UNIVERSITAT DE BARCELONA

Social determinants of major depressive disorder

Exploring the interplay of age, loneliness, and the COVID-19 pandemic

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DOCTORAL THESIS

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Social determinants of major depressive disorder: exploring the interplay of loneliness, age, and the COVID-19 pandemic

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"*Naixem sols i morim sols, i en el parèntesi,*

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compartir la vida per oblidar-la."

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Table of contents

Abbreviations and acronyms

CBT: Cognitive-Behavioural Therapy

CI: Confidence Interval

CIDI: Composite International Diagnostic Interview

CMD: Common Mental Disorders

COVID-19: Coronavirus Disease 2019

CoVs: Coronaviruses

DSM: Diagnostic and Statistical Manual of Mental Disorders

ETL: Evolutionary Theory of Loneliness

HPA: Hypothalamic-Pituitary-Adrenal

ICD: International Classification of Diseases

MDD: Major Depressive Disorder

MDE: Major Depressive Episode

MERS-CoV: Middle East respiratory syndrome coronavirus

MSPSS: Multidimensional Scale of Perceived Social Support

NPI: Nonpharmaceutical Interventions

OSSS: Oslo Social Support Scale

PCC: Post COVID-19 Condition

PHQ: Patient Health Questionnaire

PPMD: Pre-pandemic Mental Disorders

RCT: Randomized Clinical Trial

SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus

SD: Social Determinants

SES: Socioeconomic Status

UK: United Kingdom

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 4 objectives and 4 articles:

Article I: **Gabarrell-Pascuet A**, Moneta MV, Ayuso-Mateos JL, Miret M, Lara E, Haro JM, Olaya B, Domènech-Abella J. The effect of loneliness and social support on the course of major depressive disorder among adults aged 50 years and older: A longitudinal study. *Depression and anxiety*. 2022 Feb;39(2):147-155. doi: 10.1002/da.23236. Epub 2022 Jan 14. PMID: 35029840.

JCR journal impact factor and quartile: 7.4 – Q1 (JCR) – Q1 (SJR) [2022]

Article II: **Gabarrell-Pascuet A**, Varga TV, Moneta MV, Ayuso-Mateos JL, Lara E, Olaya B, Haro JM, Domènech-Abella J. What factors explain the changes in major depressive disorder symptoms by age group during the COVID-19 pandemic? A longitudinal study. *Journal of Affective Disorders*. 2023 May 1;328:72-80. doi: 10.1016/j.jad.2023.02.042. Epub 2023 Feb 16. PMID: 36806591; PMCID: PMC9933581.

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

Article III: **Gabarrell-Pascuet A**, Koyanagi A, Felez-Nobrega M, Cristóbal-Narváez P, Mortier P, Vilagut G, Olaya B, Alonso J, Haro JM, Domènech-Abella J. The Association of Age With Depression, Anxiety, and Posttraumatic Stress Symptoms During the COVID-19 Pandemic in Spain: The Role of Loneliness and Prepandemic Mental Disorder. *Psychosomatic Medicine*. 2023 Jan 1;85(1):42-52. doi: 10.1097/PSY.0000000000001146. Epub 2022 Sep 30. PMID: 36201774.

JCR journal impact factor and quartile: 3.3 – Q2 (JCR) – Q1 (SJR) [2022]

Article IV: Domènech-Abella J, **Gabarrell-Pascuet A**, García-Mieres H, Mortier P, Felez-Nobrega M, Cristóbal-Narváez P, Vilagut G, Olaya B, Alonso J, Haro JM. Loneliness during the last phase of the COVID-19 pandemic in Spain: A longitudinal study of group-based trajectories, risk factors, and consequences in mental health. *Psychiatry Research*. 2023 Aug;326:115327. doi: 10.1016/j.psychres.2023.115327. Epub 2023 Jun 30. PMID: 37413806.

JCR journal impact factor and quartile: 11.3 – Q1 (JCR) – Q1 (SJR) [2022]

Resum de la tesis

Títol

Determinants socials del trastorn depressiu major: explorant la interacció entre la soledat, l'edat i la pandèmia de la COVID-19

Introducció

La depressió és una condició altament prevalent i una de les principals causes d'anys viscuts amb discapacitat a nivell mundial. La seva prevalença global continua augmentant, amb el trastorn depressiu major (TDM) com la forma més comuna. El TDM està significativament influït pels determinants socials, especialment aquells relacionats amb les interaccions socials. El suport social i la soledat, representant dimensions objectives i subjectives de les relacions interpersonals, s'han associat amb la depressió, afectant-ne la incidència i la gravetat.

La pandèmia de la COVID-19 i les mesures de contenció han modificat les interaccions socials i estès les desigualtats socioeconòmiques, fomentant els sentiments de soledat, alteracions en les xarxes de suport social i l'empitjorament de la salut mental, especialment els símptomes depressius i el TDM.

Malgrat la investigació científica en aquest àmbit, persisteixen mancances significatives en el coneixement sobre la interacció dels determinants socials amb la depressió. Per exemple, cal entendre millor com la soledat interacciona amb els aspectes objectius de les relacions

socials afectant el risc del TDM i, concretament, el seu curs. O les causes que expliquen les diferències d'edat en l'impacte de la pandèmia de la COVID-19 en la depressió, així com l'efecte d'altres determinants socials. Basant-nos en aquestes mancances, hem formulat les diferents hipòtesis i objectius del nostre estudi.

Hipòtesis

1. Les persones amb un suport social pobre i sentiments de soledat tenen més probabilitats de presentar un curs pitjor del TDM.
2. La soledat actua com a factor mediador en l'associació entre el suport social i el TDM.
3. El risc del TDM va augmentar durant la pandèmia, especialment entre les persones més joves.
4. La diferència en el risc de TDM per grup d'edat s'explica per les disparitats en l'impacte de la pandèmia en les relacions socials i les condicions socioeconòmiques.
5. Les persones joves amb trastorns mentals pre-pandèmics (TMPP) van ser les més afectades per la soledat durant la pandèmia.
6. L'impacte de la soledat en la depressió durant la pandèmia va ser més elevat entre les persones joves amb TMPP.
7. Tot i que molts casos de soledat durant la pandèmia són transitoris, una part de la població continuarà experimentant nivells persistents de soledat i símptomes depressius.
8. Les persones que han mostrat una major vulnerabilitat a la soledat durant la pandèmia (joves, amb TMPP i baix nivell

socioeconòmic) tindran un major risc de patir cursos crònics de soledat després de la pandèmia.

Objectius

1. Investigar l'efecte mediador de la soledat en l'associació entre el suport social i el curs del TDM.
2. Avaluar l'associació longitudinal de l'edat amb els canvis en el risc de TDM abans i durant la pandèmia i analitzar potencials variables mediadores com la soledat, el suport social, la resiliència i factors socioeconòmics.
3. Examinar la relació entre l'edat i els símptomes depressius durant la pandèmia i determinar si la soledat té un efecte moderador en aquesta associació en funció de la presència o absència de TMPP.
4. Explorar els cursos de la soledat durant la pandèmia i després de l'últim estat d'emergència a Espanya i identificar les característiques de les persones en cada curs i el seu impacte en el TDM.

Mètodes

Aquesta tesi consta de quatre articles, cadascun centrat en un dels objectius de la tesi. Les dades dels estudis provenen de tres cohorts diferents, totes representatives de la població adulta espanyola.

L'Article I inclou 404 persones (majors de 50 anys amb TDM) entrevistades 3 vegades durant 7 anys abans de la pandèmia (cohort

‘Edad con Salud’ 2011). L'Article II es basa en 1.880 entrevistes realitzades abans de la pandèmia i en 1.103 realitzades a la mateixa mostra durant la pandèmia (cohort ‘Edad con Salud’ 2019). L'Article III utilitza dades de 2.000 participants de l'estudi MINDCOVID. L’Article IV utilitza el mateix conjunt de dades, juntament amb dades de seguiment de 1.300 persones.

Les escales utilitzades per mesurar les variables principals són: OSSS-3 (suport social), UCLA-3 (soledat), CIDI (TDM en ‘Edad con Salud’) i PHQ-9 (TDM en MINDCOVID). Vam construir models d’equacions estructurals (Article I), de regressió (Articles II i III) i de trajectòria basats en grups (Article IV) per testar les hipòtesis de l'estudi.

Resultats principals

1. La soledat media la relació entre el suport social i el curs del TDM. Hem identificat dos patrons significatius de mediació longitudinal: un suport social més baix preveu més soledat, que alhora preveu un augment en el TDM.
2. Entre les persones més joves (18-29 i 30-44 anys), el risc de tenir TDM durant la pandèmia va augmentar de 0,04 a 0,25 i de 0,02 a 0,11, respectivament. Aquest increment s’explica parcialment (36,6%) per l'augment de la soledat, una situació econòmica empitjorada i una menor resiliència.
3. L'edat està relacionada negativament amb els símptomes depressius i la soledat. La soledat s'associa amb més símptomes depressius. Aquesta associació és més forta en individus joves

sense TMPP i en persones grans amb TMPP. L'associació entre l'edat i la soledat és més forta amb TMPP.

4. Detectem tres cursos de soledat: (1) invariant baix (42,6%), (2) decreixent mitjà (51,5%) i (3) relativament invariant alt (5,9%). Tot i que la fi de les mesures restrictives va significar una disminució de la soledat i, per tant, dels símptomes depressius; per a molts (p.e., joves, amb TMPP, o les dones) el risc de soledat després de la pandèmia es va mantenir alt, presentant, conseqüentment, símptomes depressius més elevats.

Conclusions

Les intervencions per prevenir i millorar el curs del TDM haurien de centrar-se en el suport social, la soledat i la resiliència, amb un enfocament en poblacions vulnerables com les persones joves, amb dificultats socioeconòmiques i amb una condició psiquiàtrica preexistent.

Abstract

Introduction

Depression is a highly prevalent condition, recognized as one of the leading causes of years lived with disability worldwide. Its global prevalence continues to rise, with major depressive disorder (MDD) emerging as the most common form. MDD is significantly influenced by social determinants, particularly those related to interpersonal interactions. Social support and loneliness, representing objective and subjective dimensions of interpersonal relationships respectively, have been associated with depression, affecting its onset and severity.

The COVID-19 pandemic and its containment measures reshaped social interactions and amplified socioeconomic inequalities. It led to heightened feelings of loneliness, altered social support networks, and exacerbated mental disorders symptoms, particularly depressive symptoms and MDD.

Despite considerable attention from the scientific community, significant gaps persist in our understanding of the interplay between social determinants and depression. For instance, the way in which loneliness interacts with objective aspects of social relationships affecting the risk and disease course of MDD remains poorly understood. Similarly, the causes explaining the age differences in the impact of the COVID-19 pandemic on depression, as well as the effect of other social determinants, warrant deeper investigation. Based on

these gaps, we have formulated the different hypotheses and objectives of the present thesis.

Hypotheses

1. Individuals with poor social support and experiencing loneliness are more likely to present a worse course of MDD.
2. Loneliness acts as a mediating factor in the association between social support and MDD.
3. The risk of MDD increased during the pandemic, particularly among younger adults.
4. The different risks of MDD by age group might be explained by disparities on the impact of the pandemic on social relationships and socioeconomic conditions.
5. Younger adults with pre-pandemic mental disorders (PPMD) were the most affected by loneliness during pandemic.
6. The impact of loneliness on depression during the pandemic was higher among younger adults with PPMD.
7. While many cases of loneliness during the pandemic were transient, a portion of the population will continue to experience persistent levels of loneliness and depressive symptoms.
8. Individuals who have shown greater vulnerability to loneliness during the pandemic (young adults, with PPMD, and a low socioeconomic status) are at higher risk of experiencing chronic courses of loneliness after the pandemic.

Objectives

1. Investigate the mediating effect of loneliness in the association between social support and MDD course.
2. Asses the longitudinal association of age with changes in MDD risk before and during the pandemic and evaluate potential mediating variables such as loneliness, social support, resilience, and socioeconomic factors.
3. Examine the relationship between age and depressive symptoms during the pandemic, determine whether loneliness has a moderating effect on this association depending on the presence or absence PPMD.
4. Explore the courses of loneliness during the pandemic and after the last state of emergency in Spain, and identify the characteristics of individuals in each course and their impact on MDD.

Methods

This thesis is comprised of four articles, each one addressing one of the thesis objectives. We used data from three different cohorts, all representative of the Spanish adult population.

'Article I' included 404 individuals (50+ years having MDD) from 3 waves of the 'Edad con Salud' 2011 cohort followed-up for 7 years (before COVID-19). 'Article II' used data from 'Edad con Salud' 2019 cohort and included 1,880 individuals interviewed before the pandemic and 1,103 interviewed again during the pandemic. 'Article III' used data of 2,000

participants of the MINDCOVID study. 'Article IV', used the same dataset of 2,000 participants, along with follow-up data of 1,300 individuals.

The instruments used to assess the main variables were: OSSS-3 (social support), UCLA-3 (loneliness), CIDI (MDD in 'Edad con Salud' cohorts), and PHQ-9 (MDD in the MINDCOVID study). Cross-lagged panel models (Article I), regression models (Articles II and III), and group-based trajectory models (Article IV) were constructed to test the hypotheses of the study.

Main results

In 'Article I' we identified two significant longitudinal mediation patterns: lower social support predicted higher subsequent levels of loneliness (Coef. = −0.16; $p < .05$), which in turn predicted an increase in MDD recurrence (Coef. = 0.05; $p < .05$).

In 'Article II' we found that among the younger age cohorts (18-29 and 30-44 years) the probability of having MDD during the pandemic increased from 0.04 (95 % CI: 0.002-0.09) to 0.25 (0.12-0.39) and from 0.02 (-0.001-0.03) to 0.11 (0.04-0.17), respectively. 36.6% of the association between age and risk of MDD during the pandemic was explained by loneliness, low resilience, and worsened economic situation.

In 'Article III' we observed that age was negatively related to depressive symptoms and loneliness. Loneliness was associated with higher levels of depressive symptoms. This association was stronger in younger

adults without PPMD and in older adults with them. The association between age and loneliness was stronger in those with PPMD. Loneliness mediated the association of age with depressive symptoms.

Finally, in 'Article IV' we detected three courses of loneliness: (1) invariant low (42.6%), (2) decreasing medium (51.5%), and (3) fairly invariant high (5.9%). Younger adults more frequently reported loneliness compared to middle-aged and, particularly, older individuals. Other risk factors for loneliness were being female, unmarried, and, having PPMD.

Conclusions

1. Loneliness mediates the relationship between social support and MDD course.
2. The young had a higher risk of MDD during the pandemic, partly explained by increased loneliness, worsened economic situation, and lower resilience.
3. Loneliness acted as a moderator depending on the presence/absence of PPMD on the relationship between age and MDD.
4. Although the end of social restrictive measures meant a decrease in loneliness and therefore in depressive symptoms for many, those with PPMD, younger adults, and females had a higher risk of maintaining high levels of loneliness after the pandemic, and therefore, higher depressive symptoms.

Interventions to prevent and improve the course of MDD should target social support, loneliness, and resilience, with a focus on vulnerable populations such as younger adults, those with financial strain, and those with a pre-existing psychiatric condition.

Outline of this thesis

The thesis consists of 6 chapters. In **Chapter 1**, I provide an introduction summarizing the background and context of the study, briefly reviewing major depressive disorder, loneliness, and social support and their epidemiology, together with its associations and contextualization during the COVID-19 pandemic. The introduction ends with a published review and meta-analysis related with the topic and co-authored by me. Finally, I provide a summary of the gaps in the literature and the justification of the thesis. In **Chapter 2**, I outline the specific objectives and hypotheses of the doctorate project, followed by an ethics statement. **Chapter 3** includes the four papers that constitute the thesis methods and results section. Each article addresses one of the main objectives of the thesis. **Chapter 4** includes a general discussion, in which I first present an overview of the main findings of each paper and interpret them considering a broader perspective. Then, I discuss the implications and potential interventions derived from the thesis' findings. This is followed by an acknowledgement of the strengths and limitations of our studies. Lastly, I include a section of future perspectives, outlining how the research should be continued. **Chapter 5** presents the conclusions of the thesis. **Chapter 6** includes all the references cited in the text of the thesis dissertation. Finally, the **Annexes** include a list of activities and fieldwork carried out during the doctorate research program, as well as a list of other articles co-authored by the doctoral candidate.

INTRODUCTION

1.1.Depressive symptoms and major depressive disorder

Definition, diagnosis, and screening

Depressive disorders, hereafter referred to as depression, are a highly prevalent and life-altering condition, considered one of the leading causes of years lived with disability (YLD) (1). Since 1990, the global prevalence of depression has not ceased to increase (1,2), with 280 million people having depression in 2021 (3). In the present thesis, we are going to focus on major depressive disorder (MDD), the most common depressive disorder, affecting about 185 million people globally (4). Symptoms of MDD involve low mood, reduced interest or pleasure in previously enjoyable activities, insomnia, and fatigue. MDD is linked to economic burden, impaired functionality, decreased quality of life, and increased medical morbidity and mortality (5).

Diagnosis of MDD is based on clinical interview, mainly using the criteria outlined in either the 'Diagnostic and Statistical Manual of Mental Disorders Fifth Edition Text Revision' (DSM-5-TR) (6) or the 'International Classification of Diseases 11th Revision' (ICD-11) (7). These are the two primary diagnostic classification systems, which are commonly employed across hospital, outpatient, and community settings.

The criteria for diagnosis are comparable across diagnostic systems. In both systems, a specific set of symptoms must be satisfied for diagnosis, which clearly differ from the individual's previous general functioning and occur nearly every day during a 2-week period. The symptomatology should imply clinically significant distress or

impairment and not be a manifestation of another health condition, a substance or medication, or more appropriately explained by bereavement.

According to the DSM-5-TR, MDD involves the presence of at least one major depressive episode (MDE), which is the experience of either depressed mood or diminished interest or pleasure, for most of every day, for at least two weeks (6). MDE diagnosis also requires the presence of at least three of the following symptoms in the same 2-week period: (i) significant changes in weight or appetite; (ii) insomnia or hypersomnia; (iii) psychomotor agitation or retardation; (iv) fatigue or loss of energy; (v) feelings of worthlessness or excessive or inappropriate guilt; (vi) difficulty to concentrate and think; and (vii) recurrent thoughts of death, suicidal ideation, or suicide attempt. These symptoms must cause a clinically significant distress or impairment in important areas of functionality, such as the social or occupational areas. Furthermore, the symptomatology cannot be explained by any other disorder, medical condition, or substance use. Finally, for a MDD diagnosis, the occurrence of the MDE must not be better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorder. Additionally, there must never have been a manic episode or a hypomanic episode (6).

The ICD-11 aligns with most of the DSM-5 criteria, but it differs in aspects such as the inclusion of ‘hopelessness’ as a symptom, with a minimum of 5 out of 10 symptoms for diagnosis, as opposed to the 5 out of 9 symptoms required in the DSM-5 (8).

It is also crucial to recognize those individuals experiencing sub-threshold or sub-clinical depression, which means that their symptomatology does not reach the threshold for diagnosis as MDD. Subthreshold symptoms are a risk factor for future MDD diagnosis and new-onset chronic diseases (9–11).

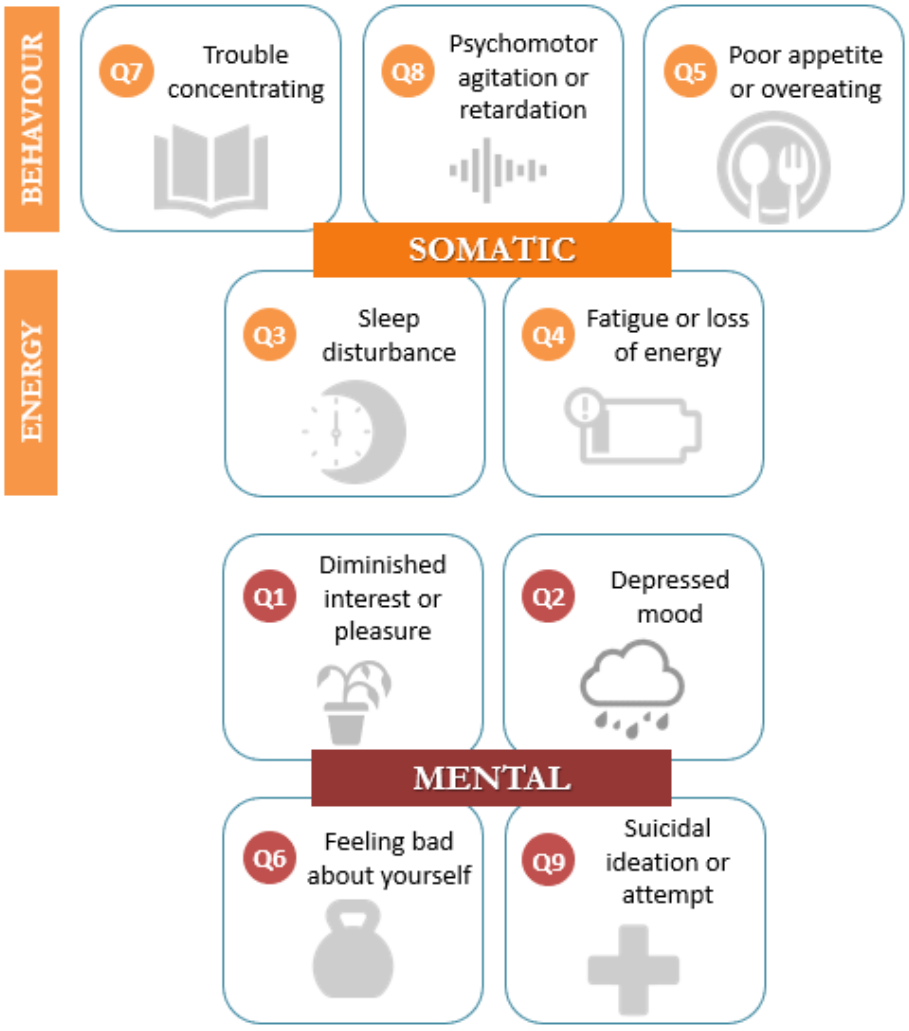
The Composite International Diagnostic Interview (CIDI) is a well-established and extensively utilized tool for evaluating the clinical diagnosis of MDD in both epidemiological and clinical research studies. It is a comprehensive and fully standardized diagnostic interview used to screen for MDD using the definitions and criteria of the ICD or DSM diagnostic systems. It must be administered by lay interviewers that have successfully completed a training program (12,13).

Alternatively, we can use the Patient Health Questionnaire-9 (PHQ-9), a nine-item self-report questionnaire and the most commonly used depression assessment tool. Its popularity in epidemiological studies is attributed to being a free and easily accessible tool that can be self-reported, its brevity, its quick scoring process, and its availability and validity in more than 30 languages (5,14). It consists of the nine criteria for depression from the DSM-IV (Figure 1) and each item is scored from 0 to 3 (0: Not at all; 1: Several days; 2: More than half of the days; 3: Nearly every day), with a total score ranging from 0 to 27, where higher values indicate greater depressive symptoms. This tool has been validated as both a diagnostic and a severity measure (15). A PHQ-9 score ≥ 10 is a well-established cut-off for detecting MDD. PHQ-9 scores can also be used to categorize individuals by depression severity in the following categories: moderate depression (PHQ-9: 10-14), moderately

severe depression (PHQ-9: 15-19), and severe depression (PHQ-9: 20-27). It is important to consider that employing the PHQ-9 scale to assess depression severity may present limitations. Depression is a highly heterogeneous condition, presenting diverse symptomatic profiles (e.g., somatic and mental). Each depression subtype is influenced by distinct risk factors and is associated with different outcomes and clinical features that should be taken into account to enable effective and targeted treatments (Figure 1) (16).

Figure 1

Items of the Patient Health Questionnaire-9 based on the DSM



Note. Items of the PHQ-9 scale grouped according to whether they are more related to the somatic or mental aspects of depression. Adapted from Gabarrell-Pascuet et al., 2023 (16).

Disease course

MDD has its typical onset in adolescence and young adulthood, which are periods of intense brain development (17), although the peak risk period persists until early 40s (18). The median age of onset is at 25 years of age (18), and is similar between women and men (1). Finally, individuals who experience childhood trauma not only face a more than twofold increased risk of developing MDD later in life, but also exhibit more severe symptoms, have a more challenging disease trajectory, and are more likely to be unresponsive to treatment compared to those without early-life trauma (19).

The course of MDD is pleomorphic, meaning that it has several variations in terms of remission and chronicity. A less favourable course is more common in individuals with more severe symptomatology, psychiatric comorbidities, and childhood trauma. Moreover, MDD with psychotic features, is linked to a more adverse illness course and greater functional impairment compared to MDD without psychotic features (20).

The prognosis becomes less favourable as the age of onset increases. According to the results of Schaakxs et al. (21), the course of MDD worsens linearly with age, therefore older adults have a more chronic symptom course, with two to three-fold increase in the probability of still having a depression diagnosis after 2 years. Moreover, they present a lower likelihood of achieving remission and less improvement in the severity of depression.

Episodes of MDD last on average between 3 to 8 months (22). In outpatient care centres, over 50% of patients still have MDD after two years (23,24). Besides, the probability of recurrence is very high, with about 80% of recovered individuals experiencing a recurrent episode at some point in their lives (25). Moreover, the likelihood of recurrence increases with each subsequent episode and with the severity of the episode (26). Despite recovering from MDD, individuals may experience residual symptoms and functional impairment. Finally, a significant proportion of patients (potentially up to 27%) do not achieve recovery and progress to manifesting a persistent depressive condition (27).

Etiology

The etiology of depression is still not clear, but it is generally acknowledged that MDD is a multifactorial disease caused by biological, genetic, environmental, and psychosocial aspects of each individual (5).

The major contributor to MDD risk is the environment. Factors such as stressful life events (e.g., life-threatening experiences, recent negative life events such as somatic diseases, financial difficulties, bereavement, being subjected to violence, separation, or loss of employment) have been widely associated with the pathogenesis of depression (28,29).

The genetic vulnerability to MDD stems from a combination of genetic factors and within-family environmental influences, with both contributing roughly equally to the overall risk (30). The progeny of individuals with MDD have twice the risk of having MDD by early adulthood than the offspring of parents without MDD (31,32).

Nevertheless, families share both genetic and environmental factors, and determining the proportional contributions of these elements to MDD susceptibility has been a focal point in genetic research. The estimated heritability of MDD ranges between 30-50% (33,34), which is considered a moderate heritability and confirms that it is the combination of biological susceptibility and environmental risk and protective factors what drives the risk of MDD.

