of the reasons for inequalities in healthcare provision in this population is the lack of co-located medical and mental health services (321). Early detection through regular screening would ensure timely medical care and treatment in case of infection, thus reducing the risk of severe outcomes and mortality.

Biological factors related to mental disorders also contribute to the increased risk of severe COVID-19 and mortality observed in individuals with these conditions. Our findings from Study II indicate that while various altered biological mechanisms may underlie this association, a pro-inflammatory state is likely a common outcome. However, current evidence suggests that there is a great heterogeneity regarding inflammation even within individuals with the same mental disorder. For instance, focusing on depression, several authors have proposed the existence of two phenotypes of depression, the “typical” depression and the “immune-metabolic” depression. Only the latter seems to be associated to immune-inflammatory dysregulations (322–325). Moreover, some authors have reported increased levels of cytokines during acute phases of mental disorders, but not in stable phases (98), and the severity of the mental disorder appears to correlate with the levels of inflammatory markers (97). Therefore, immune dysregulations should not be assumed in all individuals with

mental disorders. Given that excessive systemic pro-inflammatory responses have been linked to higher COVID-19 severity and mortality risk (240), assessing the cellular immune response and blood levels of inflammatory markers (240) in patients with pre-existing mental disorders who contract COVID-19, could have significant prognostic value. Moreover, a dysregulated inflammatory response has also been associated with severe outcomes in other common infectious diseases (326–328), suggesting that this practice could be extended to other infectious diseases or potential future epidemics. Furthermore, interventions targeting inflammation in individuals with mental disorders might potentially mitigate the heightened mortality risk associated with infectious diseases and other related physical conditions, while concurrently enhancing mental well-being. This could be addressed through three main strategies: the administration of anti-inflammatory drugs, prescription of lifestyle measures, and psychosocial interventions.

The potential use of anti-inflammatory drugs in treating mental disorders generated high expectations, so several RCTs have analysed the efficacy of various anti-inflammatory agents in psychotic disorders, bipolar disorder, and depression (329–332). While these studies indicate potential benefits, no clear recommendations can be made due to the heterogeneity in patient populations, altered biological pathways, treatment regimens, and outcomes (333). Conversely, the positive effects of interventions based on improving lifestyle habits and promoting mental health are well-documented and readily available.

Several studies have reported decreased levels of inflammation and improvements in mental health in individuals with schizophrenia following add-on exercise therapies (334,335). Moreover, a very recent meta-analysis including 218 RCTs evaluating the effectiveness of exercise interventions for depression, concluded that exercise was an effective treatment for depression, specifically

that including walking, yoga, and strength training, and that these exercises were equally effective for individuals with and without comorbidities, and with different baseline levels of depression (336). Similarly, diet interventions based on increasing the consumption of vegetables and reducing the consumption of unhealthy food have been shown to reduce inflammation and improve mental health symptoms in individuals with depression (337,338). These results suggest that educating patients about the advantages of a balanced diet and regular exercise, along with providing specific dietary and exercise guidelines, might serve as an effective preventive strategy. This approach could help mitigate the severity of mental disorders, enhance the immune system, and reduce the risk of future physical health conditions, regardless of the type of mental disorder.

Finally, psychosocial interventions have been reported to improve immunity. A systematic review including 56 RCTs assessing the effect of psychological interventions, mainly cognitive behavioural therapy (CBT), on immune markers, reported that these interventions enhanced immune system function and decreased levels of pro-inflammatory cytokines. Notably, the effects persisted for at least 6 months after the intervention (339). Despite the proven effectiveness of psychological interventions in addressing mental health symptoms and improving general well-being (340), these interventions are often scarce in public health systems. This is especially concerning for common mental disorders such as anxiety and depression. Focusing on Spain, there are six clinical psychologists for every 100,000 inhabitants in the public health system, and the number of psychiatrists is much lower than in other European countries (341). As a result, many individuals with mental disorders do not receive the care they need, and, for those that do, sessions are short and spaced in time. Moreover, many individuals do not reach specialized psychological care and are treated by primary care physicians, who are already overwhelmed and lack the time and

skills to address psychological issues, so often they end up prescribing psychotropic drugs (342). Therefore, increasing resources allocated to mental health and improving accessibility to mental health services should be considered a public health priority.

The COVID-19 pandemic has underscored the unpreparedness of mental health systems to handle sudden surges in mental health needs following global stressors like pandemics. Mental health should be a component of national emergency preparedness plans. Hence, it's imperative to allocate resources toward establishing rapid-response programs that can deliver mental health care in emergency contexts (343). Results from Studies III, IV, and V suggest that addressing anxiety and pandemic-related stress, while enhancing social support and resilience, may effectively mitigate the mental health impact during an emergency context. Smartphone use has become ubiquitous, even in remote and resource-constrained environments worldwide, making these devices a powerful medium for improving access to psychiatric care (344). Self-administered digital interventions targeting these factors can effectively alleviate psychological distress during pandemics or other periods of increased community-acquired viral infections, preventing the onset of mental disorders in the general population. These have been reported to have small but significant effects on mental health symptoms, being the effects larger when the interventions included CBT (312). Moreover, the use of chatbots could be effective in addressing the shortage of mental health specialists in emergency contexts (345).