The identified genetic causal variants for MDD seem to exert small contributions on the overall risk of the disease, so no specific genetic variation has been pinpointed as significantly escalating the risk of MDD (35–37). Moreover, we are still lacking a better understanding of the complex interactions between the environmental and genetic factors causing MDD (35–37). Recent genetic evidence suggests that the genetic basis is mainly pleotropic (i.e., a single gene affecting multiple traits) with other medical conditions. Nevertheless, MDD has a unique genetic architecture and an etiological heterogeneity that distinguishes it from other mental disorders (36). Thus, it is probable that multiple genetic factors, combined with environmental influences, are required for the onset of MDD (35,37). Later in this introduction, we will delve deeper into these environmental influences, contextualized in this thesis as the social determinants of health.

Impact on quality of life

MDD is accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function, representing a

change from their previous functioning (38). MDD is also associated with an increased risk of developing other diseases, such as heart disease, diabetes mellitus, obesity, cognitive impairment, cancer, disability, and higher mortality (39). Furthermore, previous studies have shown that cognitive decline impedes recovery from MDD and diminishes treatment effectiveness (40).

The foremost concern for individuals having MDD is the risk of suicide (22). Studies have indicated that the risk of suicide among MDD patients is nearly 20 times higher compared to the general population and half of the global 800,000 suicides per year occur during a MDE (41).

Management: prevention and treatment

Depressive disorders have significant economic implications, being associated with increased health service use (42). Vieta et al. (43) carried a retrospective, observational study in 2015-2017 based on 69,217 patients with a diagnosis of depressive disorder to estimate the costs of depressive disorders in Spain. The observed total costs in these patients amounted to almost €224 million, with direct health care costs (i.e., costs related with medical care) accounting for 18.4% of the total with the rest and largest component being associated with non-health indirect costs (i.e., costs related to lost productivity, including 18% for temporary occupational disability and 63.6% permanent disability). Considering the cost of premature death, the average cost per patient per year was €3,402, and the estimated societal costs of depressive disorders in Spain exceeded €6 million. Regarding treatment-resistant

depression, the expenses associated with managing the condition in these patients are even higher (44,45).

Therefore, preventive measures are essential to avoid the clinical development of depression and its associated costs, both at the economic, personal, and societal levels. We can distinguish between three types of primary prevention approaches depending on the degree of risk of the individual: (i) 'universal', targeting the general population without considering individual risk factors (e.g., maintaining healthy, psychoactive substance-free lifestyles)); (ii) 'selective', aimed at people exposed to depression risk factors and whose risk of developing MDD is significantly higher than average (e.g., socio-economically disadvantaged groups, migrants, disaster victims, people with a family history of psychiatric illness or a history of substance use); and (iii) 'indicated', for high-risk individuals with detectable subthreshold symptoms of depression (46,47). This last prevention subtype requires early detection to identify those subclinical cases who will likely develop further symptomatology that might lead to MDD. Aside from primary prevention, there are also secondary and tertiary prevention which target people who already meet the criteria for a disorder and include treatment and maintenance measures (47,48).

Interventions targeting MDD risk factors and promoting protective factors can reduce the burden of MDD. Preventive measures can be effective across the entire lifespan, offering benefits not only in terms of reducing or delaying the onset of MDD but also in mitigating its severity or duration.

The design of interventions must consider the multifactorial causes of depression and be multifaceted, targeting the combination of biological, psychological, and social factors affecting depression. Additionally, we also need to be aware of the difficult management of depression due to its heterogeneity in manifestation, severity, and trajectory. And finally, the integration of these approaches should also help reducing mental disorders stigma.

Until now, prevention programmes that reduce the onset of new clinical episodes have proved to be effective reducing MDD incidence (49). A recent meta-analysis of randomised controlled trials of psychological preventive interventions showed a reduction on the chances to develop a depressive disorder of 19%, compared to no preventive intervention (50).

Once diagnosed, various treatment options are available to achieve complete remission of MDD and full functional recovery, while fostering resilience. In addition, there are general measures that contribute to the reduction of symptomatology targeting factors that exacerbate depression, such as adopting better sleeping habits, addressing substance misuse, and implementing lifestyle changes such as quitting smoking, maintaining a healthy diet, and engaging in regular exercise (5).

There are four complementary treatment options, which often exhibit greater efficacy when combined: (i) psychosocial interventions (i.e., psychoeducation, low-intensity interventions, formal support groups, and support for employment and housing), (ii) psychotherapy, (iii)

pharmacotherapy, and (iv) brain stimulation (e.g., electroconvulsive therapy or transcranial magnetic stimulation) (51).

For mild depression cases, the recommended treatment is psychotherapy, while for moderate and severe cases psychotherapy is combined with pharmacotherapy. The combination of both has demonstrated better outcomes than either treatment alone (52,53).

Psychotherapy for MDD includes the following therapies: cognitive-behavioural (CBT), behavioural, psychodynamic, problem-solving, interpersonal, acceptance and commitment, and mindfulness-based cognitive therapy.

It is estimated that among MDD patients receiving treatment, 70% of them do not experience full recovery or remission (54). Some of the barriers contributing to the failure of treatment include poor adherence to treatment (55), the significant stigma associated with this disorder, the lack of investment in mental health to provide quality care, and the high comorbidity associated with the condition (56). Moreover, global treatment coverage for MDD remains insufficient, especially in low- and lower-middle-income countries. In high-income countries, although treatment rates are relatively higher, most MDD patients do not access treatment in specialized mental healthcare services (57). Strategies should aim to close the treatment gap and expand prevention campaigns.

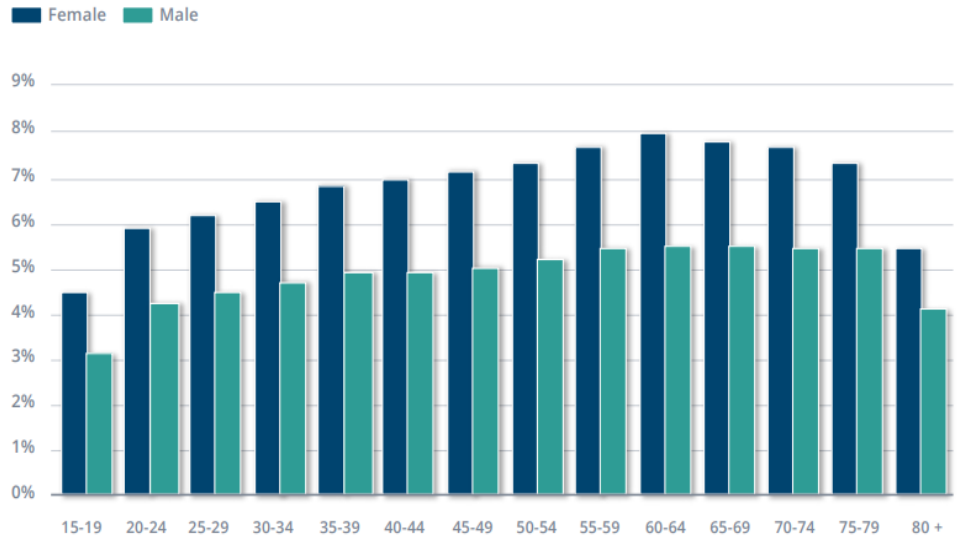
Epidemiology of major depressive disorder

MDD has a global lifetime prevalence of 10.6% (58), with a diverse range of age-of-onset and a substantial likelihood of chronic and recurring symptoms that can persist over a person's entire life. Women have depression at nearly twice the rate of men, with an average lifetime rate of 13.5% for women and 7.5% for men (58,59). Nevertheless, the three times higher global suicide rates and lower treatment rates among males suggest that male depression could be more prevalent than what is reported due to a possible distinct clinical phenotype and differences in coping strategies and help-seeking behaviours (57,60,61).

The average 12-month prevalence of MDD is around 4.5% (58), peaking in older adulthood (Figure 2 (62))**.** This prevalence is similar in high-income countries (4.8%), middle-income countries (4.6%), and low-income countries (3.6%) (58). Specifically, in Spain, the annual prevalence of MDD is 4.7% (4).

Figure 2

Global prevalence of depressive disorders, by age and sex (%)



Note. Regional data show age-standardized estimates. Graph from the World Health Organization Global Health Estimates report, 2017 (62) using data from Global Burden of Disease Study 2015 (4).

1.2.Social determinants of major depressive disorder

Social determinants (SD) of health are, according to the World Health Organization (WHO) definition, the conditions in which people are born, grow, live, work, and age which are shaped by a wider set of forces and systems (i.e., economic, social, and environmental policies and systems, development priorities, societal norms, and political systems (63). Allen et al. (64) also added to this definition the "health systems people can access".

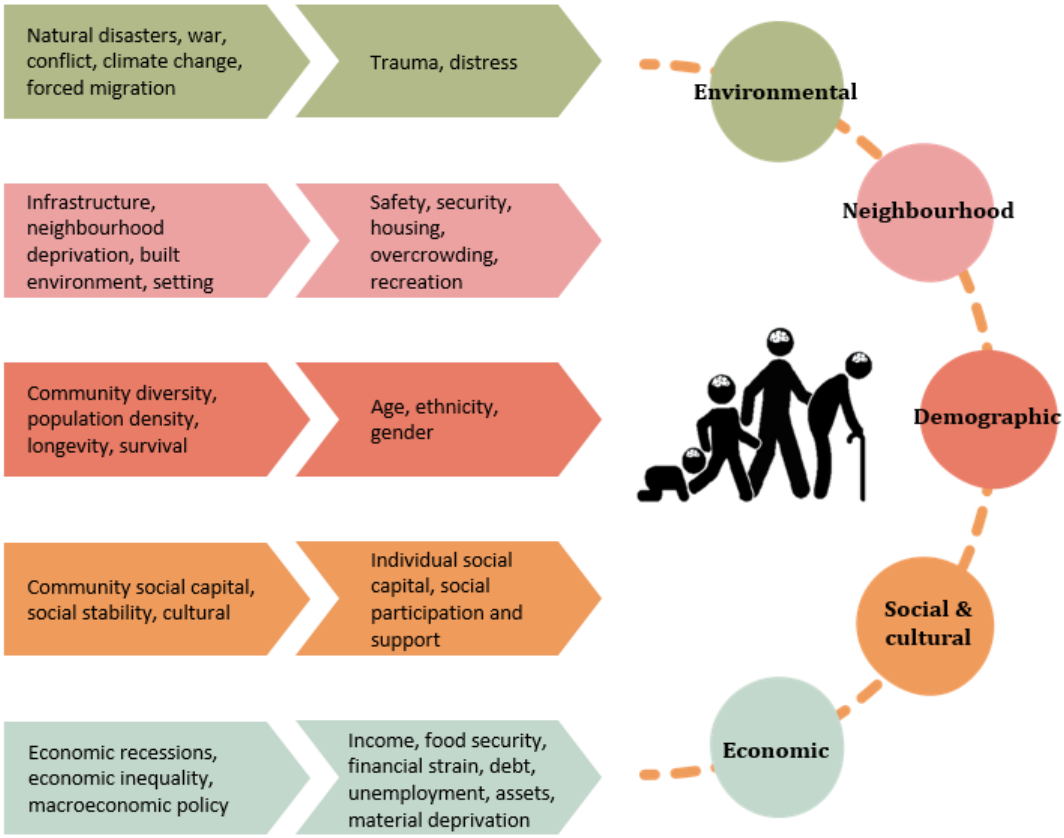
Research on the SD of mental health aims to deepen our understanding of the complex interplay of many interacting factors that influence both

at the individual and collective levels. By identifying these factors, policy makers can establish strategies and take actions to foster and safeguard optimal mental health. These actions need to be universal across the entirety of society, and adjusted to necessity, to mitigate the social gradient in mental health outcomes.

To contextualize and summarize the current state of knowledge on this topic, we are going to base our work on the conceptual framework developed by Lund et al. (65), summarized in Figure 3, that adopts an ecological approach to understand mental disorders. This framework recognizes the intricate and multidimensional interactions between SD and fundamental genetic factors, shedding light on how they collectively influence mental health conditions. It identifies five key domains: (i) demographic, (ii) economic, (iii) neighbourhood, (iv) social and cultural, and (v) environmental domain. Each domain comprises distal and proximal determinants that affect mental disorders. Proximal factors encompass individuals, objects, or events within the immediate external environment that can either heighten or diminish the risk of mental disorders. On the other hand, distal factors pertain to the broader structural arrangements or societal trends that exert their impact on mental disorders in populations. These distal factors often operate through the mediation of proximal factors (66).

Figure 3

Conceptual framework of the social determinants of mental disorder



Note. Adapted from Lund et al., 2018 (65)

Demographic domain

Demographic factors that determine mental health include sex, gender*, age, and ethnicity. These proximal factors are conditioned by distal factors such as community diversity, population density, longevity, and survival, which determine a differential exposure of individuals to adversity, social norms, and discrimination.

Depression is two times more common in women than in men from early to late adulthood (22), being MDD the leading cause of YLD among women and the second leading cause of YLD among men (67). Subclinical symptoms of depression are also more common in women (68). Regarding symptomatology, studies have reported the presence of a somatic depression phenotype in women characterized by significant somatic symptoms such as low energy, fatigue, and pain (16,69), which has been hypothesized to contribute to the overall gender difference in depression prevalence (70).

Distal factors such as gender inequality and discrimination mediate the relationship between gender and mental health, which depends on the characteristics of public institutions and the society as a whole (71). Although the evidence is limited and much research on gender risk factors for depression is still needed (71), some biopsychological and environmental factors have been suggested to contribute to the gender

*Our studies collect the variable 'sex', which refers to the biological sex as 'female' and 'male'. However, to conceptualize our work we will mainly focus on 'gender', as the social, cultural, political, psychological, juridical, and economical characteristics assigned by society based on sex. Concepts like 'gender identity' or 'gender expression' will not be covered in this thesis.

gap in depression. Biopsychological risk factors for depression in women include the different gene-environment interactions (i.e., how the environment influences the genetic expression of individuals), physiological stress responses, hormones, and differences in ruminative response style and self-conscious emotions. The environmental risk factors refer to women having a greater exposure to severe adversity like childhood sexual abuse, gender-based violence, and societal structural gender inequities (e.g., gender-based discrimination), differences in social expectations and experiences, and higher exposure and susceptibility to stress (68,72).

The life course approach has gained relevance in describing social factors, as it has been demonstrated how early-life risk exposures can have long-term effects on mental well-being or increase the likelihood of developing mental disorders years or even decades later (73). This highlights the importance of considering age as an essential variable when studying mental disorders and emphasizes that providing every child with the best start in life will yield the most significant societal and mental health benefits. Older adults are at higher risk of experiencing a more severe course of MDD (21) and are also more prone to encounter other unfavorable factors that can affect its progression, such as widowhood, limited social network, somatic diseases, and physical, functional, and cognitive impairment (74–76). Additionally, the aging population is more likely to have experienced more depressive episodes over their lifetime, and a history of depression and recurrent episodes are risk factors for a poorer diagnosis (77).

Finally, ethnicity and ethnic diversity are recognized as significant factors contributing to the variability in the prevalence of mental disorders. The increased prevalence of depression among minority groups may result from experiences of discrimination and exclusion, genetic predispositions, variations in cultural interpretations of symptoms and stigma, or a combination of these factors (78,79). Among migrants, factors such as the country of origin and destination, the reasons and expectations of migration, and conditions of the migratory process, modify the effect of migrant status on mental health (80,81). Structural racism and minority stress mechanisms can trigger deterioration of the mental health of migrants in the host country (82–84). Perceived discrimination and discrimination-related stress can have a huge impact on mental health and well-being in the migrant population (85–87). Finally, migrant populations confront challenges in accessing prompt high-quality and culturally appropriate mental health care, which significantly influences their mental health recovery and long-term consequences (88–90).

Economic domain

Distal factors, such as income inequality and macroeconomic trends (i.e., recessions and subjective financial strain) have been associated with increased risk of depression (91,92). Specifically, Rai et al. (93) found a notable variation of 13.5% of depression prevalence that could be attributed to the national-level (i.e., income inequality and gross national income) and this seemed to increase with the decreasing

economic development of countries. These distal factors affect proximal factors, which account for most of the variability in depression prevalence. Broad literature has associated a higher prevalence of depression in adults with poverty, inadequate housing, material disadvantage, unemployment, debt, and food insecurity (94–98). Levecque et al. (99) reported that the relationship between economic hardship and depression changed with age depending on the welfare state regime, highlighting the importance of considering the socio-political context when studying health. Padrosa et al. (100) study about the relationship between precarious employment and worse mental health found that this relationship was influenced by the welfare state in women but not in men, and women also reported the highest prevalence of precarious employment and poor mental health.

Socioeconomic differences have been widely reported as causes of adverse mental health outcomes, comprising the social and economic factors that determine the hierarchical position of an individual within society. To understand the socioeconomic differences on mental health, there are two main approaches: through the socioeconomic status (SES) or through the social class concepts (101). SES refers to "the social and economic factors that influence what position individuals and groups hold within the structure of society" (102). In social epidemiology, SES has traditionally been approached as the combined measure of a person's social position regarding education, occupation, and income. Each component of SES provides different resources, shows different relationships with various health-related aspects, and must be addressed differently (102). There is a consistent association

between low SES and higher rates of depression (95,103). The relationship between SES and mental health is likely to be bidirectional, as mental disorders contribute to reduced income, education, and employment opportunities, perpetuating poverty, and subsequently increasing the risk of experiencing mental disorders (104). This can be explained by the co-occurrence of two causal theories: social causation and social drift (105). Social causation refers to poverty leading to mental disorders by creating financial stress, diminishing social support and social status, worsening physical health, promoting unhealthy behaviors, and increasing the exposure to poor living conditions. Conversely, social drift means that individuals with poor mental health are more prone to entering or persisting in poverty due to heightened health-care expenses, diminished productivity, job loss and the subsequent loss of income, disability, and stigma (65,106). Depression has been associated with absenteeism, poorer academic performance, lower educational attainment, and premature dropout during childhood, adolescence, and young adulthood (107–109). In the same way that depression affects subsequent education, education positively influences cognitive reserve and resilience, so a lower educational level and alphabetization increase the risk of MDD (110,111).

Nevertheless, it has been argued that the individuals' level of education, their occupation, and income might fail to provide complete information about the social mechanisms that allowed these individuals to possess such resources. Therefore, some authors suggest the consideration of broader contextual factors explaining how economic inequalities are generated and how they may affect health (112). Such

concept is 'social class' defined as the "relations of ownership or control over productive resources (i.e. physical, financial, organizational)" (113). Muntaner et al. (112) assessed the associations of social class positions – defined as power relations within the labour process – with mental health in Spain. They reported that power dynamics within the workplace are highly associated with disparities in health. The study found that contradictory class positions (e.g., having authority but limited control) were associated with worse mental health outcomes.

Finally, mental disorders are distributed along a social gradient and economic disadvantage within society, more marked in women, adolescents, and people with chronic diseases (114–116). Specifically in Spain, those in the lowest income levels have 2.5 times more depression than individuals in the highest income levels (117).

Neighbourhood domain

Neighbourhood-level effects are those that persist even when accounting for individual or family-level socioeconomic deprivation and other exposures. These are based on the structural characteristics of neighbourhoods including protective factors for depression, such as good infrastructure, safety, availability of services, and leisure opportunities. Perceived neighbourhood social cohesion (i.e., safety, trust, positive social connections, helping others and receiving help from neighbours, and lack of crime and violence) has been associated with fewer depressive symptoms (118,119).

Residents of areas characterized by low SES and neighbourhood deprivation present an increased prevalence of depression, as they may experience more life stressors, such as exposure to violence, fear of crime, unemployment or precarious employment, disempowerment, and under-resourced facilities. Their vulnerability may further increase with fewer sources of support and resources to cope with these challenges (120–122). Furthermore, urbanicity has also been associated with a higher prevalence of depression in developed countries (123).

Environmental domain

Environmental events are disturbances to community or society function and include natural catastrophes (e.g., earthquakes), industrial incidents, armed conflict (e.g., war, terrorism, forced displacement, violence), and ecosystem disasters arising from climate change, environmental degradation or changing demographics (e.g., droughts or flooding). These environmental events can cause trauma and severe stress, in addition to adversity, insecurity, and loss of social support systems. Compared to the general population, survivors have three to four times higher symptoms of depression, anxiety, and posttraumatic stress (124).

In the present thesis, we are going to focus on the Coronavirus Disease 2019 (COVID-19) pandemic as the main environmental event impacting depression. Like previous pandemics, the outbreak was sudden, with an exponential and fast spread globally, resulting in excessive hospital admission and deaths. Moreover, it had detrimental social, economic,

and cultural long-term effects worldwide. It exacerbated existing inequalities and differences while creating new ones, and it brought to light essential societal requirements. We will delve further into this aspect in the following sections.

Social and cultural domain

The social and cultural domain includes those factors inherent to the organization of society and social interactions that affect mental health, such as family relationships, peer interactions, social networks, and group membership, which are conditioned by distal factors like culture, social stability, and community social capital.

Humans, by nature, thrive on social interactions, with these connections playing a crucial role in our overall health, well-being, and even survival (125). In 1988, House, Landis, and Umberson's (126) provocative review asserted that "social relationships, or the relative lack thereof, constitute a major risk factor for health—rivaling the effect of well-established health risk factors such as cigarette smoking, blood pressure, blood lipids, obesity and physical activity", a quote that compelled the inclusion of measures on social relationships in biomedical research.

Holt-Lunstad et al. (127) demonstrated that individuals with adequate social relationships have a 50% greater likelihood of survival compared to those with poor or insufficient social relationships, who have a higher health risk of mortality than those with excessive alcohol consumption, smoking, obesity, and physical inactivity. Importantly, the findings of a

longitudinal study throughout seven decades revealed that social relationships are better predictors of health than various biological and economic factors (128). Finally, a meta-analysis exploring the relationship between social capital and mortality found a negative association between both variables (129).

Social capital is defined as the "features of social organisations, such as networks, norms, and trust, that facilitate action and co-operation for mutual benefit" (130). It can be examined through the structural approach, also referred to as the collective approach, and the cognitive approach, alternatively known as the individual approach. Both approaches are distinct yet complementary, shedding light on its multifaceted nature. The structural component is based on objective characteristics inherent to community networks. And the cognitive component comprises subjective aspects and is based on people's perceptions, exploring trust, social belonging and integration, reciprocity, and support (131). Although results are mixed, there is stronger evidence supporting a connection between depression and cognitive social capital (132,133) compared to structural social capital. Overall social capital has been reported as a potential protective factor for depression in poor areas (134). Social capital is, in turn, essential for social cohesion, a term that encompasses the absence of latent social conflict and the presence of strong social bonds (135), which has also been found to be a protective factor against depressive symptoms (118,136).

Different cultural attitudes exist towards mental health and can contribute to the stigma associated with depression, in addition to the

cultural influence on the disease course development, presentation, symptom perception, treatment, and help-seeking sources (137,138). Stigmatization affects access to mental health care, leading to lack or delayed treatment, and may imply barriers to full social participation such as employment and family life (139,140).

Moreover, displacement from one's cultural context can lead to acculturation stress, which is experienced by migrants when adapting to the host country's cultural norms and values and is a risk factor for depression (141,142).

Ultimately, it is important to note that in this domain, the term 'social' is distinct from the one defined in the economic domain, in which it is assessed together with economic factors using composite indicators of socioeconomic position or social class (143). In the present domain 'social' refers to the objective and subjective factors of interpersonal relationships. Social support and loneliness are, respectively, widely used measures for operationalizing these two types of factors and which have consistently been shown to affect depression (144,145). In the present thesis, we will focus specifically on these variables.

1.3.Loneliness

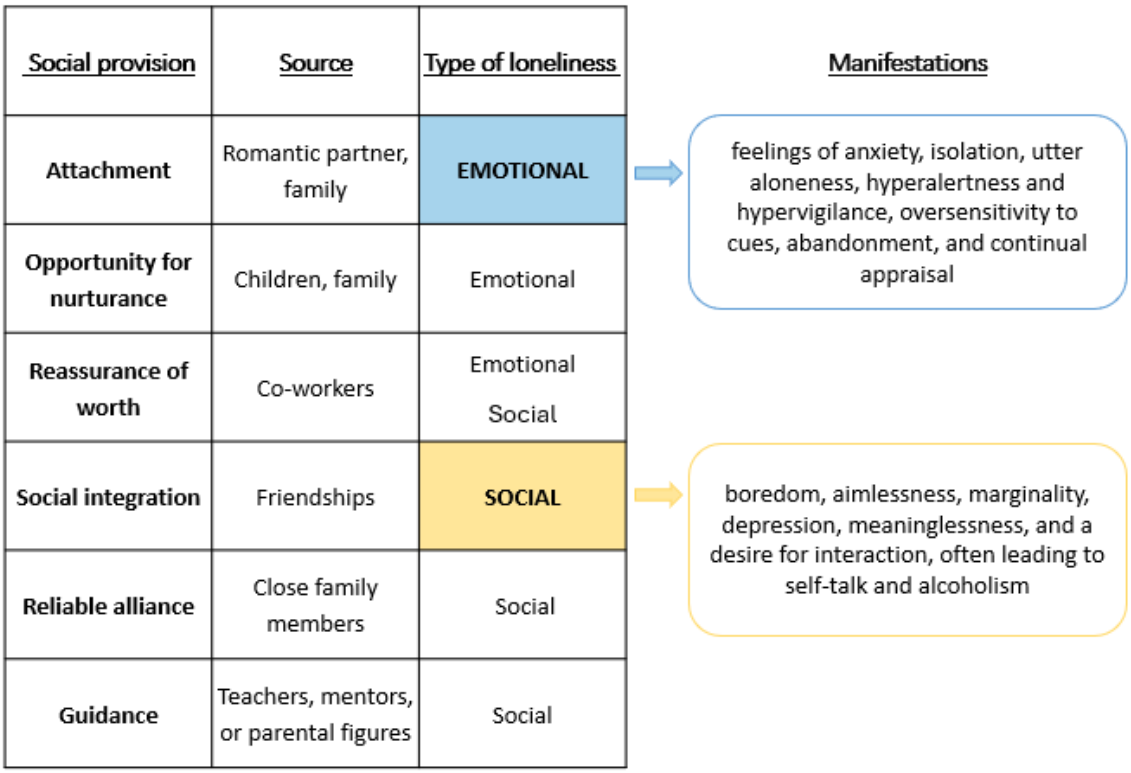
Definition and sociological theories

Loneliness can be conceptualized from the 'social needs perspective on loneliness' (146) or from the 'cognitive discrepancy model of loneliness' (147,148).