For those with pre-existing mental disorders it is important to maintain the access to their treatment. Equipping psychiatrists and psychologists with tools to switch to an online format when necessary would be especially effective in the context of pandemics or other circumstances where in-person visits are not

possible, for instance due to lack of professionals in the geographical area (346,347). Moreover, wearable devices can facilitate real-time monitoring and evaluation of patients. These devices can track physiological and behavioural data, providing continuous insights into a patient's condition (348). This real-time data can enable healthcare providers to adjust treatments promptly, improving the overall effectiveness of mental health care. Additionally, integrating telehealth and wearable technology into mental health services can enhance accessibility, reduce the burden on healthcare systems, and ensure that patients receive consistent and personalized care regardless of the context.

4.3. STRENGTHS AND LIMITATIONS

This section provides a summary of the overall strengths and limitations of this thesis, which should be considered when interpreting the results of the thesis and their implications for future research and clinical practice. The specific strengths and limitations of each individual study are detailed in Table 4.

One of the main strengths of this thesis is the utilization of large-scale electronic health records. The use of electronic health records offers the opportunity to generate reliable real-world evidence reflecting routine clinical practice, without being affected by selective participation or recall biases. This allows for more reliable and generalizable findings. Moreover, the thesis used data from the most recent available GWAS from the Psychiatric Genomics Consortium. This ensures that the genetic analyses are based on the latest and most relevant genetic findings, enhancing the validity of the results. Finally, some of the population-based studies included in the thesis were based on longitudinal data, allowing for the tracking of changes over time and providing insights into

temporal relationships. This comprehensive approach strengthens the overall conclusions drawn from the research.

Despite the strengths mentioned above, the results of the present thesis should be interpreted in light of several limitations. A notable limitation is the lack of generalizability of the results obtained from studies using genetic data (Studies II and V), as participants were predominantly of European ancestry. This restricts the applicability of the findings to other populations with different genetic backgrounds. These studies were also limited by potential genetic contributions or interactions not accounted in the analyses. This gap may result in an incomplete understanding of the genetic underpinnings of the studied associations between mental disorders and COVID-19.

Another limitation of the present thesis is the self-reported nature of the data from Studies III, IV, and V. Despite the fact that questionnaires used had been previously validated, these include the possibility of reporting and recall biases, which might affect the reliability of findings. Similarly, pre-existing mental health diagnosis in Studies III and IV we also self-reported. Moreover, in studies III and IV we lacked pre-pandemic data, which limits the ability to compare mental health outcomes before and after the pandemic, potentially affecting the interpretation of the pandemic's impact.

The lack of data on specific variables known to influence mental health and COVID-19 outcomes presents a significant limitation of this study. For example, in Study I, we were unable to obtain information on socioeconomic status, use of psychotropic drugs, and smoking habits. Similarly, in Study V, data on vaccination status were missing. These factors are critical confounders that can impact our outcomes. Furthermore, the possibility for residual confounding

exists due to other unmeasured genetic, social, and clinical factors, emphasizing the need for careful interpretation of our findings.

Table 4

Strengths and limitations of individual studies of the present thesis

Study	Strengths	Limitations
I	• Large sample size • Real-world evidence from routine clinical practice, free from selective participation or recall biases	• Lack of information on current mental health symptomatology • No information on use of psychotropic drugs • Lacked data on smoking and socioeconomic status
II	• Use of datasets from the largest available GWAS available	• Participants predominantly of European ancestry • The study design did not account for BMI or vaccination effects on COVID-19 outcomes. • Our approach might miss complex gene-gene or gene-environment interactions that contribute to phenotypic outcomes. • MR results may be biased by overlapping samples in large GWAS studies
III	• Nationally representative sample	• Cross-sectional design • MDD and GAD based on self-reported screening scales • Lack of pre-pandemic data
IV	• Longitudinal design • Use of weights to ensure sample representativeness	• Lack of pre-pandemic data • Mental health symptoms based on based on self-reported screening scales • Considerable loss of follow-up • Limited sample size for pre-existing mood disorders
V	• Large sample of individuals with depression	• Participants predominantly of European ancestry • Self-reported infection and long COVID • Lack of data on current antidepressant use

Note. GWAS: genome-wide association studies, BMI: body mass index, MR: Mendelian Randomization, MDD: major depressive disorder, GAD: generalized anxiety disorder.