The social needs approach to loneliness is based on the sociologist Robert S. Weiss theory (146), who described loneliness as the consequence of missing some social needs provided by various types of social relationships, each offering distinct social provisions. Consequently, the extent of interpersonal deficit felt by an individual upon losing a particular relationship depends on the specific social provisions provided by that relationship. Weiss identified six social provisions: (i) 'attachment' as a social provision for a sense of safety and security; (ii) 'social integration' as a network of relationships in which individuals share interests, concerns, and recreational activities; (iii) 'reassurance of worth' as a type of relationships in which the person's skills and abilities are acknowledged; (iv) 'reliable alliance' as a provision in which the person can count on assistance under any circumstances; (v) 'guidance' as provided by a relationship with trustworthy and authoritative individuals who can provide assistance and advice; and (vi) 'opportunity for nurturance' as a provision in which the person feels responsible for another's wellbeing (Figure 4). Weiss further distinguished between emotional and social loneliness. Emotional loneliness refers to the absence of an intimate attachment figure (e.g., parents for their children or a partner or intimate friend for adults); while social loneliness occurs when a person lacks the sense of social integration or community involvement that might be provided by a network of friends, neighbours, or co-workers. Although he primarily focused on the domains of attachment and social integration, subsequent authors, related the remaining domains to each type of loneliness as reported in Figure 4 (149). It is also relevant to mention

Figure 4

Weiss framework of the social needs model



Note. Representation of the 6 social provisions described by Weiss, the types of social relationships that will most likely fulfil them, the predicted type of loneliness caused by the lack of each provision, and the manifestations (i.e., symptomatology) of each type of loneliness according to Weiss. Table created with data from DiTommaso, E., & Spinner, B. (1997) (149) and Weiss, R. (1973) (146).

that later studies have not supported some aspects of Weiss's theory, such as his predictions regarding the consequences of each type of loneliness (149,150).

Following the cognitive discrepancy model of loneliness, Perlman and Peplau (151) conceptualized loneliness as a unidimensional construct, varying in perceived intensity, causes, and manifestations. They

described it as a subjective and undesired feeling experienced when there is a significant mismatch between a person's actual social relationships and his or her needed or desired social relations (151). Considering that the quantity and quality of one's social relationships differs from our expectations, people with similar lives can have very different experiences. Feelings of loneliness may or may not coincide with being alone, as it is a subjective concept that stems from insufficient meaningful connections. The objective situation of being alone or lacking social relationships is known as social isolation. This inherent subjectivity poses a fundamental challenge in standardizing its measurement and interventions to address it.

Building upon this foundation and considering part of Weiss's proposals, De Jong Gierveld (148) expanded the definition into a multidimensional phenomenon. She distinguished three dimensions of loneliness: (i) deprivation (i.e., the core of the concept involving feelings associated with the absence of an intimate attachment, encompassing sensations of emptiness or abandonment), (ii) time perspective (i.e., whether individuals interpret their loneliness situation as being hopeless or as changeable and treatable; exploring whether they attribute the situation to others or themselves), and (iii) the emotional dimension (i.e., emotional aspects such as sorrow, sadness, and feelings of shame, guilt, frustration, and desperation). Together, these dimensions provide a comprehensive understanding of the multifaceted nature of loneliness.

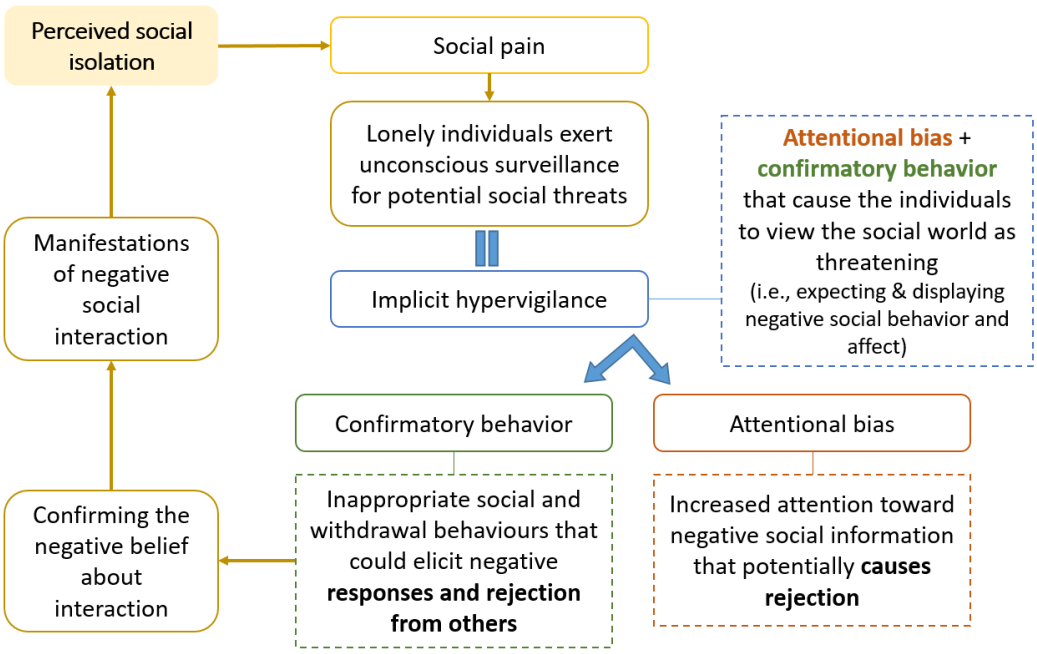
Young (152) further differentiated between transient or situational loneliness (i.e., short-term loneliness after a stressful life event) and

chronic loneliness (i.e., long-term loneliness persisting for at least two consecutive years). Transient loneliness could be an adaptive response following significant life stressors (e.g., retirement or loss of social connections) that would eventually promote reconnection with others. In contrast, chronic loneliness appears to be more intricately associated with maladaptive social cognition, diminished social support, and lack of intimate relationships (153).

Cacioppo and Cacioppo (154) explained these concepts formulating the 'Evolutionary Theory of Loneliness' (ETL). According to the ETL, loneliness can be viewed as an evolved response to hostile ancestral social environments fostering short-term survival. In this scenario, loneliness would lead to neural changes and alterations in the inflammatory biology, which is involved in how a person copes with perceived dangers and threats. Loneliness enhances vigilance for threats and intensifies feelings of vulnerability, promoting social withdrawal from such violent and conflictive social environments. Concurrently, loneliness fosters in the medium and long term a heightened desire to reconnect and repair the social bonds and establish new relationships. However, in contemporary society, these adaptations may contribute to negative outcomes due to the complexity of social interactions and the potential for deleterious long-term consequences. Implicit hypervigilance can lead to attentional bias towards negative social information and confirmatory behaviour of rejection from others, which would confirm the negative believe about social interactions and perpetuate feelings of loneliness (Figure 5). Implicit hypervigilance for social threats alters psychological processes,

Figure 5

Model of the evolutionary theory of loneliness – ETL



Note. Adapted from Hawkley, L. C. & Cacioppo, J. T., 2010 (155).

influencing physiological functioning, diminishing sleep quality, and ultimately increasing morbidity and mortality (155).

Measures

The most frequently used instruments for measuring loneliness are variations of the DeJong Gierveld loneliness scale (156) and the UCLA loneliness scale (157).

The De Jong Gierveld 11-item loneliness scale (156), if applied as a unidimensional measure, produces a global score of 0–11, where higher

scores indicate higher levels of loneliness. Nevertheless, the items were developed according to Weiss's (146) multidimensional distinction, therefore containing a subscale for social loneliness consisting of five positive items (score 0-5), and a subscale for evaluating emotional loneliness consisting of six negative items (score 0-6). Social loneliness items evaluate feelings of belongingness and primarily pertain to the absence of a broader network of acquaintances, colleagues, and friends. Conversely, emotional loneliness items mainly refer to the fact that a relationship, a partner, someone special, or a best friend are extremely missed. The UCLA loneliness scale originally had 20 items (157), but the 3-item version is the most used self-report loneliness instrument (158). Conceived as unidimensional in structure, the scale consists of the following three items: "How often do you feel that you lack companionship?"; "How often do you feel left out?"; and "How often do you feel isolated from others?". Each item is answered on a 3-point scale that is added up to produce a score from 3 to 9, with a higher score indicating a greater degree of loneliness.

In both scales the items evaluate the perception of lacking a trusted confidant for mutual support, protection, and acceptance in a meaningful social relationship, avoiding the use of the words "lonely" or "loneliness". Nevertheless, loneliness has largely been evaluated as a direct question in numerous studies. In a recent study conducted by our research group, we found that the UCLA scale revealed almost double the prevalence of loneliness compared to direct questioning, suggesting a reluctance to admit feelings of loneliness when asked directly due to social stigma (159).

Epidemiology of loneliness

In the recent years, we have witnessed an increasing prevalence of loneliness, with nearly a third of individuals in developed countries experiencing its impact (160). According to a recent meta-analysis including data from 2000 to 2019, loneliness prevalence in Europe ranges from 5.3% in young adults to 11.9% in older adults (Table 1) (161).

Predisposing factors (e.g., personality characteristics like shyness or lack of social skills) and cultural values and norms (e.g., individualistic vs. collectivistic cultures) can increase a person's risk of loneliness (162,163).

Table 1

Loneliness prevalence in Europe by age group

	EUROPE	SOUTHERN EUROPE
Young adults	5.3 (4.4 - 6.4)	5.4 (4.1 - 7.1)
Middle-aged	6.9 (5.6 - 8.6)	7.7 (6.1 - 9.6)
Older adults	11.9 (9.9 - 14.3)	15.7 (13.2 - 18.7)

Note: Results from a meta-analysis of loneliness prevalence based on single-item measures in young adults (18-29 years), middle-aged adults (30-59 years), and older adults (≥60 years) in Europe, and more specifically, in Southern European countries (i.e., Spain, Portugal, Italy, Greece). From Surkalim, et al. (2022) (161).

Loneliness usually begins with changes or unpleasant events, typically marked by a shift in an individual's existing or desired social connections (e.g., the loss of a significant relationship due to death or divorce, or the disruption of social ties resulting from a relocation to a new school, town, or job). How the individual perceives and thinks about this event influences the experience of loneliness, which is determined by cognitive processes such as social comparison and causal attribution (147). Finally, we should take into account our current context in Spain, where the current abolition of some traditional roles and rituals has contributed to increased individualism in Western societies. Furthermore, there is a prevalent and normalized use of technology, especially among the younger generation, to establish new forms of social relationships (professional, friendly, emotional, etc.). These societal changes are occurring alongside an increase in life expectancy (164).

Determinants of loneliness also vary depending on age and life stages. Loneliness might be more intuitively associated with older people and the negative life events associated with this age, such as widowhood, the loss of friends and people from our social circles, moving to a nursing home, deteriorating health, and job retirement (165). Nevertheless, older people might be better prepared for loneliness and might have acquired coping skills to deal with it during their lifetime, which young people might have not developed yet. In younger adults, personality traits have been found to be more significant determining loneliness (165). Moreover, social expectations might be more important in young adulthood and their social networks more instable,

linked to workplace or school changes and identity exploration that make them more vulnerable to exclusion (166). It has been suggested that the relationship between loneliness and age is described by a U-shaped curve, wherein both young adults and older individuals experience increased loneliness compared to those in the middle age (167–169). The relationship between loneliness and health has been found to be stronger in the younger population than in older people (170).

Women tend to present a slightly higher prevalence of loneliness than men (171–174). Research on gender differences in loneliness has generated various hypotheses, yet subsequent studies have often contradicted these initial assertions. Initial theories proposed disparities emerging during crucial life transitions, such as adolescence and old age. For instance, some posited that during adolescence, females tended to replace family time with peer interactions, while males spent it alone, leading to heightened feelings of loneliness (175). It could be argued, however, that if this solitary time was intentional and desired, it might not result in loneliness but rather solitude (176). Conversely, alternative viewpoints suggested that females faced a higher risk of internalizing problems during puberty, resulting in increased loneliness (177,178). In old age, arguments oscillate between women experiencing more loneliness due to a longer lifespan implying more health problems and widowhood (172), versus the idea that men become lonelier post-divorce or widowhood, having lost their primary confidants and struggling in the adaptation to new roles (179). However, a meta-analysis focusing on gender differences in loneliness

highlighted that the most significant disparities were observed among young adults, specifically those between 21 and 40 years, albeit with a small effect size. Therefore, the study's conclusion questions the idea of substantial gender variations in loneliness, suggesting that self-reported loneliness reveals greater similarities than differences between males and females (180). Another meta-analysis examining the link between loneliness and all-cause mortality, suggested a minimal stronger effect in men and a higher prevalence of loneliness in women (181). These results could be explained by the fact that women more readily admit feelings of loneliness, while men acknowledge it when the severity and impact of these emotions are greater (174,182). Another reason is the connection between loneliness and health, with men often exhibiting more negative attitudes towards seeking healthcare services (183). Men's increased inflammatory responses when isolated (184) and unhealthy lifestyles (185,186), such as tobacco and alcohol consumption which are associated with loneliness and are moderately more prevalent in men than in women, contribute to a stronger loneliness-mortality connection.

1.4.Social support

Definition and sociological theories

Social support is a multifaceted and complex construct that refers to the psychosocial resource or assistance that individuals receive from their interpersonal relationships within their social network, including family, friends, neighbours, religious institutions, etc. It involves the perception

or experience of being loved, cared for, esteemed, and valued, contributing to a sense of belonging and mutual obligations within the community (187,188). Social support is comprised by a structural and a functional dimension (189). The structural aspect refers to the presence and characteristics of relationships, such as their size, type, and frequency of contact within the social network. Whether the functional aspect involves the expectation of receiving support from family, friends, and neighbours, as well as the extent to which these relationships fulfil specific functions and provide resources (190). Functional support can be further classified as either instrumental (i.e., someone being available to offer help with matters that demand physical effort or financial aid, including tangible or financial support and practical assistance) or emotional (i.e., someone being present to listen or provide sympathy in time of crisis or adversity or someone available to give advice or guidance, including companionship, intimacy, caring, and empathy) (191,192). Moreover, we can distinguish between perceived and received functional social support. Perceived availability of social support refers to the subjective feeling of being supported by one's relationships and the expectation of receiving assistance in the present or future, whereas received or enacted support is grounded in past experiences of supportive behaviours (191,192). The construct of perceived social support resembles loneliness in its subjective assessment of social relationship quality and impact (193,194). Due to this conceptual overlap, we will not evaluate perceived social support in the present thesis. We will consider received social support when referring the term 'social support', which is more closely aligned with

objectively measured concepts such as social isolation or social network size (145).

Measures

Different measures to assess social support have been developed and standardized. As previously noted, we are going to focus on the perception of availability of emotional, informational, tangible, or belonging support if needed, which has been suggested to be a better predictor of mental health outcomes than the actual receipt of support (195–197). In a recent meta-analysis performed by our research group (198) analysing the association of social support with mental health between 2020 and 2022, we observed that, in general population samples, the measure of social support most commonly used was the Multidimensional Scale of Perceived Social Support (MSPSS, (199)), followed by the Oslo Social Support Scale (OSSS, (200)). The MSPSS is a 12-item measure of perceived adequacy of social support from three sources: family, friends, and significant other. Regarding the OSSS, the 3-item OSSS (OSSS-3) is its most popular version as it is brief, easy to administrate, and has been validated for population-based studies (191). The OSSS-3 inquiries about the quantity of close confidants, the perception of care from others, and the connection with neighbours, emphasizing the availability of practical assistance.

Epidemiology of social support

Because of the nature of the construct, obtaining comparable prevalences of social support is challenging. However, it is possible to present prevalences of social isolation, which also refers to the objective characteristics of social relationships and it is characterised by an objective lack of social contact and connections, which closely aligns with the definition of poor received social support. Studies often use similar or the same constructs to measure both. For example, Röhr et al. (201), used the Lubben Social Network Scale (202) which measures social support received from family and friends, and reported a social isolation prevalence of 12.3% in a German sample of more than 9,000 participants. They observed that men experienced a higher prevalence (13.8%) of social isolation compared to women (10.9%). This prevalence rose with age, ranging from 5.4% in the youngest age group (18–39 years) to 21.7% in the oldest (70–79 years). Prevalence varied significantly based on SES, with the higher prevalence among those with low SES (18.6%). A recent study, evaluating social isolation with the 10-items Index of Social Support scale, identified a cumulative prevalence rate of 17% for social isolation, significantly surpassed by the 34% prevalence of loneliness (203). Consistency was observed in demographic characteristics (including age, sex, household type, and income) among individuals experiencing loneliness and social isolation.

Throughout the lifespan our relationships vary in their closeness, quality, function (aid, affective, etc.), structure (size, frequency of contact, composition, etc.) and, concurrently, social relations are

influenced by our personal characteristics like age or gender, and situational factors such as norms or values (204).

According to the socioemotional selectivity theory (205), as individuals' age, they tend to limit their social networks, prioritizing close and emotionally significant relationships. This is driven by a sense of limited time, leading older people to concentrate their emotional energies on those who hold greater importance to them. In contrast, younger individuals, seek a more extensive social circle and engage in frequent and diverse social interactions. Overall, the theory suggests that while social contact may decline with age, the focus shifts towards cultivating deeper and more fulfilling connections among older adults, whereas younger individuals prioritize broader social interactions (205,206).

In the context of seeking social support, it has been observed that implicit social support seeking, characterized by obtaining emotional comfort from social connections without disclosing specific stressful events or problems, exhibits no variations across age groups. In contrast, explicit social support seeking, entailing the explicit solicitation of instrumental and emotional support from one's social network, is more prevalent among younger adults and shows a diminishing trend with age. However, it is noteworthy that older adults tend to engage in more frequent prosocial behaviour (207).

Social support varies by gender as differences have been reported in interpersonal behaviour and interpersonal relationships. Additionally, socialization presents differences by gender leading to different ways of participating in social relationships (208).

Numerous studies have reported that women tend to have larger, more supportive networks, and greater contact with close partners compared to men (209–211). Males have been found to be less likely to seek or provide social support, particularly emotion-focused support (212).

Gender differences extend to the type and perception of stressors and how social support is used to cope with them (213). Females perceive higher social support network quality and the approach to stress response is based on relying on them, while males either confront the stressor directly or opt to escape from the situation of stress (213–215).

1.5.Loneliness, social support, and impact on quality of life

Both poor social support and loneliness demonstrate comparable associations with demographic, socioeconomic, and health factors, both with physical and mental well-being (216,217).

Loneliness, along with its associated hypervigilance for potential social threats, is accompanied by feelings of hostility, stress, pessimism, anxiety, and low self-esteem, all of which contribute to adverse health outcomes. These outcomes manifest through health-risk behaviours and detrimental lifestyle factors such as a poor diet, physical inactivity, and obesity, as well as bad sleep quality and increased stress (155). Loneliness leads to chronic stress, which has been evidenced to impact the endocrine and immune systems, thereby increasing the risk of adverse health outcomes (218). It has been associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis,

elevated levels of cortisol, and an overactivation of downstream inflammatory pathways. These leads to an excess of pro-inflammatory markers, which are associated with altered brain function, impaired cognition, and neurodegeneration (219,220), as well as hypertension, atherosclerosis, and coronary heart disease (221–223). The detrimental effects of loneliness on physical health are well-documented, with meta-analyses reporting a 30% increase in the risk of stroke, myocardial infarction, morbidity, and mortality (181,224,225). Loneliness has been related with increased risk of cardiovascular problems, increased blood pressure, and hypertension (226). It has been associated with a worse overall health, accelerating physiological aging (227) and being associated with inflammation, diabetes, cognitive decline, and dementia (228,229). Finally, it also increases the risk of developing mental disorders, suicidal ideation, and depressive symptoms (219).

Therefore, loneliness diminishes life expectancy, lessens our chances of recovering from illness, and its resultant physical and cognitive health implications can impede social interactions and induce social withdrawal, consequently contributing to more feelings of loneliness. In this regard, it is essential to better understand the factors and indicators that can help healthcare professionals to recognize situations than can easily lead to loneliness or social isolation.

A higher social support has largely been linked to improved general health and mental health outcomes (230,231). This association can be explained through various theoretical frameworks. The ‘Stress buffering theory’ (232) posits that if the support meets the demands of the stressor (e.g., life event, illness, life transition) — meaning that the

social network provides informational, or emotional, or tangible resources that help in the evaluation, response, and coping to the stressor — social support effectively buffers against stress, thereby mitigating the increased risk of worse mental health. Alternatively, the 'Relation regulatory theory' (233) states that it is through daily life conversations and shared activities within one's social network that helps people regulate their emotions, thoughts, and actions, consequently decreasing the impact of stress events on mental health.

Conversely, the 'Main effects model' (234,235), proposes that the benefits on health provided by social relationships are not explicit – not through intended help or support from our social network – and are provided irrespective of whether individuals are under high or low levels of stress.

In this line, the 'Thriving through relationships theory' developed by Feeney and Collins (236) posit that social support promotes thriving in front of two different contexts: adversity and opportunities. Social support promotes thriving through adversity by being a source of strength and refugee, not only by buffering the negative effects of stress but also helping individuals to emerge from the stressor and cope successfully with it in ways that enable individuals to learn and grow personally. In contrast, our relationships can promote opportunities – in the absence of adversities – that broaden our resources and help us find purpose in life and set personal goals.

1.5.1. Loneliness, social support, and depression

Regarding depression, the impact of loneliness is significant, to the extent that certain diagnostic tools incorporate feelings of loneliness as a defining feature of a depressive episode (e.g., the Center for Epidemiologic Studies Depression Scale (237)). Despite their frequent co-occurrence, previous studies indicate that depression and loneliness are statistically separable and functionally distinct (238). Conceptually, depression can be distinguished from loneliness, as depression encompasses general feelings, whereas loneliness specifically relates to feelings about social connections (146).

Individuals experiencing loneliness or having low social support commonly exhibit an elevated susceptibility for depression over time. Manifestations of depressive symptoms escalate with feelings of loneliness and poorer perceived social support both in quantity and severity, even if the symptomatology does not reach the clinical threshold indicative of depression (144,145,239). Moreover, reduced levels of social support have been associated with worse social functioning, recovery from depression (145), and as a contributing factor in the transition from subthreshold depression to the development of a complete depressive disorder (10).

Loneliness is more common among individuals with MDD, with studies suggesting approximately a tenfold increase of the likelihood of experiencing loneliness compared to the general population (240,241). This likelihood is significantly reduced when adjusting for social support (240). A bidirectional relationship between loneliness and depression

has been suggested (238), yet it seems to be stronger with loneliness as the origin (242,243). Conversely, the negative association between social support and loneliness has been widely documented, as summarized by a recent meta-analysis (244).

Loneliness has been found to act as a moderator in the relationship between social network and depression (74), which means that loneliness can influence the strength of the association between social network and depression, in a way that the relationship is stronger in groups with higher feelings of loneliness. Other authors have identified loneliness as a mediator between social network-related factors and depression (245), which means that poor social relationships are associated with feelings of loneliness, which in turn lead to depressive symptoms.

1.6.The COVID-19 pandemic and depression

Regarding environmental factors influencing depression, the COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2), presents an opportunity to investigate the impact of social relationships on mental health. This situation offered a quasi-experimental framework with evident implications for both aspects.

Coronaviruses (CoVs) infections in humans typically lead to mild respiratory illnesses. However, the SARS-CoV-2 is highly pathogenic, capable of inducing severe infections, life-threatening respiratory

conditions, and lung injuries (246). SARS-CoV-2 primarily spreads through short-range airborne transmission (i.e., via small respiratory aerosols that can float and travel in airflows, infecting people who inhale them) or droplet transmission (i.e., direct contact with eyes, nose, or mouth). Poorly ventilated indoor spaces foster long-range aerosol transmission (247,248).

Although past occurrences of coronavirus epidemics, such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), highlighted the importance of preventive measures and efficient treatments, most governments were ill-prepared, slow, unable to adequately respond to the outbreak of SARS-CoV-2, did not sufficiently considered the most vulnerable groups, and were hampered by low public trust and epidemic misinformation (249).

In December 2019, the COVID-19 was first detected in Wuhan, China (250) and thereafter a rapidly global spread began. Although travel restrictions and containment of the outbreak in China reduced the further spread of the virus, the international travels before the Wuhan lockdown had already result in international importations of the virus and the WHO declared it a Public Health Emergency of International Concern on 30 January 2020 (251). In Europe, the first cases were detected in France, followed by Italy, which emerged as the primary hotspot. Spain, together with Belgium and the UK, experienced the highest death toll in Europe during the initial wave (252). On March 11, 2020, the COVID-19 outbreak was declared a pandemic by the WHO, with 774 million confirmed cases and 7 million deaths worldwide, and

14 million cases in Spain and 122 thousand deaths as of February 2024 (253).

The fast spread of the virus worldwide forced governments to implement rapid and drastic measures to contain SARS-CoV-2 spread. Such measures, also known as nonpharmaceutical interventions (NPIs), included travel restrictions, case isolation, contact tracing, physical distancing, facemask covering, limiting gatherings, and closures of businesses and schools. Additionally, complete or partial lockdowns with strict stay-at-home orders during specific periods were imposed in many countries (251,252,254), like Spain, where two emergency states were declared (Figure 6). All this measures profoundly changed people's lifestyle and affected their physical and mental well-being.

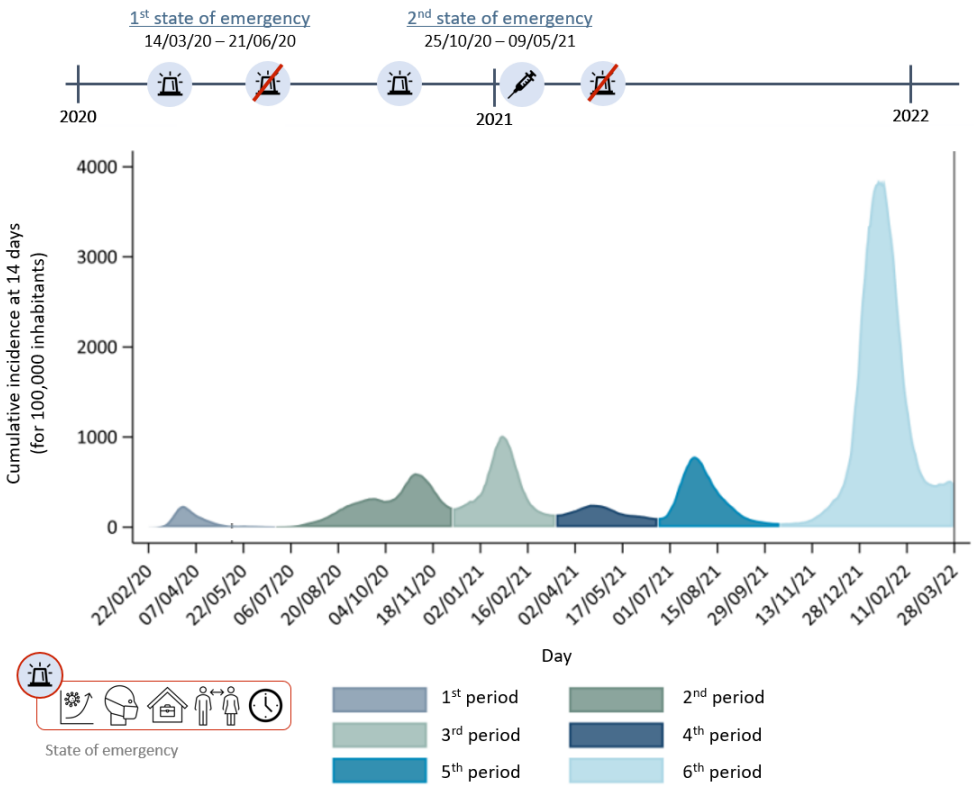
The COVID-19 pandemic has affected depression through direct effects (i.e., neuropsychiatric sequelae after the SARS-CoV-2 infection) and indirect effects (i.e., disruptive societal and economic changes and effects on the social determinants of mental health) (255).

It is estimated that 6.2% of COVID-19 survivors experience long COVID, also known as post COVID-19 condition (PCC) (256), characterized by neuropsychiatric symptoms such as sleep disturbance, fatigue, or cognitive impairment (255,257), which have been associated with depression as a risk factor and/or as a symptom (258,259). Moreover, PCC also includes depressive symptoms (260,261), although recent studies suggest that such symptomatology might not be solely attributable to SARS-CoV-2 infection, but by the pandemic context itself, the fear of contracting the virus or infecting others, and significant

alterations in social interactions and other environmental elements (257,262).

Figure 6

COVID-19 cumulative incidence of cases and epidemic periods in Spain from the COVID-19 outbreak to March 2022



Note. Adapted from CNE, ISCIII, Red Nacional de Vigilancia Epidemiológica, 2023 (390).

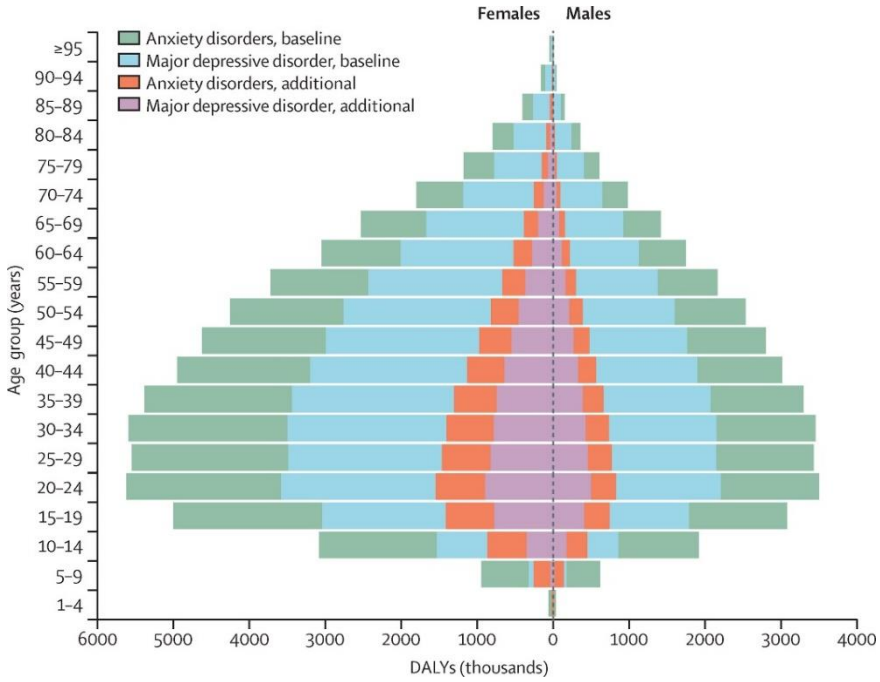
1.6.1. Epidemiology of depression during the COVID-19 pandemic

Mental disorders prevalence has not stop increasing since 1990, being the leading cause of global health related burden (1). The COVID-19 pandemic created an environment in which health risk factors and inequalities were exacerbated, further amplifying the mental health risks. The pandemic has not only led to direct psychological effects but has also influenced key social determinants of mental health. These effects may persist in the long term, resulting in enduring economic and social consequences (263).

The first meta-analysis assessing the prevalence of depression at the beginning of the pandemic (January – May 2020) included 12 studies and reported a pooled prevalence of 25% (95% CI: 18-33) (264) which was 7-fold higher than the 3.4% global estimated prevalence of depression in 2017 (265). A review analysing the global prevalence of MDD due to the COVID-19 pandemic in 204 countries estimated a significant increase of MDD of 28% (95% CI: 25-30), reporting 53.2 million additional cases (Figure 7). The review authors associated such increase with higher daily infection rates and reductions in mobility (263). Finally, a recent meta-analysis based on longitudinal studies comparing mental health outcomes in the same general population cohorts before and during the COVID-19 pandemic reported minimal worsening of depressive symptoms (266). Regarding general mental health and anxiety symptoms no changes were found. The only subgroup with significant changes were women that worsened by minimal to small amounts the symptoms of the three outcomes. The conclusions of this systematic review were that the main changes were

Figure 7

Global burden of major depressive disorder and anxiety disorders by age and sex, before (baseline) and during the pandemic (additional)



Note: Estimates of DALYs based on prevalence estimates and disability weights. DALYs=disability-adjusted life-years. From Santomauro et al., 2021 (263).

seen at the beginning of the pandemic and that the overall mental health at the population level has remained relatively stable, with only a minor negative impact on some individuals (266).

Nevertheless, these results must be carefully considered due to variations in the measures used to assess mental disorders and their symptomatology, as well as differences in study design and methodologies. Given the unprecedented nature of the situation, new

and faster research publications were necessitated, resulting in a substantial volume of literature related to COVID-19 being published exhibiting questionable scientific rigor and based on cohorts of small and non-representative samples (e.g., recruited through snowball sampling) that hamper generalization (267).

Some of the socio-demographic characteristics related with a higher increase of MDD during the pandemic were being younger and female (263).

Several studies conducted during the COVID-19 pandemic document an increased prevalence of depression in younger adults (268–272). A meta-analysis comparing the prevalence trends from 2007-2009 to 2019-2022 did not reveal a significant difference in the prevalence of depression before and during the COVID-19 pandemic. However, an increase in prevalence was observed when comparing the pandemic period to 2007-2009 among younger adults (18-34 years). The authors suggest that the rise in prevalence might not be explained by the pandemic but may be associated with an already existing trend (273).

Nevertheless, younger people who were studying during the pandemic suffered a radical change in the delivery of their education. The transition from in-person schooling to virtual interfaces meant they no longer attended classes physically, interacting with peers and educators only through screens. The absence of shared physical spaces and outdoor activities had a significant impact on their learning experience, impeding both their academic progress and social interactions with peers, at an age where social interactions outside the family context are

pivotal, and therefore having detrimental consequences for their mental well-being (274–276).

Young adults, who were employed during that period, experienced higher rates of layoffs and were greatly impacted by the economic repercussions of the pandemic compared to older adults, who usually have more savings and secure and stable jobs. In Spain, during the first weeks of the lockdown, the unemployment rate for young adults (16-29 years) more than doubled, compared with the population aged 30 to 64 years (277).

Mental disorders prevalence has typically been higher among females, except for some disorders like substance use or suicide (278,279). This gap was widened during the COVID-19 pandemic, which magnified pre-existing social and economic disparities that usually affect more severely women (280). This resulted in larger increases in mental disorders in women, with meta-analytic effect sizes ranging between 44% and 75% compared to pre-pandemic values (263,281–283).

This reflects more stressors and significant disruptions in women's daily life. For instance, increased childcare responsibilities, as the lockdown implied schools' closures, and in most countries, gendered social norms allocate household and childcare responsibilities predominantly to women, diminishing their available time and capacity to participate in paid labour. Moreover, women typically assume the responsibility of caring for dependent relatives or family members in the event of illness, so women were disproportionally affected by increases in unpaid duties throughout the pandemic. Specifically in 2021 in Spain, the gender

difference in the labour force participation rate was almost 10%. This discrepancy may be attributed to the fact that nearly 600,000 women were not actively seeking employment due to their engagement in caregiving responsibilities, a figure that has increased by 33% since the onset of the pandemic (284). Crises also expose women to greater economic repercussions, as women usually have less savings, lower salaries, more insecure employments, and jobs in the sectors more severely affected by the pandemic, such as the hospitality industry or as domestic workers (285). The most pronounced gender disparity was seen in employment and unpaid labour. Globally, 26% of women reported job loss compared to 20% of men in September 2021 (285).

Furthermore, females reported more school dropouts and the rates for domestic violence also increased with the lockdown and stay-at-home orders, which are factors strongly related with increased prevalence of mental disorders (263,285). Consequently, all the aforementioned factors could have exacerbated the pre-existing gender disparities in depression levels before the pandemic. Finally, the socio-economic repercussions of public health and economic crises (e.g., banking crises, currency crises, sovereign debt crises, and inflation crises) on women tend to persist well beyond the end of the crises (286).

Furthermore, to comprehend the effects of the pandemic on mental health, we also need to consider elements such as income loss and financial strain, both widely reported during the pandemic and longitudinally correlated with greater depressive symptoms (92,287). The economic recession resulting from the pandemic is already showing us that the effects on the healthcare system and mental health will be

lasting (288). Resilience and adaptation are well-known key protective factors against disruptive and stressful situations, like the COVID-19 pandemic, in which resilience has been found to be protective against depressive symptoms (255,289,290). Finally, the most vulnerable groups were those disproportionately affected by the pandemic, such as individuals with pre-existing mental disorders. The pandemic and its consequences not only accentuated existing health disparities but could have also aggravated already existing mental disorders symptomatology (255).

1.6.2. The impact of loneliness and social support on MDD during the pandemic

Survey responses allowed us to get information about how people were responding psychologically and socially to the pandemic and see how the answers changed when compared with the information gathered before the lockdowns.

We carried a systematic review and a meta-analysis to assess whether the strength of the associations between loneliness and social support with symptoms of depression, anxiety, and posttraumatic stress had changed due to the COVID-19 pandemic in the general population (198). Seventy-three quantitative studies published between 2020 and 2022 were included. Loneliness was moderately correlated with depressive symptoms (r=0.49, N=36), while social support was only weakly correlated with depressive symptomatology (r=0.29, N= 31). Our results suggest that the effect sizes of the associations are similar

to pre-pandemic evidence (239,291). We could hypothesize that the increase in the prevalence of depressive symptoms observed during the pandemic in most cohorts may be partially due to changes in loneliness and social support prevalence, rather than being explained by changes in the robustness of the associations between these variables. Further subgroup analyses indicated that certain correlations could be influenced by the sociodemographic characteristics of the study samples, such as age, sex, region, and COVID-19 stringency index, and by methodological moderators, such as sample size, collection date, methodological quality, and the measurement scales.

Article – review and meta-analysis

The association of social support and loneliness with symptoms of depression, anxiety, and posttraumatic stress during the COVID-19 pandemic: a meta-analysis

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Systematic Review

The Association of Social Support and Loneliness with Symptoms of Depression, Anxiety, and Posttraumatic Stress during the COVID-19 Pandemic: A Meta-Analysis

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Abstract: Background: Research suggests that changes in social support and loneliness have affected mental disorder symptoms during the COVID-19 pandemic. However, there are a lack of studies comparing the robustness of these associations. Aims: The aims were to estimate the strength of the associations of loneliness and social support with symptoms of depression, anxiety, and posttraumatic stress during the COVID-19 pandemic (2020–2022) in the general population. Method: The method entailed a systematic review and random-effects meta-analysis of quantitative studies. Results: Seventy-three studies were included in the meta-analysis. The pooled correlations of the effect size of the association of loneliness with symptoms of depression, anxiety, and posttraumatic stress were 0.49, 0.40, and 0.38, respectively. The corresponding figures for social support were 0.29, 0.19, and 0.18, respectively. Subgroup analyses revealed that the strength of some associations could be influenced by the sociodemographic characteristics of the study samples, such as age, gender, region, and COVID-19 stringency index, and by methodological moderators, such as sample size, collection date, methodological quality, and the measurement scales. Conclusions: Social support had a weak association with mental disorder symptoms during the COVID-19 pandemic while the association with loneliness was moderate. Strategies to address loneliness could be highly effective in reducing the impact of the pandemic on social relationships and mental health.

Keywords: depressive symptoms; anxiety symptoms; posttraumatic stress symptoms; loneliness; social support; COVID-19

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1. Introduction

Since the appearance of the coronavirus disease (COVID-19) in December 2019, one of the greatest concerns has been its effects on the general population's mental health in both the short- and long-term. For example, the implementation of public health and social measures during the pandemic could have had a negative impact on social relationships [1,2], which in turn could have resulted in an adverse impact on mental health outcomes [3,4]. Indeed, the current evidence concerning the impact of the pandemic on the prevalence of mental disorders and their symptoms shows a significant increase in the general population [5]. Although the available studies consistently report an increasing

trend, the use of different measures to assess mental disorders or their symptoms makes comparison between studies difficult, with a wide variation being reported. Specifically, the reported prevalence of depression ranges from 16% to 34%, anxiety from 15% to 38% [1,6–8], and post-traumatic stress disorder (PTSD) from 18% to 33% [9,10].

The effect of social relationships on mental health has been widely documented. Researchers have distinguished between subjective and objective aspects of social relationships, which often interact with each other as moderators [11] or mediators [12] impacting mental health. Objective factors refer to the characteristics of a social network described through quantifiable measures such as the number of close contacts or social interactions, whereas subjective factors refer to how individuals feel regarding that social network [13,14]. Social support and loneliness are, respectively, widely used measures for operationalizing these two types of factors. Social support has been defined as the instrumental, informational, and emotional support provided by a social network that includes family, friends, and neighbours [15] while loneliness has been defined as the unpleasant feeling that occurs because of the difference between the desired and the available social relationships, both quantitatively and qualitatively [16].

According to previous research, loneliness and low social support are among the social determinants most closely related to mental health compared to socioeconomic, material, and behavioural factors [13,17]. These relationships mainly occur with loneliness as the origin [18]. Pre-pandemic and during the pandemic investigations indicate that low social support boosts the development of loneliness [19–22] and that the effect of social support on mental health is mediated by loneliness [23–25]. Both factors increase the odds of having symptoms of depression and anxiety [18,11]. Post-traumatic stress symptoms (PTSS), as already observed during and after the SARS pandemic of 2003, are likely to appear and increase in the long-term following the COVID-19 pandemic, particularly among the most vulnerable groups (e.g., COVID-19 patients and their close contacts, health care workers and other hospital staff, persons with a psychiatric illness history or with underlying health conditions, older people, individuals who reside in high COVID-19 prevalence areas, etc.) [26–28]. This increase could also be aggravated by the effects of loneliness and poor social support [4].

The COVID-19 pandemic has generated unprecedented situations and posed unique challenges globally, leading to a fast and constantly growing body of scientific evidence related to the topic. Although there is now an expanding literature about objective and subjective aspects of social relationships, it is still unclear which constructs (i.e., social support or loneliness) have a higher impact on mental health and how this impact differs from the symptoms of one mental disorder to another. Clarifying these aspects would provide relevant information for the design of psychosocial interventions aimed at improving the population's mental health, which is particularly necessary in the COVID-19 pandemic context.

Thus, the aim of this study was to systematically review quantitative studies published from 2020 to 2022 exploring the associations of loneliness and/or social support with mental disorder symptoms (i.e., depression, anxiety, and post-traumatic stress) during the COVID-19 pandemic. In order to estimate the strength of the associations among these variables, we aimed to perform a statistical meta-analysis, so as to be able to objectively combine and analyse the results of the selected studies.

2. Methods

The review's protocol was registered in PROSPERO, which is an international prospective register of systematic reviews with protocols related to COVID-19 (registration number: CRD42021260142). The methodology followed the recommendations published in the PRISMA statement [29].

2.1. Eligibility Criteria

Literature included in this review was limited to journal articles using general population-based cohort studies measuring the associations of social support or loneliness (i.e., independent variables [IV]) with symptoms of depression, anxiety, or posttraumatic stress (PTS) (i.e., dependent variables [DV]). All the main variables had to be measured quantitatively using validated scales.

The publication period was restricted to the first three years from the appearance of COVID-19 (i.e., from January 2020 (1 January 2020) to October 2022 (3 October 2022)). Observational studies, both cross-sectional and longitudinal with cross-sectional associations between the variables of interest, were included. Only publications in English and Spanish were included.

Studies on the general adult population were included in this review, excluding cohorts of specific populations that the pandemic may have affected differently (e.g., medical staff, caregivers, patients of specific diseases or those in a hospital setting, pregnant women, etc.). We also excluded studies focused on older adults (>60 years) or on children (<16 years) due to the differences regarding mental health outcomes in these specific age groups [30–32]. Moreover, eligibility was restricted to studies with a sample size of 450 participants or more to guarantee that the included articles had enough statistical power to provide substantial estimates of the general population [33,34].

Finally, regarding the measures of interest, studies in which the variables (at least one IV and one DV) were measured quantitatively were included. We ruled out those studies that did not (i) use a valid mode of ascertainment of the measures of interest (e.g., studies that assessed the main variables with a single-item measure or with a non-validated scale, including self-developed scales and adaptations of valid scales), (ii) report disjoint data for each variable (e.g., studies reporting overall mental health as the DV), or (iii) contain relevant and/or complete data for the associations between the variables of interest.

2.2. Article Search, Identification, and Selection

The PubMed, ScienceDirect, and Web of Science databases were searched for relevant studies due to their relevance to the review's objectives and scope. Separate search strategies were developed for each database (Table S1). Key search terms for mental health outcomes were 'depression', 'anxiety', 'post-traumatic stress', and 'mental health'. For the social determinants, the terms included were 'loneliness', 'social connectedness', 'social isolation', 'social network', 'social relationships', and 'social support'. For the COVID-19 pandemic, we searched for 'COVID-19', 'lockdown', 'pandemic', and 'quarantine'.

Figure 1 is a flow diagram of the search and inclusion process. The literature search resulted in 6211 publications (Figure 1). For the study selection, Rayyan reference manager app was used. After removing duplicates, 5239 publications were screened based on their titles and abstracts and categorized as 'include', 'maybe', or 'exclude' by two independent reviewers (AG-P & JD-A) based on the eligibility criteria (researchers were blinded to each other's decisions). Subsequently, decisions of the two reviewers were merged, yielding a percentage of agreement higher than 95%. Discrepancies between the reviewers were resolved by consensus. Finally, the two reviewers independently reviewed the full text articles in the 'include' and 'maybe' categories (n = 259). The 186 studies excluded at the full-text screening stage were tabulated alongside the reason for exclusion in accordance with best practice guidelines [29,35].

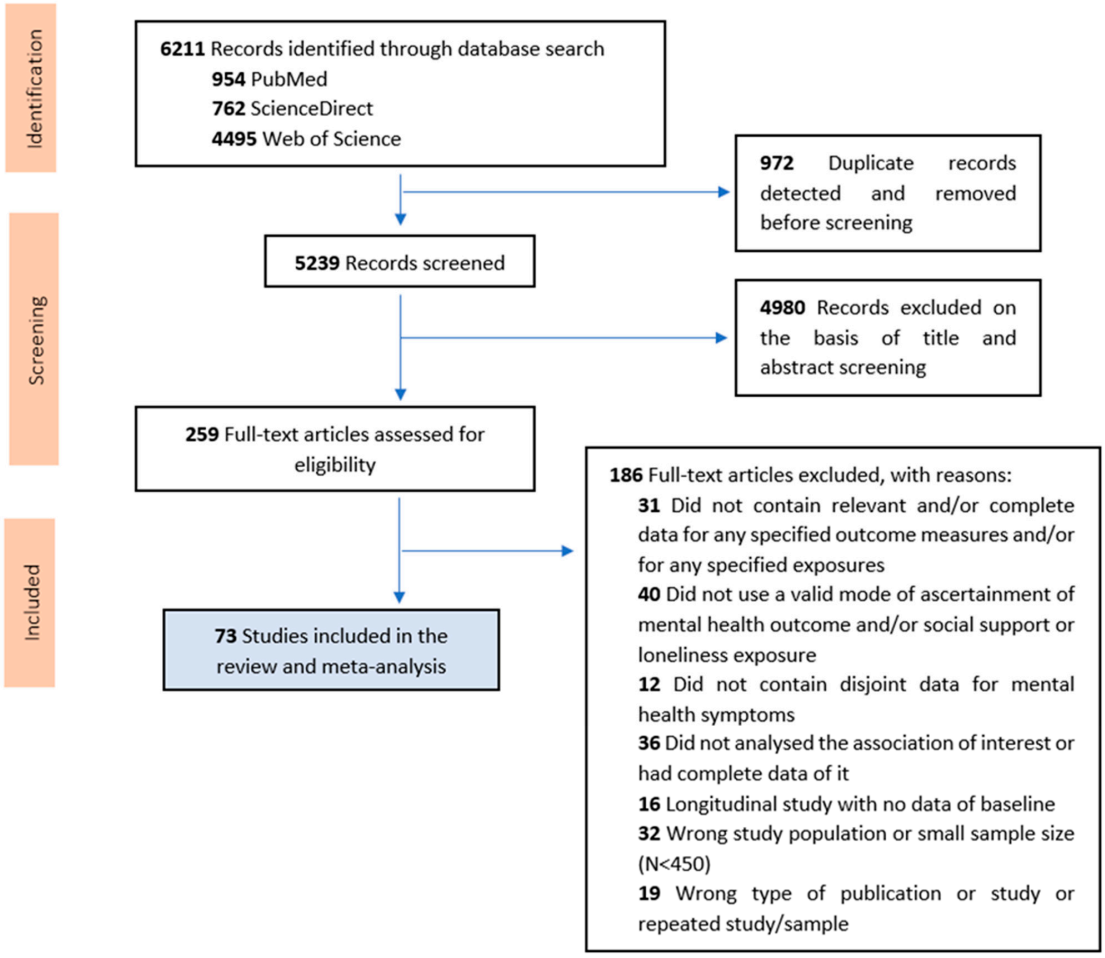


Figure 1. PRISMA flow diagram outlining results of the study selection process.

2.3. Data Extraction

A total of 73 studies were included in the present review and meta-analysis. One systematic reviewer (AG-P) extracted the data from the selected studies into a structured template and assessed their methodological quality. A second reviewer validated all the extracted data (JD-A). The following data were extracted (where available): study details (first author, publication date, article title, study design, country, collection date, main inclusion/exclusion criteria, sample size (N), type of population, aims of the study, and data collection methods), sample characteristics (age, sex), statistical methods, social relationships and mental health measurements, adjustment for covariates, estimates of associations, and key findings. In the case of longitudinal studies, as just few studies used this design and they used distinct follow-up periods, we just included their cross-sectional baseline data.

2.4. Quality Assessment

To evaluate the methodological quality of the studies, we used an adapted version of the Newcastle Ottawa Scale (NOS) [36] for cross-sectional studies, used in previous systematic reviews [37,38] (Supplementary Material File S2). The NOS checklist has three sections that examine different characteristics of the studies (i.e., selection, comparability,

and outcome). Some items are rated with one star and others with two. The total score for each section is what determines the quality of the studies (i.e., 1 = 'poor', 2 = 'fair', or 3 = 'good'). Any discrepancies in terms of rating were resolved between the reviewers.

2.5. Meta-Analytical Method

2.5.1. Calculating Effect Sizes

All the analyses were done using the *meta* package [39] for R software [40].

For the meta-analysis, we required the correlation values of the cross-sectional relationships of interest between continuous variables. When correlations were not available, we converted equivalent statistical measures (e.g, odds ratio (OR)) to correlations. Regarding OR, it was necessary to use a single cut-off point that allowed comparison of people feeling loneliness or having poor social support with the rest of the population. Priority was given to non-adjusted OR and, when not available, to OR adjusted for basic sociodemographic variables (e.g., age and sex), but not for other variables with a potentially mediating role. When the independent variable had more than one category (e.g., low/moderate/high social support), it was dichotomized, and the OR was calculated comparing those with low social support to the remaining sample. Finally, ORs were transformed to Pearson's *r* according to the following conversions [41–43]:

Odds ratio to Cohen's *d*: $d = LogOddsRatio \times \frac{\sqrt{3}}{\pi}$

Cohen's d to Pearson's *r*: $r = \frac{d}{\sqrt{d^2+4}}$

In cases where the independent variable was divided into different dimensions from the construct 'loneliness' or 'social support', the average overall correlation between the different dimensions was obtained [44]. If the study met the inclusion criteria and none of the aforementioned options were possible, the corresponding authors of the original articles were contacted to obtain the required unreported data. Correlations were reported as positive when the relationship was what was expected (i.e., lower social support or higher loneliness directly related to greater mental disorder symptoms).

2.5.2. Statistical Analysis

We conducted a series of random-effects meta-analyses, according to the relationships reported for each study [45]. We used the random effects model due to the high heterogeneity across studies. We assessed statistical heterogeneity using restricted maximum likelihood as a heterogeneity variance estimator with the I^2 statistic, which describes the percentage of total variation across studies that is due to heterogeneity rather than to chance, and the among-study variance τ^2, which is the random effects variance of the true effect sizes [46].

2.5.3. Sources of Heterogeneity

In order to assess the sources of heterogeneity identified in the meta-analysis, we performed subgroup analyses. We evaluated (i) sociodemographic moderator variables and (ii) methodological moderator variables.

Sociodemographic moderator variables were proportion of females in the sample, mean age of the sample, economic region where the study was conducted, and COVID-19 stringency index. The COVID-19 stringency index [47] is a composite score between 0 and 100 designed to compare countries' policy responses to the pandemic, where higher values represent greater strictness of 'lockdown policies' (i.e., closure and containment measures). For each study, the COVID-19 stringency index was determined according to the study setting and the first day of data collection.