4.4. FUTURE PERSPECTIVES

The unprecedented COVID-19 pandemic has underscored the profound challenges that emerging pathogens pose to both physical and mental health, particularly underscoring the vulnerability of some populations, such as those with pre-existing mental disorders. The intricate relationship between mental disorders and infectious diseases is shaped by a complex interplay of genetic, social, and clinical factors. To fully understand this interplay, further research should aim to elucidate the underlying mechanisms that heighten the vulnerability to COVID-19 and other infections in individuals with pre-existing mental disorders. These studies should be conducted across diverse populations to ensure the generalizability of results, as existing literature predominantly focuses on North American and European populations.

Longitudinal studies could provide valuable insights into how mental health trajectories influence susceptibility to infections. Future studies employing the constantly evolving statistical genetic methods will enhance our understanding of genetic overlap and causality between mental disorders and infections, potentially identifying new genes involved. Integrating GWAS data with transcriptomic and proteomic data will help identify shared biological pathways and potential biomarkers, leading to the discovery of new treatment targets. Our findings, together with existing evidence, indicate that inflammation might play a role in this association. However, literature indicates that inflammation is not consistently present in all individuals with mental disorders or at all times (98,322). Therefore, initial studies should focus on identifying specific subgroups, based on stable biomarkers, who may benefit from anti-inflammatory treatments. Longitudinal studies with repeated measurements of immune markers are crucial to elucidate these relationships. This knowledge

could pave the way for exploring new therapeutic targets and drug repositioning strategies for medications traditionally used in immune-related disorders, tailored to each patient subgroup. Such approaches hold promising potential to improve both mental health symptoms and outcomes for infections and other conditions related to inflammation in individuals with pre-existing mental health conditions.

Current evidence does not indicate a disproportionate mental health impact of the COVID-19 pandemic on individuals with pre-existing mental disorders. However, comprehensive studies are essential to assess the long-term impact of the COVID-19 pandemic and its consequences on mental health in this population, as such research will provide a deeper understanding of potential delayed or cumulative effects. Furthermore, while digital health interventions and telepsychiatry hold promising results in mental health prevention and improving psychological distress (312), further studies are required to confirm its effectiveness in different populations, and specifically in those with pre-existing mental conditions.

The COVID-19 pandemic has emphasized the critical need for rigorous standards and advancements in scientific research and publication. The global urgency to understand COVID-19 and its impact on mental health resulted in an unprecedented surge of scientific papers on this subject. However, this rapid influx of research also exposed significant challenges, including the questionable utility of findings due to rushed methodologies and inadequate peer review processes. Moreover, the high number of retracted papers highlighted weaknesses in the scientific publishing system (349,350), underscoring the necessity for enhanced oversight and quality control. These experiences should serve as instructive lessons to prioritize methodological rigor, transparency, and thorough peer review in future pandemics or emergency contexts requiring swift

dissemination of information. This approach will ensure that published research is not only reliable but also valuable in guiding effective public health responses and interventions.

The evidence gathered from the COVID-19 crisis must be used to improve countries' preparedness for future emergencies and to invest in effective public health policies. Importantly, mental health must be a component of national emergency preparedness plans. Only by doing so we can guarantee a swift and efficient response that minimizes the impact of future health crises on populations and health systems. Robust investment and strategic planning in public health are essential to protect the health and well-being of people worldwide.

5 Conclusions

It is empowering to know I am doing something,

I am taking a stand, I am disrupting

- Greta Thunberg

Based on the findings of the present thesis, we can conclude:

1. The patterns of SARS-CoV-2 infection and COVID-19 hospitalization risks were not equal across types of mental disorders. However, nearly all mental health diagnoses were associated with an increased risk of COVID-19-related death.
2. Alterations in various genes were shared between different mental disorders and COVID-19 infection and hospitalization, all of which have been linked to immune function.
3. Potential causal associations were found between having a mental disorder, specifically ADHD, depression, and PTSD, and an increased risk of SARS-CoV-2 infection and hospitalization.
4. Higher COVID-related stress and lower social support predicted increased risk of major depressive disorder and generalized anxiety disorder during the early pandemic, with greater consequences for those with pre-existing mental disorders.
5. A general increase in depressive and anxiety symptoms was observed from the early to mid-pandemic in Spain across groups of mental health diagnoses. For those with comorbid depression and anxiety, depressive symptoms remained high and stable.
6. The effect of COVID-related stress, social support, and resilience on depressive and anxiety symptoms did not differ according to the type of pre-existing mental disorder.
7. The polygenic risk scores for depression, bipolar disorder, schizophrenia, and anxiety did not predict risk of SARS-CoV-2 infection and long COVID in individuals with depression.

8. Pandemic interventions should focus on reducing anxiety symptoms to effectively support people with depression, regardless of their genetic susceptibility.

6 References

I let the actions of my life stand for what I am as a human being. Contend with that, not the words

- Meryl Streep

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