Methodological moderator variables were sample size, collection date, study methodological quality, and type of measure to assess the dependent and independent variables. To classify the scales to measure the main variables, we distinguished between the most commonly used measures (i.e., UCLA for loneliness [48], PHQ for depressive

symptoms [49], GAD for anxiety symptoms [50], and MSPSS for social support [51]) and "Others". In the case of the measures used to assess PTSS, due to the concern about flawed published work caused by measuring PTSD related to the pandemic without adequately considering PTSD criteria [52], we performed sub-group analyses distinguishing between those studies that assessed traumatic stress symptoms relative to the COVID-19 pandemic compliant with the DSM-5 criteria [53], using updated measures, and specifying the symptomatic timeframe and those that did not. All the studies that met these criteria also used the PTSD Checklist for DSM-5 (PCL-5) scale [54], so the subgroup was called "PCL5"; while the studies that did not meet any of the criteria were classified in the "Other" group.

The studies that did not have available data regarding a covariate were excluded when carrying out the subgroup analysis for that covariate.

3. Results

3.1. Study Characteristics

The meta-analysis included 73 studies reporting 137 effect sizes from a correlation of either total social support or loneliness with symptoms of depression, anxiety, or PTS (Table 1). The total number of participants involved in the analysis was 1,020,461 (466 – 746,217 participants), with a mean age of 33.23 (SD = 10.39, not reported in 5 studies), and with around 61.5% (SD = 12.0%, [39.9%–87.8%]) of the sample being female (not reported in 2 studies). Most of the study participants were from the general population (62%, N = 45), one third were college students (33%, N = 24), and 4 studies (5%) used samples of the general population with an overrepresentation or inclusion of only young adults (18–35 years). Studies were conducted mainly in China (29%, N= 21), in European countries (29%, N = 21), and in the United States (14%, N = 10). Due to the isolation and social-distancing measures that characterized the initial stages of the COVID-19 pandemic, study data collection was mainly with non-probabilistic sampling techniques via online platforms, social media channels, and email.

Table 1. Overview of included studies.

Authors	N	Mean (SD) Age [Age Range]	Gender (% Female)	Country	Measures of Loneliness and Social Support	Measures of Mental Health Symptomatology	Quality Rating	Reported Relationships
[55]	736	45 *	58.3	China	ss, SSRS	anx, STAI	Fair	ss-anx
[56]	1004	25.41 (7.80)	48.2	Bangladesh	lon, UCLA-3	anx, GAD-7 dep, PHQ-9	Good	lon-anx lon-dep
[57]	923	20.66 (4.27)	71.2	Portugal	ss, MSPSS	anx, DASS-21 dep, DASS-21	Poor	ss-anx ss-dep
[58]	3936	21.7 (4.00)	70.6	France	ss, MSPSS	anx, GAD-7	Fair	ss-anx
[59]	715	31.70 (10.81) [11,18–71]	71.5	Italy	lon, ILS-20	anx, DASS-21	Fair	lon-anx
[60]	747	41.26 (11.57) [11,22–75]	49.0	US	lon, UCLA-3	ptss, PCL-5	Good	lon-ptss
[61]	2583	22.84 (4.79)	65.5	Turkey	lon, UCLA-3	dep, CES-D-8	Poor	lon-dep
[62]	1921	29.28 (10.66) [11,16–67]	69.5	China	ss, MSPSS	anx, SAS	Fair	ss-anx

[63]	466	22.24 (2.68) [11,18–28]	45.5	Italy	lon, UCLA	anx, DASS-21 dep, DASS-21	Poor	lon-anx lon-dep
[64]	2101	47.80 (12.9)	87.8	US	lon, UCLA	anx, GAD-7	Good	lon-anx
[65]	2369	42.6 *	45.93	Germany	ss, OSSS-3 lon, De Jong	anx, GAD-7 dep, PHQ-9	Good	lon-anx lon-dep
[66]	3500	49.25 (15.64) [11,18–93]	51.5	Spain	ss, OSSS-3	anx, GAD-7; dep, PHQ-8	Good	ss-anx ss-dep
[67]	89588	24 * [11,18–29]	56.3	China	ss, MSPSS	anx, GAD-7	Poor	ss-anx
[68]	1115	45 * [11,18–84]	50.5	Poland	ss, MOS-SSS	anx, GAD-7; dep, PHQ-9	Poor	ss-anx ss-dep
[69]	1390	30.7 * [11,14–66]	57.19	China	ss, MSPSS-6	ptss, PCL-5	Good	ss-ptss
[70]	578	45.2 (16.15)	57	Israel	lon, UCLA-3	anx, GAD-7 dep, PHQ-9	Good	lon-anx lon-dep
[71]	539	37.04 (12.91) [11,18–75]	75.7	Brazil	lon, UCLA	anx, GAD-7; dep, CES-D;	Fair	lon-anx lon-dep
[72]	3480	37.92 [11,18–79]	75.0	Spain	ss, MSPSS; lon, UCLA-3	anx, GAD-2; dep, PHQ-2; ptss, PCL-C-2	Poor	lon-anx lon-dep lon-ptss ss-anx ss-dep ss-ptss
[73]	5320	48.5 *	59.9	Canada	ss, MSPSS; lon, UCLA-3	anx, GAD-7 dep, PHQ-9	Good	lon-anx lon-dep ss-anx ss-dep
[74]	2020	24 *	50.0	Lebanon	ss, MSPSS; lon, UCLA-3	anx, GAD-7; dep, PHQ-9	Poor	lon-anx lon-dep ss-anx ss-dep
[75]	1958	37.01 (12.81) [11,18–86]	69.8	UK	lon, UCLA-3	dep, PHQ-9	Fair	lon-dep
[76]	1278	20.1 *	64.6	China	ss, PSSS	anx, DASS-21 dep, DASS-21	Fair	ss-anx ss-dep
[77]	1786	22.15 (3.53)	79.6	Slovakia	lon, UCLA-3	anx, GAD-7 dep, PHQ-9	Poor	lon-anx lon-dep
[78]	691	37.08 (10.85) [11,20–77]	43.6	US	lon, UCLA	dep, CES-D10	Good	lon-dep
[79]	2503	45.99 (17.77)	53.1	Germany	lon, UCLA-3	anx, HADS-6	Good	lon-anx
[80]	10061	36.00 (13.5) [11,18–85]	78.2	Norway	lon, UCLA-8	anx, GAD-7; dep, PHQ-9	Good	lon-anx lon-dep

[81]	1008	28.09 (4.1) [11,18–34]	48.2	US	ss, SC-15; lon, UCLA	anx, GAD-7; dep, CES-D-10	Fair	lon-anx lon-dep ss-anx ss-dep
[82]	771	54	54	China	ss, MSPSS	anx, GAD-7 dep, CES-D	Good	ss-anx ss-dep
[83]	3113	20.83 (1.53)	71.4	China	ss, PSSS	anx, DASS-21 dep, DASS-21	Good	ss-anx ss-dep
[84]	734	20.35 (1.65)	46.9	China	lon, UCLA	anx, SAS dep, CESD20	Good	lon-anx lon-dep
[85]	37810	45 *	74.1	Spain	ss, OSSS-3	anx, GAD-7; dep, PHQ-8	Good	ss-anx ss-dep
[86]	2688	20.49 [20,21]	NA	China	ss, SSRS	dep, SDS	Poor	ss-dep
[87]	653	40.3 *	84.4	Australia	lon, UCLA	anx, GAD-7 dep, PHQ-9	Poor	lon-anx lon-dep
[88]	1492	40.30 (11.8) [11,19–64]	50.1	South Korea	lon, UCLA-3	dep, PHQ-9	Fair	lon-dep
[89]	890	44.3 (16.1)	50.8	Poland	lon, R-UCLA	anx, HADS-M dep, HADS-M	Good	lon-anx lon-dep
[90]	517	19.52 (1.26)	57.4	US	lon, Context	anx, GAD-7 dep, CES-D	Poor	lon-anx lon-dep
[91]	3382	23.98 (4.66) [11,17–60]	70.2	Germany	ss, ESSI; lon, UCLA-3	dep, PHQ-9	Poor	lon-dep ss-dep
[92]	779	NA	61	Ethiopia	ss, OSSS-3	dep, CES-D	Poor	ss-dep
[93]	2640	20.66 [18–25]	68.8	China	ss, SSQ	anx, SAS	Poor	ss-anx
[94]	1562	48.8 [11,18–90]	84.2	Australia, UK, US	lon, UCLA	dep, PHQ-8	Good	lon-dep
[4]	898	24.5 [11,18–29]	81.3	US	ss, MSPSS; lon, UCLA-3	anx, GAD-7; dep, PHQ-8; ptss, PCL-C	Fair	lon-anx lon-dep lon-ptss ss-anx ss-dep ss-ptss
[95]	654	19.98 (1.80) [11,18–28]	50.31	China	lon, UCLA-8	dep, SDS	Fair	lon-dep
[96]	1681	20 *	64.8	China	ss, MSPSS	dep, CES-D	Good	ss-dep
[97]	746217	20.20 *	55.6	China	ss, MSPSS	anx, GAD-7; dep, PHQ-9; ptss, IES-6	Good	ss-anx ss-dep ss-ptss
[98]	14636	48 *	51.7	US	lon, UCLA-3	anx, PROMIS-4 dep, PHQ-8	Good	lon-anx lon-dep
[99]	578	39.22 (14.27) [11,18–78]	59.5	US	lon, De Jong-6	anx, DASS-21 dep, DASS-21	Good	lon-anx lon-dep

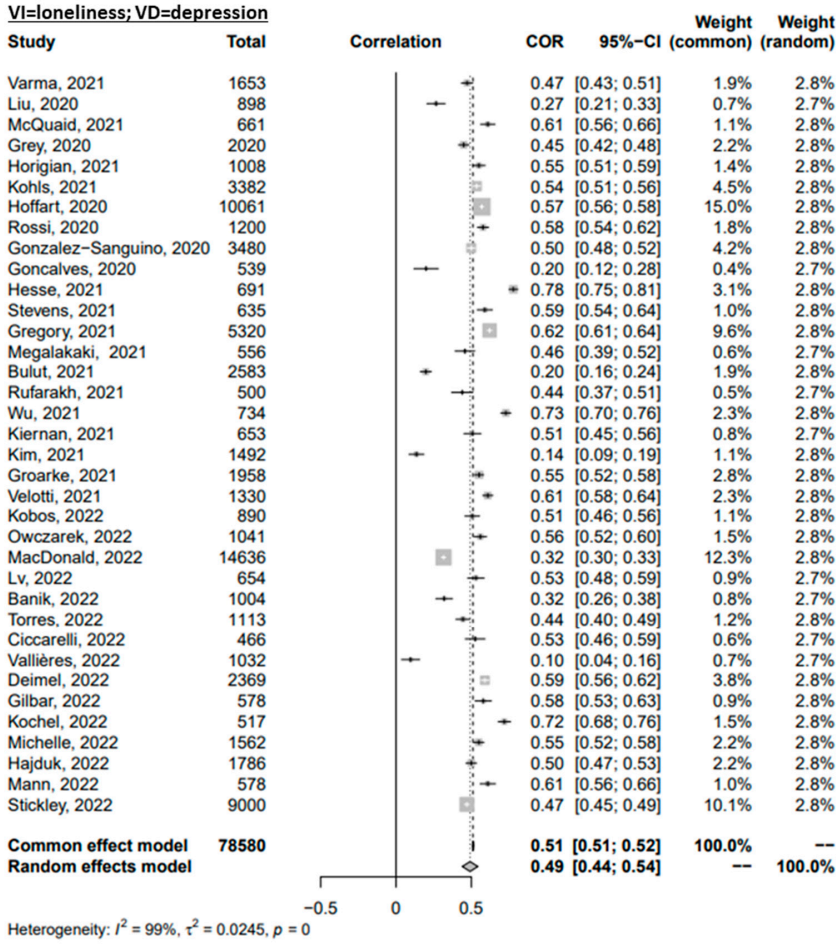
[100]	661	44 *	77.3	Canada	lon, UCLA-8	anx, GAD-7; dep, PHQ-9	Good	lon-anx lon-dep
[101]	556	30.06 (14.38) [11,18–86]	75.5	France	lon, UCLA-3	anx, GAD-7 dep, PHQ-9	Fair	lon-anx lon-dep
[102]	1414	NA	50.6	China	ss, SSRS	dep, SCL-90	Poor	ss-dep
[103]	996	29.00 (8.89)	48.1	Nigeria	ss, MSPSS	anx, HADS dep, HADS	Fair	ss-anx ss-dep
[104]	824	20.41 (1.29) [17–25]	55.09	Mexico	lon, De Jong	anx, BAI	Poor	lon-anx
[105]	655	38.6 * [11,18–85]	62.6	Israel	ss, MSPSS	anx, GAD-7 dep, PHQ-9	Fair	ss-anx ss-dep
[106]	1041	44.97 (15.76) [11,18–87]	51.5	Ireland	lon, UCLA-3	anx, GAD-7 dep, PHQ-9	Good	lon-anx lon-dep
[107]	630	39.20 [11,24–78]	73.0	Turkey	ss, MSPSS	anx, STAI	Poor	ss-anx
[108]	1200	39.33 (12.283) [11,18–80]	81.9	Italy	lon, UCLA	anx, SCL-90R; dep, SCL-90R	Good	lon-anx lon-dep
[109]	500	NA [11,18–39]	50.6	Pakistan	lon, UCLA	anx, DASS-21 dep, DASS-21	Poor	lon-anx lon-dep
[110]	1032	36.5 *	57	Turkey	ss, MSPSS	anx, DASS-42 dep, DASS-42	Good	ss-anx ss-dep
[111]	467	33.14 (12.96) [11,18–84]	63.6	US	ss, MSPSS	anx, GAD-7 dep, PHQ-9 ptss, PCL-5	Good	ss-anx ss-dep ss-ptss
[112]	3274	42.39 (13.41)	79.4	Brazil	ss, MOS-SSS	dep, PHQ-9	Poor	ss-dep
[113]	2734	20 [16–24]	48.24	China	ss, SSRS	anx, SAS	Poor	ss-anx
[114]	560	40.22 (11.60) [11,18–78]	74.0	Austria	ss, MSPSS	anx HADS; dep, HADS	Good	ss-anx ss-dep
[115]	635	43.52 (18.41)	48.5	Australia	lon, UCLA-3	dep, DASS-21	Good	lon-dep
[116]	9000	49.4 *	50.4	China	lon, UCLA-3	anx, GAD-7 dep, PHQ-9	Good	lon-anx lon-dep
[117]	1912	20.28 (2.10) [11,18–48]	69.8	China	ss, MSPSS	anx, GAD-7; dep, PHQ-9; ptss, IES	Fair	ss-anx ss-dep ss-ptss
[118]	3563	NA	68.57	China	ss, SSRS	dep, DBI-II	Poor	ss-dep
[119]	1113	21.45 (5.25) [11,18–99]	70.2	USA, Mexico, Ecuador, Spain, Chile	ss, MSPSS lon, UCLA	dep, PHQ-9 ptss, PCL-5	Fair	lon-dep lon-ptss ss-dep ss-ptss
[120]	1032	44.86 (15.74)	51.9	Ireland	lon, UCLA-3	anx, GAD-7 dep, PHQ-9	Good	lon-anx lon-dep

[121]	1653	42.90 (13.63)	69.7	63 countries	lon, UCLA-3	anx, STAI; dep, PHQ-9	Poor	lon-anx lon-dep
[122]	1330	NA	NA	Italy	lon, UCLA	anx, DASS-21 dep, DASS-21	Fair	lon-anx lon-dep
[123]	2685	27.00	39.9	China	ss, PSSS	anx, GAD-7	Fair	ss-anx ss-dep
[124]	12945	21.5 * [11,17–25]	57.3	China	ss, MSPSS	dep, PHQ-9	Fair	ss-dep
[125]	1021	45.30 (16.46) [11,18–89]	52.3	US	ss, F-SozU K-6	anx, DASS-21 dep, DASS-21 ptss, PTGI	Good	ss-anx ss-dep ss-ptss
[126]	1017	20 *	53.3	China	ss, SSQ-6	anx, GAD-7; dep, PHQ-9	Good	ss-anx ss-dep

NOTE: N = frequency; NA = not available; * = mean age calculated from study data; lon = loneliness; ss = social support; anx = anxiety symptoms; dep = depressive symptoms; ptss = posttraumatic stress symptoms. Variables assessment measures: BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies-Depression (8 or 20 items); Context = Loneliness in Context scale; DASS = Depression Anxiety Stress Scales; De Jong = De Jong Gierveld Loneliness scale (6 or 11 items); ESSI = Enriched Social Support Instrument; F-SozU K-6 = Social Support Questionnaire short form; GAD = Generalized Anxiety Disorder (7 items); HADS = Hospital Anxiety and Depression Scale; IES = Impact of Event Scale; ILS = Italian Loneliness Scale (20 items); MOS-SSS= Medical Outcomes Study—Social Support Survey; MSSPS = Multidimensional Scale of Perceived Social Support (6 or 12 items); OSSS = Oslo Social Support Scale; PCL = Posttraumatic Stress Disorder Checklist ('-C' based on DSM-IV or '-5' based on DSM5); PHQ = Patient health questionnaire (2, 8, or 9 items); PROMIS = Patient-Reported Outcome Measurement Information System; PSSS = Perceived Social Support Scale; PTGI = Posttraumatic Growth Inventory; SAS = Self-rating anxiety scale; SC = Social Connectedness Scale (15 items); SCL-90 = Symptom Checklist 90; SDS= Self-Rating Depression Scale; SF-CiOQ = Short form of the changes in outlook questionnaire; SSQ= Social Support Questionnaire; SSRS = Social Support Rating Scale; STAI = State-Trait Anxiety Inventory; UCLA = University California–Los Angeles loneliness scale (3,8, or 20 items).

3.2. Meta-Analysis

Through random-effects meta-analyses, the six relationships of interest were studied: loneliness-depressive symptoms, loneliness-anxiety symptoms, loneliness-PTSS, social support-depressive symptoms, social support-anxiety symptoms, and social support-PTSS. The effect sizes of the association between loneliness and the mental health outcomes are presented in Figure 2. The pooled effect size for the association of loneliness with symptoms of depression, anxiety, and PTS were r = 0.49, r = 0.40, and r = 0.38, respectively. The three pooled effects represent a medium effect [127] characterised by a large degree of heterogeneity (I^2= 99%, I^2= 99%, and I^2= 98%, respectively). The correlations of the association between social support and mental health outcomes are presented in Figure 3. The pooled effect size for the association between social support and symptoms of depression, anxiety, and PTS were r = 0.29, r = 0.19, and r = 0.18, respectively. The effect of social support on the studied mental health outcomes was smaller when compared to loneliness. The pooled effects were characterised by a large degree of heterogeneity (I^2= 98%, I^2= 99%, and I^2= 97%, respectively).


VI=loneliness; VD=depression
Study
Total
Correlation
COR
95%−CI
Weight (common)
Weight (random)
Varma, 2021 1653 0.47 [0.43; 0.51] 1.9% 2.8%
Liu, 2020 898 0.27 [0.21; 0.33] 0.7% 2.7%
McQuaid, 2021 661 0.61 [0.56; 0.66] 1.1% 2.8%
Grey, 2020 2020 0.45 [0.42; 0.48] 2.2% 2.8%
Horigian, 2021 1008 0.55 [0.51; 0.59] 1.4% 2.8%
Kohls, 2021 3382 0.54 [0.51; 0.56] 4.5% 2.8%
Hoffart, 2020 10061 0.57 [0.56; 0.58] 15.0% 2.8%
Rossi, 2020 1200 0.58 [0.54; 0.62] 1.8% 2.8%
Gonzalez−Sanguino, 2020 3480 0.50 [0.48; 0.52] 4.2% 2.8%
Goncalves, 2020 539 0.20 [0.12; 0.28] 0.4% 2.7%
Hesse, 2021 691 0.78 [0.75; 0.81] 3.1% 2.8%
Stevens, 2021 635 0.59 [0.54; 0.64] 1.0% 2.8%
Gregory, 2021 5320 0.62 [0.61; 0.64] 9.6% 2.8%
Megalakaki, 2021 556 0.46 [0.39; 0.52] 0.6% 2.7%
Bulut, 2021 2583 0.20 [0.16; 0.24] 1.9% 2.8%
Rufarakh, 2021 500 0.44 [0.37; 0.51] 0.5% 2.7%
Wu, 2021 734 0.73 [0.70; 0.76] 2.3% 2.8%
Kiernan, 2021 653 0.51 [0.45; 0.56] 0.8% 2.7%
Kim, 2021 1492 0.14 [0.09; 0.19] 1.1% 2.8%
Groarke, 2021 1958 0.55 [0.52; 0.58] 2.8% 2.8%
Velotti, 2021 1330 0.61 [0.58; 0.64] 2.3% 2.8%
Kobos, 2022 890 0.51 [0.46; 0.56] 1.1% 2.8%
Owczarek, 2022 1041 0.56 [0.52; 0.60] 1.5% 2.8%
MacDonald, 2022 14636 0.32 [0.30; 0.33] 12.3% 2.8%
Lv, 2022 654 0.53 [0.48; 0.59] 0.9% 2.7%
Banik, 2022 1004 0.32 [0.26; 0.38] 0.8% 2.7%
Torres, 2022 1113 0.44 [0.40; 0.49] 1.2% 2.8%
Ciccarelli, 2022 466 0.53 [0.46; 0.59] 0.6% 2.7%
Vallières, 2022 1032 0.10 [0.04; 0.16] 0.7% 2.7%
Deimel, 2022 2369 0.59 [0.56; 0.62] 3.8% 2.8%
Gilbar, 2022 578 0.58 [0.53; 0.63] 0.9% 2.8%
Kochel, 2022 517 0.72 [0.68; 0.76] 1.5% 2.8%
Michelle, 2022 1562 0.55 [0.52; 0.58] 2.2% 2.8%
Hajduk, 2022 1786 0.50 [0.47; 0.53] 2.2% 2.8%
Mann, 2022 578 0.61 [0.56; 0.66] 1.0% 2.8%
Stickley, 2022 9000 0.47 [0.45; 0.49] 10.1% 2.8%
Common effect model 78580 0.51 [0.51; 0.52] 100.0% --
Random effects model 0.49 [0.44; 0.54] -- 100.0%
−0.5
0
0.5
Heterogeneity: I^2 = 99%, τ^2 = 0.0245, p = 0

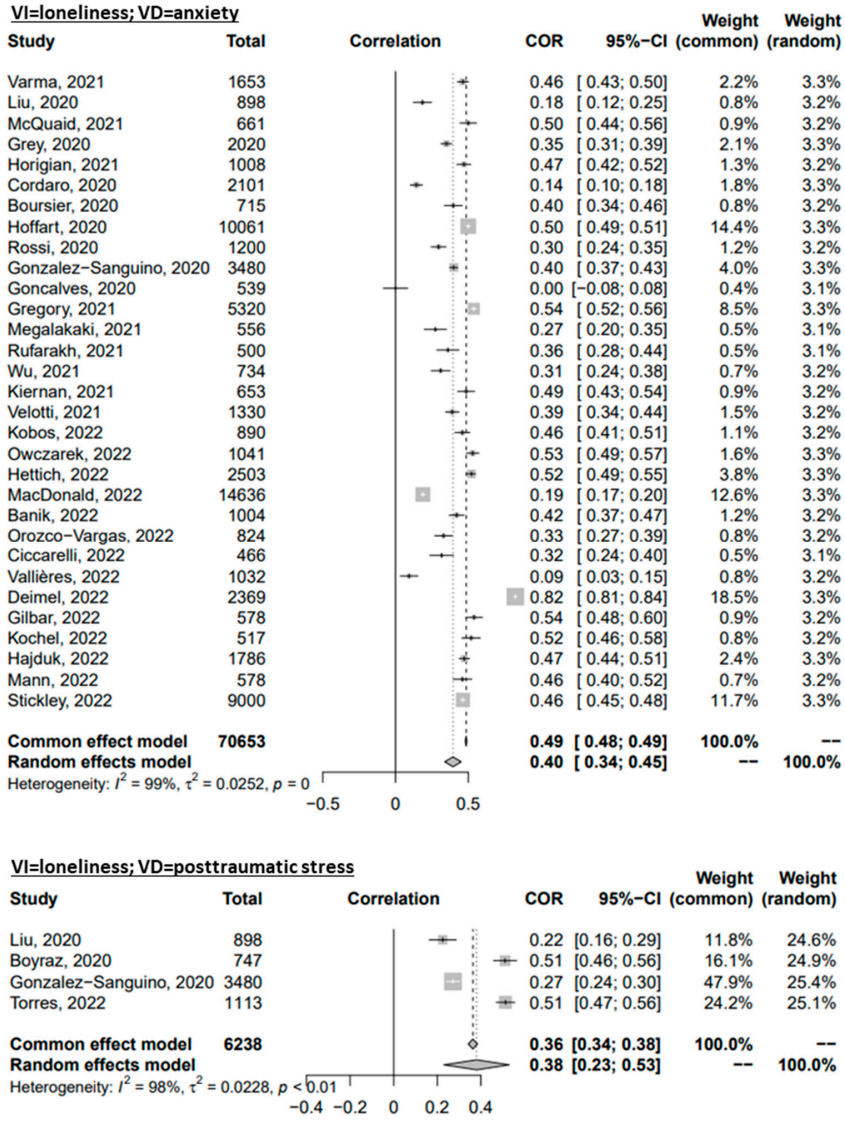
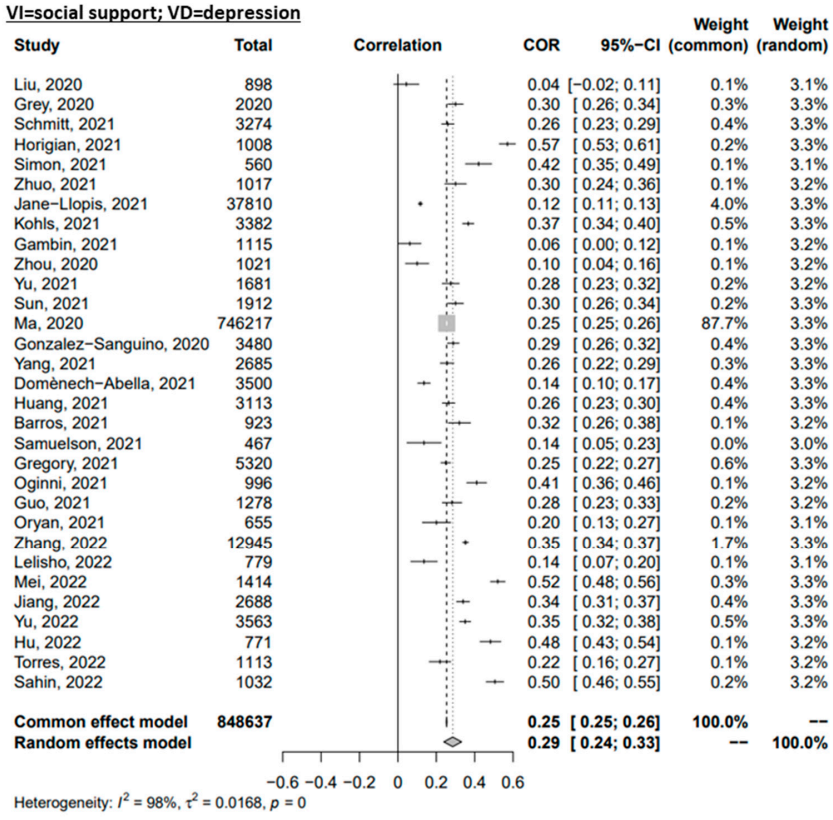
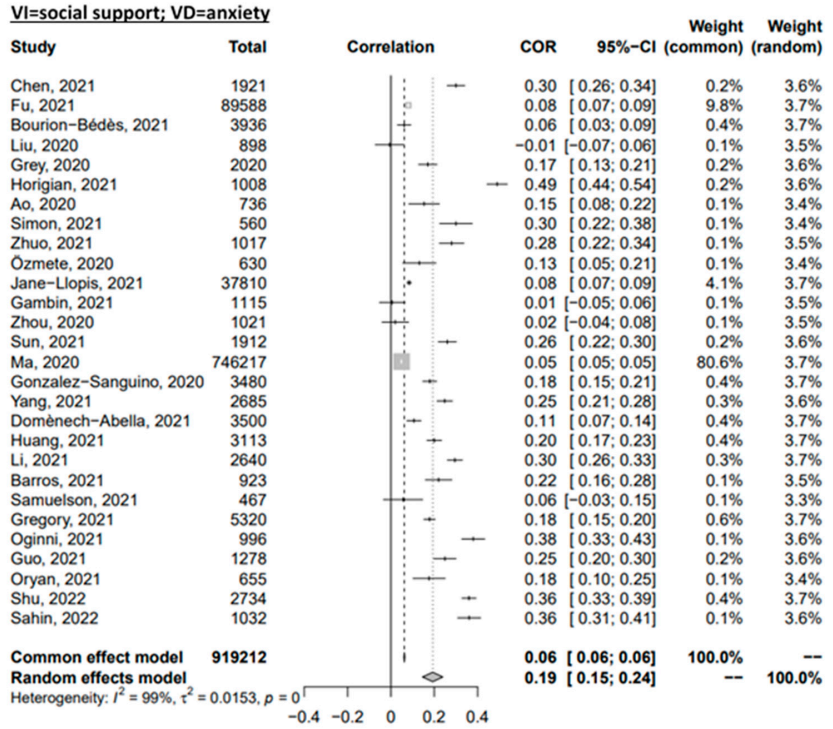


Figure 2. Forest plot of the Omnibus Test for the correlations of loneliness with mental disorder symptoms. References: Banik , 2022 [56]; Boursier , 2020 [59]; Boyraz , 2020 [60]; Bulut , 2021 [61]; Ciccarelli , 2022 [63]; Cordaro , 2021 [64]; Deimel , 2022 [65]; Gilbar , 2022 [70]; Gonçalves , 2020 [71]; González-Sanguino , 2020 [72]; Gregory , 2021 [73]; Grey , 2020 [74]; Groarke , 2021 [75]; Hajduk , 2022 [77]; Hesse , 2021 [78]; Hettich , 2022 [79]; Hoffart , 2020 [80]; Horigian , 2021 [81]; Kiernan , 2021 [87]; Kim , 2021 [88]; Kobos , 2022 [89]; Kochel , 2022 [90]; Kohls , 2021 [91]; Lim , 2022 [94]; Liu , 2020 [4]; Lv , 2022 [95]; MacDonald , 2022 [98]; Mann, 2022 [99]; McQuaid , 2021 [100]; Megalakaki, 2021 [101]; Orozco-Vargas, 2022 [104]; Owczarek , 2022 [106]; Rossi , 2020 [108]; Rufarakh , 2021 [109]; Stevens , 2021 [115]; Stickley, 2022 [116]; Torres , 2022 [119]; Vallières , 2022 [120]; Varma , 2021 [121]; Velotti , 2021 [122]; Wu , 2022 [84].


VI=social support; VD=depression
Study
Total
Correlation
COR
95%−CI
Weight (common)
Weight (random)
Liu, 2020 898 0.04 [−0.02; 0.11] 0.1% 3.1%
Grey, 2020 2020 0.30 [0.26; 0.34] 0.3% 3.3%
Schmitt, 2021 3274 0.26 [0.23; 0.29] 0.4% 3.3%
Horigian, 2021 1008 0.57 [0.53; 0.61] 0.2% 3.3%
Simon, 2021 560 0.42 [0.35; 0.49] 0.1% 3.1%
Zhuo, 2021 1017 0.30 [0.24; 0.36] 0.1% 3.2%
Jane−Llopis, 2021 37810 0.12 [0.11; 0.13] 4.0% 3.3%
Kohls, 2021 3382 0.37 [0.34; 0.40] 0.5% 3.3%
Gambin, 2021 1115 0.06 [0.00; 0.12] 0.1% 3.2%
Zhou, 2020 1021 0.10 [0.04; 0.16] 0.1% 3.2%
Yu, 2021 1681 0.28 [0.23; 0.32] 0.2% 3.2%
Sun, 2021 1912 0.30 [0.26; 0.34] 0.2% 3.3%
Ma, 2020 746217 0.25 [0.25; 0.26] 87.7% 3.3%
Gonzalez−Sanguino, 2020 3480 0.29 [0.26; 0.32] 0.4% 3.3%
Yang, 2021 2685 0.26 [0.22; 0.29] 0.3% 3.3%
Domènech−Abella, 2021 3500 0.14 [0.10; 0.17] 0.4% 3.3%
Huang, 2021 3113 0.26 [0.23; 0.30] 0.4% 3.3%
Barros, 2021 923 0.32 [0.26; 0.38] 0.1% 3.2%
Samuelson, 2021 467 0.14 [0.05; 0.23] 0.0% 3.0%
Gregory, 2021 5320 0.25 [0.22; 0.27] 0.6% 3.3%
Oginni, 2021 996 0.41 [0.36; 0.46] 0.1% 3.2%
Guo, 2021 1278 0.28 [0.23; 0.33] 0.2% 3.2%
Oryan, 2021 655 0.20 [0.13; 0.27] 0.1% 3.1%
Zhang, 2022 12945 0.35 [0.34; 0.37] 1.7% 3.3%
Lelisho, 2022 779 0.14 [0.07; 0.20] 0.1% 3.1%
Mei, 2022 1414 0.52 [0.48; 0.56] 0.3% 3.3%
Jiang, 2022 2688 0.34 [0.31; 0.37] 0.4% 3.3%
Yu, 2022 3563 0.35 [0.32; 0.38] 0.5% 3.3%
Hu, 2022 771 0.48 [0.43; 0.54] 0.1% 3.2%
Torres, 2022 1113 0.22 [0.16; 0.27] 0.1% 3.2%
Sahin, 2022 1032 0.50 [0.46; 0.55] 0.2% 3.2%
Common effect model 848637 0.25 [0.25; 0.26] 100.0% --
Random effects model 0.29 [0.24; 0.33] -- 100.0%
−0.6 −0.4 −0.2 0 0.2 0.4 0.6
Heterogeneity: I^2 = 98%, τ^2 = 0.0168, p = 0


VI=social support; VD=anxiety
Study
Total
Correlation
COR
95%−CI
Weight (common)
Weight (random)
Chen, 2021 1921 0.30 [0.26; 0.34] 0.2% 3.6%
Fu, 2021 89588 0.08 [0.07; 0.09] 9.8% 3.7%
Bourion−Bédès, 2021 3936 0.06 [0.03; 0.09] 0.4% 3.7%
Liu, 2020 898 −0.01 [−0.07; 0.06] 0.1% 3.5%
Grey, 2020 2020 0.17 [0.13; 0.21] 0.2% 3.6%
Horigian, 2021 1008 0.49 [0.44; 0.54] 0.2% 3.6%
Ao, 2020 736 0.15 [0.08; 0.22] 0.1% 3.4%
Simon, 2021 560 0.30 [0.22; 0.38] 0.1% 3.4%
Zhuo, 2021 1017 0.28 [0.22; 0.34] 0.1% 3.5%
Özmete, 2020 630 0.13 [0.05; 0.21] 0.1% 3.4%
Jane−Llopis, 2021 37810 0.08 [0.07; 0.09] 4.1% 3.7%
Gambin, 2021 1115 0.01 [−0.05; 0.06] 0.1% 3.5%
Zhou, 2020 1021 0.02 [−0.04; 0.08] 0.1% 3.5%
Sun, 2021 1912 0.26 [0.22; 0.30] 0.2% 3.6%
Ma, 2020 746217 0.05 [0.05; 0.05] 80.6% 3.7%
Gonzalez−Sanguino, 2020 3480 0.18 [0.15; 0.21] 0.4% 3.7%
Yang, 2021 2685 0.25 [0.21; 0.28] 0.3% 3.6%
Domènech−Abella, 2021 3500 0.11 [0.07; 0.14] 0.4% 3.7%
Huang, 2021 3113 0.20 [0.17; 0.23] 0.4% 3.7%
Li, 2021 2640 0.30 [0.26; 0.33] 0.3% 3.7%
Barros, 2021 923 0.22 [0.16; 0.28] 0.1% 3.5%
Samuelson, 2021 467 0.06 [−0.03; 0.15] 0.1% 3.3%
Gregory, 2021 5320 0.18 [0.15; 0.20] 0.6% 3.7%
Oginni, 2021 996 0.38 [0.33; 0.43] 0.1% 3.6%
Guo, 2021 1278 0.25 [0.20; 0.30] 0.2% 3.6%
Oryan, 2021 655 0.18 [0.10; 0.25] 0.1% 3.4%
Shu, 2022 2734 0.36 [0.33; 0.39] 0.4% 3.7%
Sahin, 2022 1032 0.36 [0.31; 0.41] 0.1% 3.6%
Common effect model 919212 0.06 [0.06; 0.06] 100.0% --
Random effects model 0.19 [0.15; 0.24] -- 100.0%
Heterogeneity: I^2 = 99%, τ^2 = 0.0153, p = 0
−0.4 −0.2 0 0.2 0.4

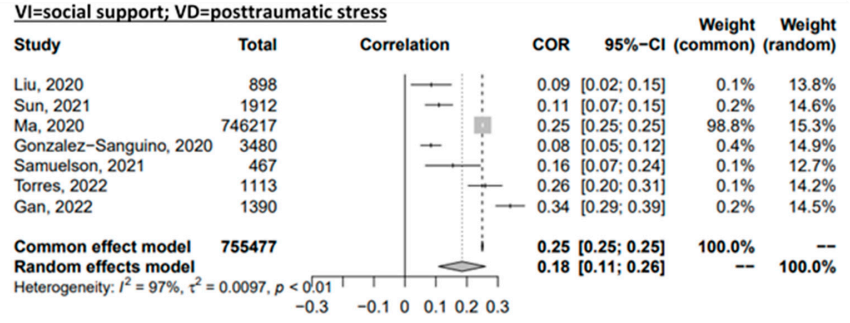


Figure 3. Forest plot of the Omnibus Test for the correlations of social support with mental disorder symptoms. References: Ao , 2020 [55]; Barros, 2021 [57]; Bourion-Bédès , 2021 [58]; Chen , 2021 [62]; Domènech-Abella , 2021 [66]; Fu , 2021 [67]; Gambin , 2021 [68]; Gan , 2022 [69]; González-Sanguino , 2020 [72]; Gregory , 2021 [73]; Grey , 2020 [74]; Guo , 2021 [76]; Horigian , 2021 [81]; Hu , 2022 [82]; Huang , 2021 [83]; Jané-Llopis , 2021 [85]; Jiang , 2022 [86]; Kohls , 2021 [91]; Lelisho, 2022 [92]; Li, 2021 [93]; Liu , 2020 [4]; Ma , 2020 [97]; Mei , 2022 [102]; Oginni , 2021 [103]; Oryan , 2021 [105]; Özmete, 2020 [107]; Sahin , 2022 [110]; Samuelson , 2021 [111]; Schmitt , 2021 [112]; Shu , 2022 [113]; Simon , 2021 [114]; Sun , 2021 [117]; Yu, 2022 [118]; Torres , 2022 [119]; Yang , 2021 [123]; Yu , 2021 [96]; Zhang , 2022 [124]; Zhou , 2020 [125]; Zhuo , 2021 [126].

3.3. Moderator Analysis

The heterogeneous results were analysed with subgroup analyses. For each of the subgroups, the total effects and associated heterogeneity measures were calculated and the results are reported in Tables 2 and 3.

Table 2. Subgroup analysis for the associations between loneliness and mental disorder symptoms.

DV = Loneliness; IV = Depression						
Covariate	**K**	**r**	**Lower CI**	**Upper CI**	**Heterogeneity**	***p*-Value**
Proportion of females (k = 35)						
<50%	8	0.57	0.47	0.67	98%	
50 to 70%	15	0.45	0.36	0.55	99%	<0.001
>70%	12	0.48	0.41	0.55	95%	
Age groups (k = 34)						
<30 years	12	0.48	0.39	0.57	98%	
30 to 40	8	0.53	0.42	0.64	98%	<0.001
>40 years	14	0.47	0.38	0.56	99%	
Region (k = 36)						
China	3	0.58	0.42	0.73	99%	
Europe	13	0.51	0.44	0.58	96%	<0.001
Developed	15	0.52	0.43	0.60	99%	
Developing	5	0.32	0.21	0.43	96%	
Stringency index (k = 29)						
<70	10	0.52	0.42	0.61	98%	
70–80	13	0.49	0.39	0.59	99%	<0.001
>80	6	0.48	0.41	0.56	93%	
Sample size (k = 36)						
<1000	15	0.54	0.46	0.62	97%	
1000–2000	12	0.45	0.35	0.55	98%	<0.001
>2000	9	0.47	0.38	0.56	99%	
Collection date (k = 31)						

January-June 2020	21	0.47	0.39	0.55	99%	
July-December 2020	8	0.54	0.48	0.60	97%	<0.001
2021–2022	2	0.38	0.26	0.51	91%	
Methodological quality (k = 36)						
Poor	10	0.48	0.41	0.56	98%	
Fair	9	0.42	0.31	0.53	98%	<0.001
Good	17	0.53	0.46	0.61	99%	
Depression measures (k = 36)						
PHQ	22	0.46	0.40	0.52	99%	
CES	6	0.53	0.32	0.74	99%	<0.001
Other	8	0.55	0.51	0.59	78%	
Loneliness measures (k = 36)						
UCLA	33	0.48	0.42	0.53	99%	<0.001
Other	3	0.64	0.56	0.72	93%	
DV = Loneliness; IV = Anxiety						
Covariate	**K**	**r**	**Lower CI**	**Upper CI**	**Heterogeneity**	***p*-Value**
Proportion of females (k = 30)						
<50%	6	0.45	0.29	0.61	100%	
50 to 70%	13	0.42	0.34	0.50	99%	<0.001
>70%	11	0.33	0.24	0.43	98%	
Age groups (k = 29)						
<30 years	9	0.38	0.31	0.44	92%	
30 to 40	7	0.34	0.21	0.46	97%	<0.001
>40 years	13	0.44	0.34	0.55	100%	
Region (k = 31)						
China	2	0.39	0.24	0.54	95%	
Europe	13	0.42	0.33	0.52	99%	<0.001
Developed	11	0.41	0.32	0.50	99%	
Developing	5	0.29	0.15	0.44	94%	
Stringency index (k = 26)						
<70	7	0.53	0.42	0.63	99%	
70–80	12	0.35	0.25	0.45	99%	<0.001
>80	7	0.34	0.24	0.44	96%	
Sample size (k = 31)						
<1000	14	0.37	0.29	0.45	94%	
1000–2000	8	0.39	0.30	0.49	96%	<0.001
>2000	9	0.44	0.30	0.57	100%	
Collection date (k = 31)						
January-June 2020	17	0.37	0.28	0.47	100%	
July-December 2020	7	0.48	0.44	0.41	88%	<0.001
2021–2022	1	0.42	0.37	0.47	-	
Methodological quality (k = 31)						
Poor	9	0.41	0.37	0.46	87%	
Fair	6	0.29	0.16	0.43	96%	<0.001
Good	16	0.42	0.34	0.51	100%	
Anxiety measures (k = 31)						
GAD	19	0.41	0.32	0.49	99%	
DASS	5	0.39	0.35	0.43	51%	<0.001
Other	7	0.37	0.28	0.46	99%	
Loneliness measures (k = 31)						

UCLA	26	0.37	0.32	0.43	99%	<0.001
Other	5	0.51	0.34	0.68	99%	
DV = Loneliness; IV = Posttraumatic Stress						
Covariate	**K**	**r**	**Lower CI**	**Upper CI**	**Heterogeneity**	***p*-Value**
Proportion of females (k = 4)						
<50%	1	0.51	0.46	0.56	-	
50 to 70%	0	-	-	-	-	<0.01
>70%	3	0.34	0.16	0.51	98%	
Age groups (k = 4)						
<30 years	2	0.37	0.09	0.65	98%	
30 to 40	1	0.27	0.24	0.30	-	<0.01
>40 years	1	0.51	0.46	0.56	-	
Region (k = 4)						
China	0	-	-	-	-	
Europe	1	0.27	0.24	0.30	-	<0.01
Developed	3	0.42	0.23	0.60	97%	
Developing	0	-	-	-	-	
Stringency index (k = 3)						
<70	0	-	-	-	-	
70–80	3	0.34	0.16	0.51	97%	-
>80	0	-	-	-	-	
Sample size (k = 4)						
<1000	2	0.37	0.09	0.65	98%	
1000–2000	1	0.51	0.47	0.56	-	<0.01
>2000	1	0.27	0.24	0.30	-	
Collection date (k = 4)						
January-June 2020	3	0.34	0.16	0.51	97%	
July-December 2020	0	-	-	-	-	<0.01
2021–2022	1	0.51	0.47	0.56	-	
Methodological quality (k = 4)						
Poor	1	0.27	0.24	0.30	-	
Fair	2	0.37	0.09	0.65	98%	<0.01
Good	1	0.51	0.46	0.56	-	
PTSS measures (k = 4)						
PCL5	1	0.51	0.46	0.56	-	<0.01
Other	3	0.34	0.16	0.51	98%	
Loneliness measures (k = 4)						
UCLA	4	0.38	0.23	0.53	98%	<0.01
Other	0	-	-	-	-	

NOTE: Some studies were excluded from the subgroup analysis due to missing values.

Table 3. Subgroup analysis for the associations between social support and mental disorder symptoms.

DV = Social Support; IV = Depression						
Covariate	**K**	**r**	**Lower CI**	**Upper CI**	**Heterogeneity**	***p*-Value**
Proportion of females (k = 30)						
<50%	4	0.38	0.25	0.52	98%	
50 to 70%	17	0.27	0.21	0.34	98%	<0.001
>70%	9	0.26	0.18	0.33	98%	

Age groups (k = 28)						
<30 years	17	0.31	0.26	<0.001	97%	
30 to 40	4	0.29	0.13	0.44	97%	<0.001
>40 years	7	0.19	0.10	0.28	97%	
Region (k = 31)						
China	12	0.33	0.28	<0.001	98%	
Europe	7	0.24	0.14	0.34	99%	<0.001
Developed	8	0.25	0.12	0.39	98%	
Developing	4	0.28	0.17	0.39	93%	
Stringency index (k = 27)						
<70	6	0.36	0.24	0.47	98%	
70–80	15	0.26	0.20	0.32	97%	<0.001
>80	6	0.21	0.13	0.30	97%	
Sample size (k = 31)						
<1000	8	0.27	0.16	0.38	96%	
1000–2000	10	0.31	0.21	0.42	98%	<0.001
>2000	13	0.27	0.23	0.31	99%	
Collection date (k = 28)						
January-June 2020	17	0.23	0.17	0.30	99%	
July-December 2020	5	0.32	0.19	0.44	98%	<0.001
2021–2022	6	0.37	0.29	0.46	94%	
Methodological quality (k = 31)						
Poor	10	0.30	0.22	0.37	96%	
Fair	9	0.29	0.20	0.39	97%	<0.001
Good	12	0.27	0.19	0.35	99%	
Depression measures (k = 31)						
PHQ	17	0.23	0.18	<0.001	99%	
CES	4	0.37	0.17	0.56	99%	<0.001
Other	10	0.35	0.28	0.43	78%	
Social support measures (k = 31)						
MSPSS	19	0.29	0.25	<0.001	96%	<0.001
Other	12	0.27	0.18	0.37	99%	

DV = Social support; IV = Anxiety

Covariate	K	r	Lower CI	Upper CI	Heterogeneity	*p*-value
Proportion of females (k = 28)						
<50%	5	0.33	0.22	0.44	97%	
50 to 70%	15	0.17	0.11	0.23	98%	<0.001
>70%	8	0.14	0.08	0.21	94%	
Age groups (k = 26)						
<30 years	16	0.23	0.16	<0.001	99%	
30 to 40	7	0.18	0.09	0.28	92%	<0.001
>40 years	5	0.12	0.05	0.19	93%	
Region (k = 28)						
China	11	0.22	0.17	<0.001	99%	
Europe	7	0.13	0.06	0.21	93%	<0.001
Developed	7	0.18	0.05	0.32	98%	
Developing	3	0.23	0.08	0.38	96%	
Stringency index (k = 27)						
<70	5	0.21	0.12	0.31	95%	<0.001
70–80	14	0.20	0.13	0.27	99%	

>80	8	0.14	0.07	0.22	98%	
Sample size (k = 28)						
<1000	8	0.18	0.09	0.27	93%	
1000–2000	8	0.25	0.13	0.36	97%	<0.001
>2000	12	0.17	0.11	0.22	99%	
Collection date (k = 26)						
January-June 2020	21	0.16	0.11	0.22	98%	
July-December 2020	3	0.27	0.17	0.38	97%	<0.001
2021–2022	2	0.29	0.15	0.43	91%	
Methodological quality (k = 28)						
Poor	8	0.18	0.10	0.26	98%	
Fair	10	0.23	0.14	0.32	97%	<0.001
Good	10	0.16	0.09	0.24	98%	
Anxiety measures (k = 28)						
GAD	16	0.15	0.09	<0.001	98%	
DASS	5	0.21	0.10	0.32	94%	<0.001
Other	7	0.28	0.21	0.35	89%	
Social support measures (k = 28)						
MSPSS	19	0.19	0.14	<0.001	98%	<0.001
Other	9	0.20	0.09	0.31	99%	
DV = Social support; IV = Posttraumatic stress						
Covariate	**K**	**r**	**Lower CI**	**Upper CI**	**Heterogeneity**	***p*-value**
Proportion of females (k = 7)						
<50%	0	-	-	-	-	
50 to 70%	4	0.22	0.12	0.32	95%	<0.01
>70%	3	0.14	0.03	0.26	93%	
Age groups (k = 7)						
<30 years	4	0.18	0.09	<0.01	95%	
30 to 40	3	0.19	0.04	0.35	97%	<0.01
>40 years	0	-	-	-	-	
Region (k = 7)						
China	3	0.23	0.10		96%	
Europe	1	0.08	0.05	<0.01	-	<0.01
Developed	3	0.17	0.06	0.27	88%	
Developing	0	-	-	-	-	
Stringency index (k = 6)						
<70	0	-	-	-	-	
70–80	6	0.17	0.09	0.26	97%	-
>80	0	-	-	-	-	
Sample size (k = 7)						
<1000	2	0.11	0.05	0.18	36%	
1000–2000	3	0.24	0.10	0.37	96%	<0.01
>2000	2	0.17	0.00	0.33	99%	
Collection date (k = 7)						
January-June 2020	6	0.17	0.09	0.26	97%	
July-December 2020	0	-	-	-	-	<0.01
2021–2022	1	0.26	0.20	0.31	-	
Methodological quality (k = 7)						
Poor	1	0.08	0.05	0.12	-	<0.01
Fair	3	0.15	0.05	0.26	91%	

Good	3	0.25	0.16	0.35	89%	
PTSS measures (k = 7)						
PCL5	2	0.25	0.07	<0.01	92%	<0.01
Other	5	0.16	0.08	0.24	98%	
Social support measures (k = 7)						
MSPSS	7	0.18	0.11	<0.01	97%	<0.01
Other	0	-	-	-	-	

NOTE: Some studies were excluded from the subgroup analysis due to missing values.

Although, in many cases, the moderation effects could not be tested in the relationships with PTSS due to a low number of studies, in general we observed that the associations of social support and loneliness with mental disorder symptoms were stronger in samples with a lower proportion of females and COVID-19 stringency index, in those studies adequately using the PCL-5 (Blevins et al., 2015), and conducted in China, whereas those studies using the Patient Health Questionnaire (PHQ) [49] to measure depressive symptoms and the UCLA loneliness scale [48] to measure loneliness showed weaker associations. In the case of the relationship between loneliness and mental disorder symptoms, the associations were stronger when the interviews were carried between July and December 2020 in studies with high methodological quality and in those studies using the Generalized Anxiety Disorder (GAD) scale [50] to measure anxiety symptoms while in developing countries, these associations were weaker. Regarding the relationship between social support and mental disorder symptoms, the correlation values were lower in those studies carried in Europe and with an earlier collection date. In the case of the sample size, the results were discordant between the studied associations.

3.4. Publication Bias

Publication bias was assessed by constructing funnel plots (Figures S1 and S2) followed by Egger tests. The results indicated insignificant levels of publication bias for all relationships, except for the associations of social support and loneliness with anxiety ($p < 0.05$).

4. Discussion

This meta-analysis sought to explore the correlation of social support and loneliness with symptoms of depression, anxiety, and posttraumatic stress during the COVID-19 pandemic. The results show that social support had a weak association with mental disorder symptoms, whereas loneliness had a moderate association with symptoms of anxiety, posttraumatic stress, and, particularly, depression during the COVID-19 pandemic. If we compare the pooled correlations with guidelines for interpreting the magnitude of correlation coefficients [128], we observe the effect of the association between loneliness and mental health outcomes to be in the upper third distribution of correlation coefficients. In all cases, the results were characterized by a high level of heterogeneity.

In general, our results suggest that the effect sizes of the associations of social support and loneliness with symptoms of mental disorders are similar to pre-pandemic evidence. A previous meta-analysis reported almost the same effect size of loneliness on depression (r = 0.50) [129] as the one obtained in the present study, whereas another meta-analysis showed a weaker association between social support and depression (r = 0.17) [130]. A systematic review defined the association between loneliness and anxiety as moderate (r = 0.42), whereas the association between social support and anxiety was seen to be less clear [17]. Finally, the effect size of the association between social support and PTSS reported in the present meta-analysis was lower than that reported in a previous study with pre-pandemic data (r = 0.26) [131], which may be explained by the diversity of traumatic events considered. No reviews were found about the effect of loneliness on PTSS in the general population.

Therefore, the increase in mental health problems during the COVID-19 pandemic could be partially explained by an increase in the prevalence of loneliness and a decrease in social support [1,2] rather than by more robust associations between social relationships and mental health. The smaller effect size obtained in those associations where social support was the independent variable could be explained by (i) the fact that loneliness might mediate the relationship between social support and mental health [23,24] and (ii) the substantial overlap between these two constructs and the instruments used to measure them. Loneliness and social support are both strictly linked with an individual's social system and are interconnected concepts that affect one another. They partially share some conceptual aspects but are distinguished by the theoretical interpretation and definition of the concepts, the individual's experience, perceptions, and social exchanges, and its public connotations [132,133].

Most of the moderation effects detected in our analysis can be explained by previous literature. The stronger association of social support with mental disorder symptoms among younger individuals can be explained by the different relational needs that exist across age groups. Following the socioemotional selectivity theory [134], although social contact declines across adulthood, social goals change and the close and emotionally satisfying relationships prevail, and these may have remained more stable during the pandemic. In contrast, young people rely more on frequent and diverse social interactions, which might have been more greatly affected by social restrictions [134,135]. On the other hand, this pattern is not seen for the impact of loneliness, as subjective aspects of social relationships do not necessarily correspond with objective ones.

Our results are also in line with previous evidence suggesting that the beneficial effects of social support on mental health are stronger in the most deprived regions and neighbourhoods (i.e., with lower socioeconomic conditions and social capital and higher poverty), where inhabitants would be more likely to establish reciprocity networks with neighbours due to the absence of other resources [136–138].

In addition, the stronger associations seen in those studies with a higher proportion of males in the sample could be explained by the cultural differences in the socialization process of men and women, as men might be more vulnerable to the negative consequences of loneliness and low social support on mental health since they have fewer relational resources due to different socialization processes between genders. Socialization among men tends to lead to an emotional independence from general social support, with men relying on their partners for social and emotional support, whereas socialization among women tends to lead to a more complex social and emotional life [139].

The differences among variable measurement instruments may be partially explained by the scales having been designed to measure different types of symptoms, the use of different terminology, and variations in recall time frames [140]. In the case of COVID-19 related (post) traumatic stress symptoms, the associations were stronger when the DSM-5 criteria had been strictly followed; nevertheless, we should be cautious when interpreting these results, due to the low number of studies that fit in the "PCL5" category.

Finally, the moderation effect of the collection date and the COVID-19 stringency index, which is based on the public health and social measures imposed by the governments, reflect the changing course of the pandemic and its stages, which have affected social relationships and mental health differently.

Strengths and Limitations

This is the first meta-analysis to focus on synthesizing correlational data of social support and loneliness with symptoms of depression, anxiety, and posttraumatic stress during the COVID-19 pandemic. A strength of the study is the exhaustive search of both published and unpublished data (i.e., multiple attempts to contact authors to obtain missing data) that it involved. However, the cross-sectional nature of the data from the included studies limited the possibility of examining causal relationships. It would have strengthened the meta-analysis to include prospective and longitudinal studies, but few

studies used this design, and they used distinct follow-up periods, which impeded their inclusion. Second, the gathered data were based on self-reported questionnaires, which may have resulted in recall or reporting bias. In addition, self-reported measurements are related with the distorted perception of individuals with mental disorder symptoms and their mood state, which could have influenced some of the findings [141]. Third, although 22 out of the 73 included studies had a poor methodological quality, the exclusion of the poor quality studies did not have an impact on our overall results, as it can be seen in the subgroup analyses. Finally, the funnel plots revealed significant publication bias for the relationships with anxiety as the outcome. The asymmetry could be the result of publication and citation bias, as studies giving stronger results are more likely to be published and to be cited and, thus, are more likely to be included in meta-analyses [142,143]. However, no significant publication bias was detected in the remaining associations, although all of them reported a high level of heterogeneity ($I^2 > 95\%$). We explored methodological and theoretical factors moderating the correlation of the associations, but it is likely that other factors such as sociodemographic and socioeconomic characteristics of the study samples may have also contributed to the heterogeneity of the results. Therefore, we should cautiously interpret the findings of the present study, and future studies should try to identify further explanatory factors.

5. Conclusions

The current review shows that social support had a weak association, whereas loneliness had a moderate one, with mental disorders symptoms during the COVID-19 pandemic. Therefore, strategies focused on loneliness could be highly effective in reducing the impact of a pandemic on mental health. The synergy between objective aspects of social relationships, such as social support, and subjective aspects, such as loneliness, that configure the population's mental health suggests that these interventions should be oriented both toward the individual and the community of social networks. These interventions directed towards people feeling loneliness should aim (i) to provide psychological assistance promoting changes in their social behaviour (i.e., targeting their maladaptive social perception and cognitive biases towards loneliness [144,145]) and (ii) to increase their chances of establishing satisfactory social contacts while considering the target population and the effects of moderator variables, such as gender, setting, and age.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph20042765/s1. Supplementary Material File S1, Figure S1: Funnel plots representing the standard error by Fisher's Z for the loneliness' effect sizes showing the symmetry of the data in relation to publication bias; Figure S2: Funnel plots representing the standard error by Fisher's Z for the social support effect sizes showing the symmetry of the data in relation to publication bias; Table S1: Overview of the search terms used in each database; Supplementary Material File S2: Adapted version of the Newcastle Ottawa Scale (NOS).

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1.7.Thesis justification

Understanding the complex interrelations of variables leading to depression, a highly prevalent and heterogeneous disorder, is crucial for developing effective prevention strategies and targeted interventions. Even before the COVID-19 pandemic, MDD prevalence was alarming and, on the rise, with social determinants playing a significant role in its impact, particularly those factors related to social interactions. Despite numerous studies examining the association between loneliness and social networks with depression, our understanding of how objective and subjective aspects of social relationships interact and their influence on both the incidence and, especially, the course of depression, is still very limited.

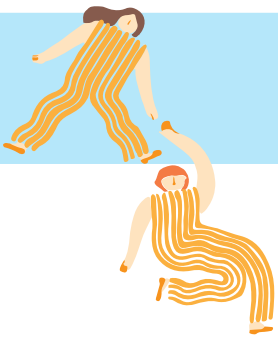
The sudden and widespread measures implemented during the pandemic to contain SARS-CoV-2 spread, including explicit confinement and limitation of social interactions, exacerbated feelings of loneliness, and led to significant changes in social support networks. The associated uncertainties, misinformation, fear of infection, and the profound stress caused by the pandemic affected individuals across all societal levels.

There is a need to better understand how social relationships and other social determinants impact mental health and depression, and especially how the pandemic has affected this association. It is essential to ascertain which are the most vulnerable socioeconomic and sociodemographic profiles, how different risk factors interact with each

other, and whether the impact of the pandemic on social relationships and mental health will persist in the medium and long term.

By reviewing previous evidence and further exploring the complex interaction between loneliness, social support, and depression before, during, and after the COVID-19 pandemic, and considering factors such as age, sex, socioeconomic conditions, and pre-existing psychiatric disorders, we can offer valuable insights into the intricate relationships determining MDD and contribute to the development of targeted and effective interventions.

HYPOTHESES & OBJECTIVES



2.1.Hypotheses

The present thesis studies the impact of social support and loneliness on MDD before, during, and after the COVID-19 pandemic, and the hypotheses proposed are tailored to each of these temporal contexts:

- Independently of the context of the pandemic, loneliness and social support not only impact the incidence of depression but also its course.
- The COVID-19 pandemic has impacted on the feelings of loneliness and perceived social support of the general population, thereby increasing depressive symptoms and MDD, with different effects across distinct age groups.

In order to delineate a more precise and systematic investigation we addressed several subhypotheses addressing specific aspects related to the main hypotheses:

- Individuals with poor social support and experiencing loneliness are more likely to exhibit a lack of improvement in their course of MDD.
- Loneliness acts as a mediating factor in the association between social support and MDD course.
- The risk of MDD increased during the pandemic, particularly among younger adults.

- The different risks of MDD by age group might be explained by disparities on the impact of the pandemic on social relationships and socioeconomic conditions.
- Younger adults with PPMD were the most affected by loneliness during pandemic.
- The impact of loneliness on depression during the pandemic was higher among younger adults with PPMD.
- While many cases of loneliness during the pandemic are transient, a portion of the population will continue to experience persistent levels of loneliness and its associated impact on depressive symptoms even after the social restriction measures have ceased.
- Individuals who have shown greater vulnerability to loneliness during the pandemic (young adults, those with PPMD, and those with a low socioeconomic status) will be at higher risk of experiencing chronic courses of loneliness after the pandemic.

2.2.Objectives

The aim of the present thesis is to analyse the relationship between loneliness and social support with depressive symptoms and MDD before and during the COVID-19 pandemic differentiating these associations by age group and identifying potential variables that may mediate and moderate these relationships. Three different population cohorts will be used to pursue this aim (Figure 8).

The specific objectives that will allow the achievement of the main objective of the present thesis are:

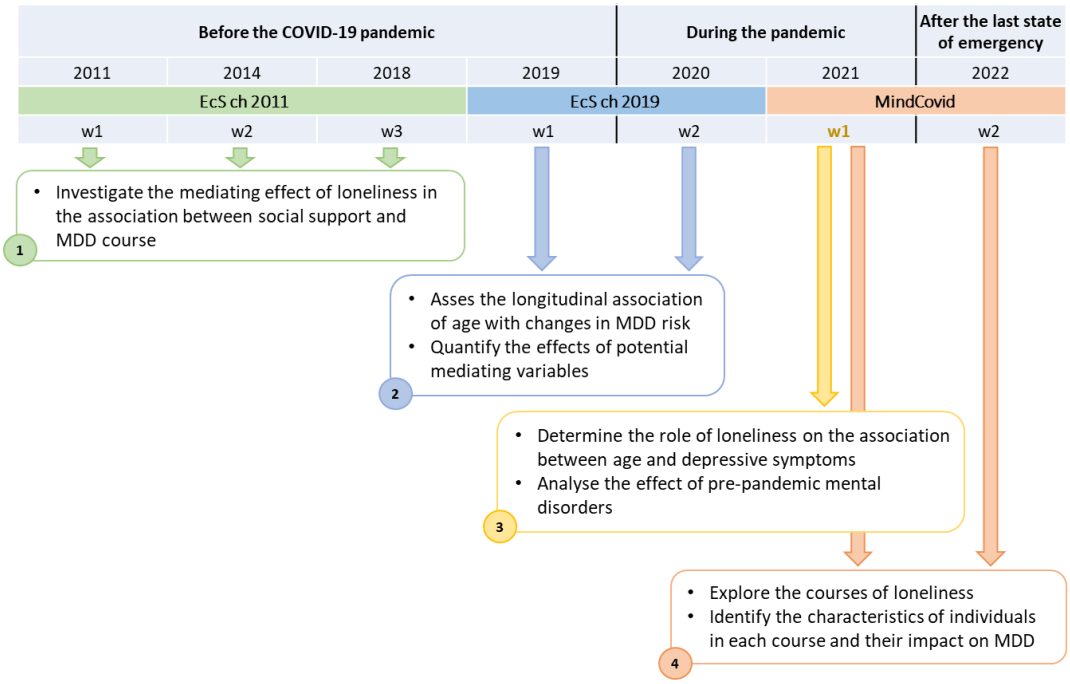
1. Investigate the mediating effect of loneliness in the association between social support and MDD course in a sample of adults aged 50 years or older having MDD in the 12 months before the baseline assessment and followed for 7 years before the pandemic.
2. Asses the association of age with changes in MDD risk before and during the COVID-19 pandemic and quantify the effects of potential mediating variables such as loneliness, social support, resilience, and socioeconomic factors in a sample of the general population interviewed before (2019) and again during (2020) the pandemic.
3. Examine the relationship between age and depressive symptoms during the pandemic, determine whether loneliness has a mediating and moderating effect on this association, and

analyse whether these effects could vary depending on the presence or absence of PPMD in a sample of the general population interviewed during the pandemic (2021).

4. Explore the courses of loneliness during the pandemic and after the last state of emergency and identify the characteristics of individuals in each loneliness course and their impact on MDD in a sample of the general population interviewed during the pandemic (Feb-March 2021) and 9 months later (Nov-Dec 2021).

Figure 8

Objectives of the doctoral thesis across pandemic periods and cohorts utilized

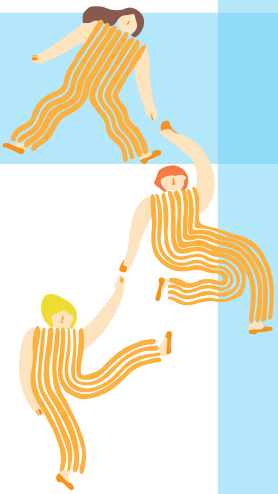


Note. Scheme of the cohorts and waves employed to achieve each objective of the thesis. From left to right, the 'Edad con Salud' 2011 cohort, comprising 3 waves prior to the COVID-19 pandemic in 2011, 2014, and 2018, has been used to fulfil objective 1, addressed in 'Article I'. 'Edad con Salud' 2019 cohort, comprising 2 waves, one before the COVID-19 pandemic in 2019, and the other during the pandemic in 2020. These data have been used to fulfil objective 2, addressed in 'Article II'. MINDCOVID cohort comprises wave 1 carried during the pandemic in 2021 and used to fulfil objective 3, addressed in 'Article III'. Finally, objective 4 is addressed in 'Article IV' and used wave 1 from the MINDCOVID study, and wave 2, which was carried after the last state of emergency in 2022. MDD = Major Depressive Disorder; EcS ch = Edad con Salud cohort.

Ethics statement

The authors declare that all procedures involved in 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. All the studies included in the present thesis obtained the corresponding ethical approvals and informed consent was obtained from all participants. For 'Article I' and 'Article II' using the cohorts of the 'Edad con Salud' project, ethical approvals were obtained for each wave from the ethics review committees of Parc Sanitari Sant Joan de Déu, Barcelona, and Hospital Universitario La Princesa, Madrid. For 'Article III' and 'Article IV' ethical approvals were provided by Parc Sanitari Sant Joan de Déu and by the Parc de Salut Mar Clinical Research Ethics Committee.

MATERIAL, METHODS & RESULTS



Article I

The effect of loneliness and social support on the course of major depressive disorder among adults aged 50 years and older: A longitudinal study

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RESEARCH ARTICLE

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The effect of loneliness and social support on the course of major depressive disorder among adults aged 50 years and older: A longitudinal study

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Abstract

Background: Previous research indicates that social support, loneliness, and major depressive disorder (MDD) are interrelated. Little is known about the potential pathways among these factors, in particular in the case of adults aged 50 years and older and suffering from MDD. The objective was to investigate whether loneliness mediates the association between low social support and recurrent episodes of MDD.

Methods: We used data from a cohort of the Spanish general population interviewed at three time-points over a 7-year period. We included 404 individuals aged 50+ suffering from MDD in the baseline assessment. A 12-month major depressive episode was assessed with the Composite International Diagnostic Interview (CIDI) at each interview. The University of California, Los Angeles Loneliness Scale was used to measure loneliness, whereas social support was assessed through the Oslo Social Support Scale. We tested cross-lagged and autoregressive longitudinal associations using structural equation modeling.

Results: We identified two significant longitudinal mediation patterns: lower social support predicted higher subsequent levels of loneliness (Coef. = −0.16; $p < .05$), which in turn predicted an increase in MDD recurrence (Coef. = 0.05; $p < .05$).

Conclusions: Interventions focused on promoting social support among older adults suffering from MDD may decrease feelings of loneliness and prevent recurrent episodes of MDD.

KEYWORDS
loneliness, longitudinal study, major depressive disorder, older adults, recurrence, social support

1 | INTRODUCTION

Major depressive disorder (MDD) is characterized by the presence of sadness, loss of interest, and anhedonia, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function (American Psychiatric Association, 2013). Globally, depressive disorders affect over 300 million people, which is equivalent to 4.4% of the world's population, and this percentage is increasing (World Health Organization, 2017a). In addition, depressive disorders have remained at the top of the leading causes of years lost to disability over the last few decades (James et al., 2018), entailing a public-health priority and having substantial economic consequences.

The course of MDD shows considerable variations in remission, chronicity, and episode duration (13–30 weeks). Although in population-based samples approximately 70%–90% of patients with MDD recover in 1 year, the chances of recurrence are very high (e.g., around 80% of MDD patients in remittance experience at least one recurrence in their lifetime; Otte et al., 2016). Specifically, in older adults, the course of MDD appears to be slightly less favorable than in younger patients (Schaakxs et al., 2018). Indeed, depression is one of the most prevalent mental health problems within this group (Rodda et al., 2011; World Health Organization, 2017b) and has been associated with all-cause mortality, higher risk of suicide, worse physical and cognitive health, acceleration of brain aging, and increased health service use (Blazer, 2003; Colton & Manderscheid, 2006; Djernes, 2006; John et al., 2019).

Low social support is a risk factor for depression (Santini et al., 2015; Schwarzbach et al., 2014) and is also related to poor recovery from MDD (Joseph et al., 2011; Leskelä et al., 2006). Aside from objective factors related to social connectedness (e.g., social support), loneliness—defined as a subjective feeling of distress, derived from the perception of a deficient or unfulfilling available network of social relations in a quantitative or qualitative sense (Perlman & Peplau, 1981)—has also been found to be closely related to depression (Cacioppo et al., 2010; Domènech-Abella et al., 2017). The dysfunctional interpersonal processes of lonely individuals contribute to mental health problems, creating a vicious cycle in which loneliness is both a causal and a sustaining factor of MDD (Nenov-Matt et al., 2020). Moreover, social behavior is often severely disrupted in individuals with MDD (Kupferberg et al., 2016; Porcelli et al., 2019), with residual social dysfunction (i.e., composite of loneliness, social disability, and small social network) remaining even after complete remission of depressive symptoms (Kennedy et al., 2007; Ormel et al., 1993; Saris et al., 2020). Van Den Brink et al. (2018) found, in a clinical sample of MDD patients (n = 1181) followed-up for a 2-year period, that social support and loneliness are predictors of an unfavorable course of MDD, independently of other predictors.

Several intervention studies have tried to improve mental health outcomes by reducing loneliness. Studies aimed at reducing maladaptive social cognition have shown greater effectiveness in reducing loneliness than others based on increasing social support and communication skills (Masi et al., 2011). This is consistent with previous studies in which the association between social isolation and loneliness was only weak-to-moderate among older adults (Cornwell & Waite, 2009). However, when focusing on older adults suffering from MDD, the role of available social support could be more relevant, as having a small social network seemed to impact depression substantially in lonely people, when compared with a sample without feelings of loneliness (Domènech-Abella et al., 2017). Therefore, it is important to improve the understanding of the effects of loneliness and social support as factors related to depression. In this regard, some longitudinal studies have identified loneliness as a mediator in the relationship between social support and depressive symptoms (Domènech-Abella et al., 2021; Santini et al., 2016).

Since studies about the potential mediating mechanisms of loneliness in the association between social support and MDD recurrence are lacking, the aim of the present study was to analyze its mediating effect in a sample of Spanish adults aged 50 years and older suffering from MDD with a 7-year follow-up period. We hypothesized that lower social support would be associated with MDD recurrence and this relation would be partially explained by feelings of loneliness.

2 | MATERIALS AND METHODS

2.1 | Study design

Data from the "Edad con Salud" cohort (Edad con Salud, 2021), a longitudinal study including a nationally representative Spanish sample of the noninstitutionalized adult population (aged 18 years or older), were used. The baseline survey (Wave 1 [W1]) was part of the Collaborative Research on Ageing in Europe (COURAGE in Europe) study (Leonardi et al., 2014) and was undertaken between July 2011 and May 2012. Potential participants were selected with a stratified multistage clustered design according to the Spanish regions and population size, with one individual being randomly selected from each household. Data on households were provided by the Spanish Statistical Office. Wave 2 (W2) was conducted from December 2014 to June 2015, and Wave 3 (W3) during 2018.

Participants underwent structured face-to-face interviews with the use of computer-assisted personal interviewing. The survey also included standardized physical examinations and a neuropsychological test battery assessment. If the respondent had a noticeable physical or cognitive impairment that precluded participation in the survey, a shorter version of the questionnaire was administered to a proxy respondent. Further details about the collection procedure can be found elsewhere (Miret et al., 2014).

A total of 4753 individuals were initially interviewed at W1, of whom 2528 (53.2%) were interviewed again in W2, and 1576 (33.2%) in W3. The present study focuses on participants aged 50 years or older, which implied the exclusion of 962 individuals at baseline. Of the remaining 3791 individuals, those who fulfilled the criteria of MDD—according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (1994)—in W1 were included in the study, yielding a baseline sample of 404 individuals of

whom 217 (53.7%) were interviewed again in W2 and 128 (31.7%) in W3.

2.2 | Ethics statement

Ethical approvals were obtained from the ethics review committees of Parc Sanitari Sant Joan de Déu, Barcelona, and Hospital Universitario La Princesa, Madrid. Informed consent was obtained from all participants in the three waves.

2.3 | Measurements

Loneliness was assessed with the Spanish version of the three-item University of California, Los Angeles Loneliness Scale (Hughes et al., 2004; Sancho et al., 2020; Trucharte et al., 2021), which consists of the following three items: "How often do you feel that you lack companionship?"; "How often do you feel left out?"; and "How often do you feel isolated from others?." Each item was answered on a 3-point scale (1 = *hardly ever*; 2 = *some of the time*; 3 = *often*). The scores for each item were added up to produce a loneliness scale score from 3 to 9, with a higher score indicating a greater degree of loneliness.

The Oslo Social Support Scale (OSSS-3) was used to assess social support. It has three items: "How many people are so close to you that you can count on them if you have great personal problems?" (4 "more than 5," 3 "from 3 to 5," 2 "from 1 to 2," 1 "none"); "How much interest and concern do people show in what you do?" (5 "a lot," 4 "some," 3 "uncertain," 2 "little," 1 "none"); and "How easy is it to get practical help from neighbors if you should need it?" (5 "very easy," 4 "easy," 3 "possible," 2 "difficult," 1 "very difficult"). Responses were summed up for a total score ranging from 3 to 14, with a higher score indicating a stronger level of social support (Kocalevent et al., 2018).

We used an adapted version of the Composite International Diagnostic Interview (CIDI 3.0) to assess the presence of depression in the previous 12 months (Haro et al., 2006). An algorithm based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) was used (American Psychiatric Association, 1994).

Sociodemographic characteristics were included as covariates; these were sex, age, partner status (married or living with an intimate partner vs. not), and educational level (categorized as less than primary, primary, secondary, and tertiary). All covariates were based on baseline data, except for partner status and educational level, which were considered as time-variant covariates.

We also considered general health as a time-variant covariate; this was assessed with a validated health metric that included factors associated with the aging process. Briefly, a set of 45 items was included, comprising questions related to impairments in body functions, limitations in activities of daily living (ADL), limitations in instrumental ADL, and a set of tests covering cognitive functioning and walking speed. The theoretical range of the health metric score was from 0 to 100, with a higher value being indicative of better health status (Sanchez-Niubo et al., 2020).

2.4 | Statistical analysis

Descriptive analyses were conducted to characterize the study sample. These analyses included frequencies and proportions for categorical variables, and means and standard errors for continuous variables. Analyses of repeated measures (using PROC MIXED, SAS) were performed to compare the means of general health, loneliness, and social support from W1 to W3. Proportions of partner status and educational level from W1 to W3 were compared using χ^2 tests.

We tested cross-lagged and autoregressive associations among social support, loneliness, and MDD using the cross-lagged panel model (CLPM), which is commonly used to estimate reciprocal effects (Guralnik et al., 1989). We conducted CLPM through structural equation modeling (SEM) with the observed variables for MDD, loneliness, and social support, adjusting for sex, age, partner status, educational level, and general health. To maximize statistical power while minimizing bias, we used the maximum likelihood for missing values (MLMV) estimation method (Finkel, 1995). The MLMV method includes the assumption that missing values are missing at random, which means that missingness on outcomes is uncorrelated with the values of unobserved variables, after adjusting for observed variables (Acock, 2013). We analyzed if attrition from both death and non-response was correlated with the individual characteristics and the outcome variables (i.e., loneliness, social support, and MDD). To test it, we carried two logistic regression models with dropout in W2 and W3, respectively, as the dependent variables; and the variables of interest (i.e., loneliness, social support, and MDD) and adjustment variables in the preceding wave (i.e., age, sex, partner status, educational level, and general health) as independent variables. We also assumed synchronicity (i.e., the measures at each time point occurring at the same exact times) and constancy of structural effects. Therefore, they were constrained to the equality of autoregressive and cross-lagged associations (i.e., from W1 to W2, and from W2 to W3). We also constrained the correlations of residual variances between variables within follow-up waves so as to be equal. Beta coefficients and 95% confidence intervals (95% CIs) of cross-lagged and autoregressive associations were reported, whereas correlation coefficients included in the CLPM were not reported (but are available upon request). To clarify the results of the CLPM, coefficients and predicted linear value graphs of the statistically significant cross-lagged associations are reported.

The model fit was assessed with several indices comparing the tested model with the saturated model. The absolute fit index of minimum discrepancy χ^2 *p*-value, which must be greater than 0.05, can be ignored if the sample size is greater than 200 (Allison, 2001). We considered the relative χ^2, dividing it by degrees of freedom (χ^2/DF), which is an index of how much the fit of data to model has been reduced by dropping one or more paths. The accepted thresholds for χ^2/DF should be less than 3 (Jöreskog & Sörbom, 1996). The root mean square error of approximation (RMSEA) and its 90% CI estimate lack of fit compared to the saturated model. It is recommended that RMSEA be up to 0.05, whereas up to 0.08 is considered a fair fit (Marsh & Hocevar, 1985). Finally, the

comparative fit index (CFI) and the Tucker–Lewis index (TLI) are commonly used indices about the quality of fit. The values for these indices should be greater than 0.90 (Browne & Cudeck, 1992).

Stata 13 (STATA, 2013) was used in all statistical analyses.

3 | RESULTS

The characteristics of the study sample collected throughout the 7-year period at three time-points (Waves 1, 2, and 3) are shown in Table 1. The sample was mainly female (73%), and the mean age of respondents was 65.8 years at baseline. About 50% of the sample was married or in partnership in all three waves. In W3, there was an increase in participants with tertiary studies (from 3.5% to 5.5%), whereas people with less than primary education was about 48% in all waves. The analyses of repeated measures showed differences in the means of loneliness and general health. Loneliness levels significantly decreased ($p < .001$) from W1 to W3, and general health levels increased during the study ($p < .001$). In contrast, no significant differences in social support were observed ($p = .4791$) between waves. The prevalence of participants with MDD decreased slightly from W2 to W3.

Regarding the multivariate logistic regression models, none of the characteristics of W1 or W2 predicted dropout at the following wave; except for social support at W1, which was found to be related with dropout at W2, but with minor statistical significance ($p > .01$). Therefore, our data is quite coherent with the assumption that missing values are missing at random in our study (see Table SA).

All autoregressive associations (i.e., association of a variable with itself in two distinct time points) beta coefficients were statistically significant ($p < .05$), except for MDD. Two statistically significant cross-lagged associations (i.e., the association between a variable at the first time point with another variable at the next time point) were found. As Table 2 and Figure 1 show, lower social support predicted higher levels of loneliness (Coef. = −0.155; $p < .05$), which in turn predicted an increase in MDD recurrence chances (Coef. = 0.048; $p < 0.05$). The predicted linear values of the statistically significant cross-lagged associations from W1 to W2, which are generalized from W2 to W3, are represented in Figure 2, which shows how feelings of loneliness and having more social support are inversely related, whereas feelings of loneliness are positively related with the probability of MDD recurrence. In our final model, the results of our fit indices were $\chi^2/DF = 1.29$, RMSEA = 0.03 (0.00, 0.05), CFI = 0.96, and TLI = 0.91, indicating a good fit for the model.

4 | DISCUSSION

As far as we know, this is the first study to assess how social support and loneliness are interrelated, as well as the mediating pathways through which they contribute to MDD recurrence among adults aged 50 years and older with MDD. The hypothesis posed at the beginning of this study was confirmed. Loneliness was found to be predicted by lower levels of social support, and loneliness also predicted the recurrence of MDD. Therefore, loneliness is a mediator in the association between social support and MDD recurrence.

TABLE 1 Characteristics of the study sample

Characteristic	Wave 1 $n = 404$	Wave 2 $n = 217$, 53.71%	Wave 3 $n = 128$, 31.68%	p Value w1 → w3
Age (+50)	65.75 (10.30)	64.33 (9.56)	63.39(9.20)	–
Female, *n* (%)	294 (72.77)	152 (70.05)	87 (67.97)	–
Married or in partnership, *n* (%)	205 (50.74)	108 (49.77)	65 (50.78)	0.994
Education, *n* (%)				
Less than primary	194 (48.14)	103 (47.47)	63 (49.22)	0.629
Primary	115 (28.54)	59 (27.19)	31 (24.22)	
Secondary	80 (19.85)	47 (21.66)	27 (21.09)	
Tertiary	14 (3.47)	8 (3.69)	7 (5.47)	
General health (0–100)	36.66 (14.13)	41.12 (15.13)	39.50 (14.90)	$p < .001$
Loneliness (3–9)	5.12 (2.24)	4.45 (2.03)	4.51 (2.12)	$p < .001$
Social support (3–14)	11.31 (2.25)	11.27 (2.29)	11.33 (2.28)	0.479
MDD, *n* (%)	–	43 (19.82)	24 (18.75)	–

Note: Means and standard deviations in parenthesis are shown for age, general health, loneliness, and social support, whereas frequency and percentages are displayed for the remaining variables. Outcomes from W1 to W3 were compared using χ^2 tests for categorical variables and repeated measures analyses through PROC MIXED for continuous variables. The total number of participants in some categories is lower due to missing values.

Abbreviations: MDD, major depressive disorder; *n*, frequency; SD, standard deviation.

Our results are consistent with a previous longitudinal study reporting that subjects with a chronic course depression had smaller social network sizes and increased feelings of loneliness over time (Houtjes et al., 2014). The mediating role of loneliness in the association between available social support and MDD recurrence is also in line with prior research showing that negative life events affecting social relationships and related with old age (e.g., losing a partner, social network reduction, a disease diagnosis, functional decline, moving to a nursing home, etc.) can increase the risk of experiencing loneliness and depression (Mikkelsen et al., 2019), whereas the availability of social support and the quality of the existing relationships may promote emotional well-being and act as a mental health protector (Santini et al., 2016). Moreover, this could partly explain previous findings on the differences between transient and chronic loneliness as risk factors for MDD (Martín-María et al., 2020). According to our results, the lack of available social support could lead to chronic loneliness and, consequently, to greater chances for experiencing MDD.

Surprisingly, the autoregressive associations between MDD were not statistically significant in our study, meaning that having MDD at W2 was not statistically related to the probability of suffering from MDD in W3. This may be due to the cyclical nature of MDD, with 70%–90% of people with MDD usually recovering within a year, and also the fact that recurrent MDD episodes will generally start during the five years after the initial episode (Burcusa & Iacono, 2007; Otte et al., 2016). We measured MDD in the 12 months before the interview; therefore, recurrent MDD episodes might not have happened yet in the follow-up wave (3 years later) or might have happened before the recall period captured by the survey.

Our data suggest that evaluation by health care providers of loneliness and social support in older adults could be used to prevent further development of MDD. Concurrently, it should also be considered that the relationship between structural and functional aspects of social support and mental health outcomes could be bidirectional, as social adversity fosters mental health problems, while mental health conditions limit social connections and hinder the capability of increasing the level of social support (Almquist et al., 2016; Goldberg et al., 2003). Specifically, interpersonal characteristics of individuals with MDD, those recovered from MDD, and those with MDD in remission may interfere with their social reconnection and prompt rejection by others, eventually leading to poor quality relationships and social withdrawal. This may consequently maintain or increase the risk of experiencing loneliness (Nenov-Matt et al., 2020; Twenge et al., 2007), and negatively impact MDD illness severity and course. In addition, MDD is associated with a high risk of recurrence, and following each new episode, the disease progression is exacerbated and the risk of further relapses is increased (Kessing et al., 2004).

Improved understanding of the pathways leading to MDD recovery may have important implications for the prevention of MDD across the lifespan. Knowing the order of appearance of loneliness and MDD is essential to treatment development, making this 7-year longitudinal study necessary to bring new insights on these factors and their associations to prevent the adverse outcomes linked to MDD and social life deterioration in older adults. Our study underlines the need to shed light on the complex relationships and pathways relating social determinants and mental health outcomes, to identify modifiable risk factors, and advance prevention and implementation of interventions (Collins et al., 2011; Giacco et al., 2017). The present study identified social support and loneliness as potential targets for intervention in people with MDD.

TABLE 2 Cross-lagged and autoregressive associations of social support, loneliness, and major depressive disorder (MDD)

	Social support At Time 2	Loneliness At Time 2	MDD At Time 2
Social support at Time 1	**0.393*** *(0.283, 0.502)*	**-0.155** **(−0.249, −0.061)**	−0.009 (−0.027, 0.009)
Loneliness at Time 1	−0.065 (−0.189, 0.059)	**0.329*** *(0.225, 0.432)*	**0.048*** **(0.027, 0.068)**
MDD at Time 1	0.060 (−0.962, 1.082)	0.105 (−0.721, 0.931)	0.116[a] *(−0.051, 0.283)*

Note: Beta coefficients and 95% confidence intervals are displayed. In bold, significant associations (*$p < .05$, **$p < .01$, ***$p < .001$). In italics, autoregressive associations. Time 1 (before) and Time 2 (after) are displayed since coefficients were constrained so as to be the same across waves (from W1 to W2 and from W2 to W3). Adjusted for sex, age, educational level, partnership status, and general health.

[a]Since all participants were suffering from MDD at W1, MDD autoregressive associations are referred from W2 to W3.

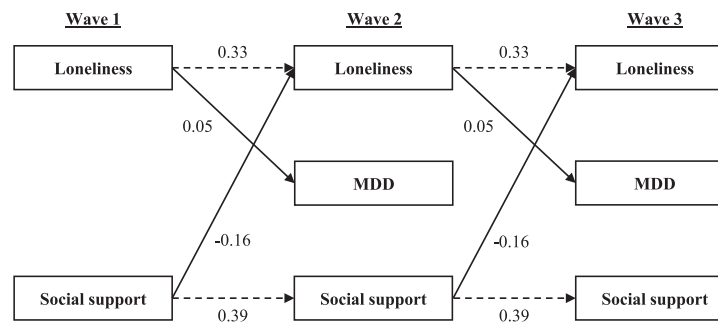

FIGURE 1 Autoregressive (dotted line) and cross-lagged longitudinal associations among loneliness, social support, and major depressive disorder (MDD). Statistically significant ($p < .01$) associations are shown

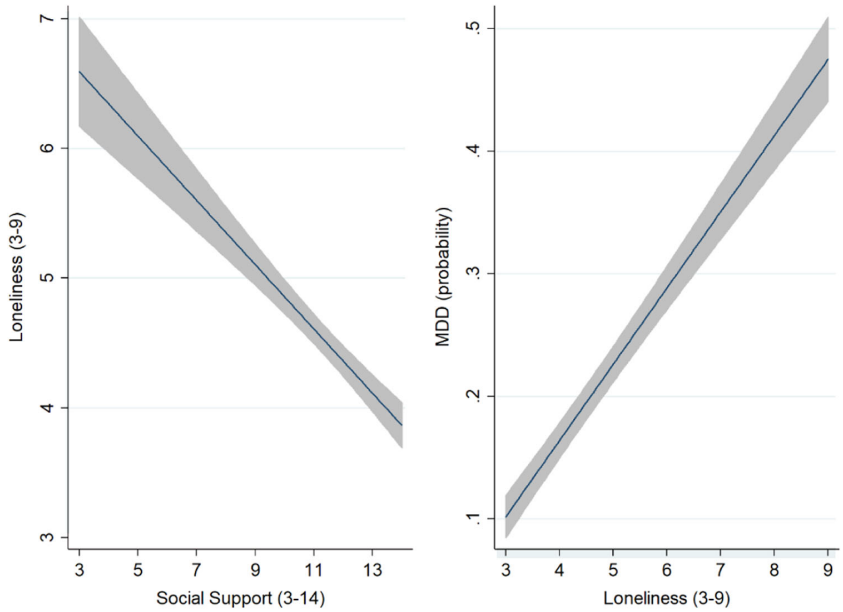

FIGURE 2 Cross-lagged associations of loneliness, social support, and major depressive disorder (MDD). Coefficients were constrained so as to be the same across waves (from W1 to W2 and from W2 to W3). Predicted values and 95% confidence interval of the statistically significant ($p < .01$) associations are shown

Initiatives designed to alleviate loneliness and increase social support, by creating opportunities for social interaction focusing on the sense of community belonging, are needed to reduce depressive symptoms. Future studies should test possible cultural differences (Schwarzbach et al., 2014) and interventions to corroborate our results.

4.1 | Limitations and strengths

The strengths of this study include its use of data from a large nationally representative sample of the Spanish population followed up for 7 years, the ability to control for confounding factors, and the assessment of the study variables with a range of validated scales, such as the evaluation of MDD based on DSM-IV diagnostic criteria. However, a number of potential limitations need to be noted. First, we need to be aware of the possibility of having Type I or Type II errors derived from (i) the assumption of synchronicity in the SEM which could be affected by some variability in the time gap between waves, (ii) the dichotomy of the MDD variable, and (iii) the low rates of MDD at W2 and W3, limiting the power to identify cross-lagged relationships. However, previous researchers have suggested cut-offs criteria for fitting indexes to minimize these errors (Hu & Bentler, 1999). Our results are in accordance with their recommendations, which involve using one of the relative fit indexes close to 0.95 or higher—such as CFI—in combination with an absolute fit index—such as RMSEA with a cut-off value close to 0.06. Moreover, the goodness of fit cut-off points applied herein have been previously used in similar studies (Bosmans & van der Velden, 2017; Domènech-Abella et al., 2021; Schuez-Havupalo et al., 2018). Second, our data are based on self-reported questionnaires, so reporting or recall bias could be present. However, in our study, recall periods were short and well-defined, to minimize recall bias. Other potential problems with self-reported measurements are related to the distorted perception of individuals with depressive symptoms (Amann, 1991) regarding the assessment of some variables, so the findings may be influenced by the participants' mood state.

5 | CONCLUSION

The evidence from this study points towards the prospect that interventions focused on promoting social support among adults aged 50 and olderhaving MDD may alleviate feelings of loneliness and prevent recurrent episodes of MDD. Moreover, our results should encourage health care practitioners to pay attention to the availability of social support and the presence of feelings of loneliness among older adults with MDD, those who recovered from MDD, and those with MDD remission, and to target these factors to improve the disease course. Since the number of older people is expected to continue to increase over the coming decades (United Nations, 2016), and considering the elevated presence of loneliness among this age group (National Academies of Sciences, Engineering, and Medicine, 2020), additional work is needed to study these relationships in people with MDD, with a special focus on age and other

social determinants. Finally, interventions targeting these variables and centered on MDD patients are essential for testing the effectiveness of applying these hypotheses.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

The study design was made by Aina Gabarrell-Pascuet, María V. Moneta, José L. Ayuso-Mateos, Marta Miret, Elvira Lara, Josep M. Haro, Beatriz Olaya, and Joan Domènech-Abella. Aina Gabarrell-Pascuet and Joan Domènech-Abella conducted the data analyses and drafted the article. Josep M. Haro and Joan Domènech-Abella supervised the data analyses and development of the paper. The paper was edited and reviewed by all the authors.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

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Article II

What factors explain the changes in major depressive disorder symptoms by age group during the COVID-19 pandemic? A longitudinal study

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What factors explain the changes in major depressive disorder symptoms by age group during the COVID-19 pandemic? A longitudinal study

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ABSTRACT

Background: Data collected during the COVID-19 pandemic suggest an increase in major depressive disorder (MDD) among younger adults. The current study aims to assess the association of age groups and MDD risk before and during the COVID-19 pandemic and quantify the effect of potential mediating variables such as loneliness, social support, resilience, and socioeconomic factors.

Methods: A representative sample of Spanish adults was interviewed before (2019, N = 1880) and during (2020, N = 1103) the COVID-19 pandemic. MDD was assessed using the CIDI, loneliness through the UCLA scale, social support through the OSSS-3, resilience with the 6-BRS, and worsened economic circumstances and unemployment through a single question. Mixed-models were used to study changes in MDD by age group. Regression models were constructed to quantify the association between age and potential mediators, as well as their mediating effect on the association between age group and MDD.

Results: Among the younger age cohorts (18-29 and 30-44 years) the probability of having MDD during the pandemic increased from 0.04 (95 % CI: 0.002-0.09) to 0.25 (0.12-0.39) and from 0.02 (-0.001-0.03) to 0.11 (0.04-0.17), respectively. Some 36.6 % of the association between age and risk of MDD during the pandemic was explained by loneliness (12.0 %), low resilience (10.7 %), and worsened economic situation (13.9 %).

Limitations: Reliance on self-report data and generalizability of the findings limited to the Spanish population.

Conclusions: Strategies to decrease the impact of a pandemic on depressive symptoms among young adults should address loneliness, provide tools to improve resilience, and enjoy improved financial support.

1. Introduction

The COVID-19 pandemic is a global pandemic of coronavirus disease (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) (Yousefi et al., 2020). The pandemic has aggravated mental health problems, including depressive disorder symptoms in the general population (Chen et al., 2021; Li et al., 2020; Vindegaard and Benros, 2020; Xiong et al., 2020).

Depression affects approximately 280 million people, equivalent to 3.8 % of the world's population (WHO, 2021). Major depressive disorder (MDD) is among the leading causes of years lost to disability (James et al., 2018) and has been associated with diminished quality of life, medical morbidity, and worse physical and cognitive health (Ferrari et al., 2013; Herrman et al., 2002).

Several studies carried out during the COVID-19 pandemic report higher prevalence of depression among younger adults (Beutel et al.,

Abbreviations: MDD, Major Depressive Disorder; COVID-19, Coronavirus disease; CIDI, Composite International Diagnostic Interview.

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2021; Morin et al., 2021; Nwachukwu et al., 2020; Varma et al., 2021; Xiong et al., 2020). The psychological, social, and economic effects of the pandemic may impact each age group differently. Therefore, it is critical to identify potential mediating factors that explain what makes younger adults more vulnerable to depression in a pandemic context, so that consistent public health and social measures can be developed accordingly.

Loneliness and low social support are predictors of depression (Cacioppo et al., 2010; Gariépy et al., 2016; Santini et al., 2015), and are of particular concern in the COVID-19 pandemic context. During the first year of the pandemic, public health and social measures to contain COVID-19's spread were based on physical distancing and stay-at-home orders, which may have led to changes in loneliness (Ernst et al., 2022).

Pre-pandemic data identified older adult populations at higher risk for loneliness, social isolation, and social network reduction due to age-related changes and life events affecting social relationships (e.g., losing a partner, moving to a nursing home, functional decline, a disease diagnosis, etc.) (Mikkelsen et al., 2019). Following the socioemotional selectivity theory (Carstensen, 1993), although social contact declines across adulthood, social goals change and the close and emotionally satisfying relationships prevail, and these may have remained more stable during the pandemic. In contrast, young people rely more on frequent and diverse social interactions which might have been more greatly affected by social restrictions (Carstensen, 1993; Nicolaisen and Thorsen, 2017). Studies carried during the COVID-19 pandemic identified younger adults as a high-risk group for loneliness and lower social support (Bu et al., 2020; Lee et al., 2020; Losada-Baltar et al., 2021; Varga et al., 2021; Varma et al., 2021).

Resilience is based on how people respond to challenges and adversities, and it has been negatively correlated with depression during the pandemic (Killgore et al., 2020; Ran et al., 2020). Older adults usually present a more stable and settled lifestyle, while young adults are still going through a critical period of interpersonal development, education, and career building, which makes them more vulnerable to economic crises and adverse experiences (Lee et al., 2020). Older adults have been found to be more resilient (Gooding et al., 2012; Losada-Baltar et al., 2021; Varma et al., 2021), especially with respect to emotional regulation ability and problem solving (Gooding et al., 2012).

Finally, the risk of depression in developed countries is associated with lower socioeconomic status (Rojas-García et al., 2015). The economic adversities caused by the COVID-19 pandemic, such as unemployment, low income, and financial strain, might exacerbate mental health problems in the short and long term (Liu et al., 2021; Margerison-Zilko et al., 2016). During the first weeks of lockdown in Spain, the unemployment rate for young adults (16-29 years) more than doubled, compared with the population aged 30 to 64 years (Injuve, 2020a). Thus, the global economic effects of the pandemic have impacted age groups differently, which may partially explain the mental health disorder increase among the younger.

Longitudinal studies comparing pre-pandemic data with pandemic data in representative samples of the general population are essential to determine the factors that account for increases in depression among younger populations.

We aimed to assess the association of age with changes in MDD risk between before and during the COVID-19 pandemic in two Spanish regions, and to quantify the effects of potential mediating variables such as loneliness, social support, resilience, and socioeconomic factors, on the observed associations.

2. Methods

2.1. Study design

We used data from the 'Edad con Salud' 2019 cohort (C19) (Edad con Salud, 2022; Lara et al., 2022), a representative sample of the non-institutionalized adult population (18+ years) of Barcelona and Madrid, the two largest provinces in Spain. The C19 baseline data was collected between 2019 and 2021, and 3002 adults were interviewed. To achieve an appropriate representation of the Barcelona and Madrid populations, a stratified multistage clustered area probability method was used considering sex, age group, and municipality of residence. Trained professional interviewers administered structured face-to-face interviews with the use of computer-assisted personal interviewing (CAPI). Further details about the collection procedure can be found elsewhere (Lara et al., 2022).

For the present analyses, we only considered those participants that were interviewed before the COVID-19 pandemic broke out – between June 17, 2019 and March 14, 2020 – and who could answer the questionnaire without a proxy respondent (N = 1880, pre-pandemic data, termed *T1*). During the pandemic these participants were re-contacted to carry out a shorter survey with COVID-19-specific questions and mental health follow-up screenings. 1103 participants responded to this survey (during pandemic data, termed *T2*), showing a response rate of 58.7 %. These interviews were also performed by professional lay interviewers with computer-assisted telephone interviews (CATI) between May 21 and June 30, 2020.

2.2. Ethics statement

The authors declare that all procedures involved in 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. Ethical approvals were obtained from the ethics review committees of Parc Sanitari Sant Joan de Déu (PIC-129-17), Barcelona, and Hospital Universitario La Princesa (register n°: 2801), Madrid. Informed consent was obtained from all participants at the two time points.

2.3. Measures

2.3.1. Main study variables

The current study focuses on major depressive disorder (MDD), which is characterized by a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities (World Health Organization, 1993). MDD in the previous 12 months for the pre-pandemic interviews and in the previous 30 days in the interviews carried out during the pandemic were assessed with an adapted version of the Composite International Diagnostic Interview (CIDI 3.0) (Kessler and Üstün, 2004), a comprehensive, fully structured interview designed to be used by trained lay interviewers with algorithms based on the definition of depression and criteria of the International Classification of Diseases (ICD-10) (World Health Organization, 1993). Algorithms based on the ICD-10 for the assessment of a depressive episode require the following criteria to be fulfilled: (i) at least two of the following three symptoms are present: depressed mood, loss of interest, and decreased energy; (ii) an additional symptom or symptoms (i.e., loss of confidence and self-esteem, unreasonable feelings of self-reproach or guilt, recurrent thoughts of death, suicide, or any suicidal behavior, complaints or evidence of diminished ability to think or concentrate, change in the psychomotor activity, sleep disturbance of any type, and change in appetite with corresponding weight change) are present, having at least four symptoms in total; (iii) symptoms should last for at least 2 weeks; (iv) criteria for hypomanic or manic episode at any time in the individual's life have been discarded; and (v) the episode is not attributable to any psychoactive substance use or to any organic mental disorder.

Age at T1 was categorized into four groups: 18–29 years, 30–44 years, 45–64 years, and 65 years or older.

Loneliness was measured through the Spanish version of the three-item University of California, Los Angeles (UCLA) loneliness scale (Hughes et al., 2004; Sancho et al., 2020; Trucharte et al., 2021). Responses were summed up to generate a total score from 3 to 9, with a

higher score indicating greater feelings of loneliness.

Social support was assessed using the Oslo Social Support Scale (OSSS-3) (Kocalevent et al., 2018). The total score was obtained by adding the responses of the three items and ranging them from 3 to 14, with higher values representing stronger levels of social support. Social support was categorized as low (3-8), moderate (9-11), and high (12-14) (Kocalevent et al., 2018).

Resilience was measured through the Spanish adaptation of the 6-item Brief Resilience Scale (BRS) (Rodríguez-Rey et al., 2016; Smith et al., 2008), which is designed to measure the ability to bounce back or recover from stress. It is a self-report scale with a 5-point response scale ranging from 1 (strongly disagree) to 5 (strongly agree). The responses were added up and divided by six, yielding a score from 1 to 5, with a higher score indicating a greater degree of resilience. The total score was dichotomized using a cut-off of $\geq$3 to determine normal/high vs. low resilience (Smith et al., 2013).

Finally, socioeconomic factors (i.e., worsened economic situation and unemployment) were assessed through direct questions. We asked participants if their economic situation worsened due to the COVID-19 pandemic and its consequences, and if the participants became (temporarily or permanently) unemployed due to the COVID-19 pandemic.

All variables were time-variant, so measures at T1 and T2 were considered in the analyses, except for the socioeconomic factors and resilience, which were only asked about in T2.

2.3.2. Covariates

All covariates were based on baseline data and were selected based on previous studies including variables with a statistically significant relationship with MDD during the COVID-19 pandemic; these were sociodemographic variables such as self-reported sex, age, educational level, partner status, physical and mental health-related variables, and socioeconomic indicators (González-Sanguino et al., 2020; Palgi et al., 2020). We also included province of residence as a covariate since the COVID-19 cases and the public health and social measures differed slightly between these two provinces (Villalonga, 2022).

General health was assessed with a validated metric composed of 45 items, comprising questions related to impairments in body functions, limitations in activities of daily living (ADL) and instrumental ADL, and a set of evaluations about cognitive functioning and walking speed. The health metric score ranges from 0 to 100, with higher values indicating a better health status (Sanchez-Niubo et al., 2020).

2.4. Statistical analysis

The statistical analyses were adjusted to the stratified study design. Post-stratification corrections were made to weights to adjust for the population distribution obtained from the national census (INE, 2022) and for survey non-response.

The study sample was characterized by descriptive analyses, which included weighted means and standard errors for continuous variables, and weighted proportions and unweighted frequencies for categorical variables. Differences between individuals with MDD in T1 and T2 were assessed with Student's *t*-test for general health and loneliness, and with χ^2 tests for sex, age, educational level, partner status, province of residence, social support, resilience, worsened economic situation, and unemployment.

A mixed-effects logistic regression model was constructed to study changes in MDD depending on age group comparing pre-pandemic and during the pandemic data (T1 and T2). The model used age-group as a fixed factor, time point (T1 or T2) as a within-participants repeated factor, and participants ID as a random factor. The model tested the interaction between age group and time point with MDD (both before and during pandemic) as the outcome. The model was adjusted for sex, education, partner status, province of residence, and health. To interpret our results, probabilities for MDD depending on age and stratified by time point were calculated through margins (Williams, 2012). Control variables were centred at mean according to their distribution in the sample.

Several regression models were created to assess the association between age groups and potential mediating factors at T2 (i.e., social support, loneliness, resilience, worsened economic situation, and unemployment). Models were adjusted for the same control variables as the mixed model. For dichotomous outcomes (resilience, worsened economic situation, and unemployment), logistic regression models were constructed, whereas for the ordinal variables (social support and loneliness) ordered logistic regression models were employed. Models with loneliness and social support as an outcome included loneliness and social support at T1 as covariates, respectively. From these regression models, probabilities for each potential mediation factor depending on age were calculated through margins (Williams, 2012). In the case of social support and loneliness, we calculated the probabilities of not reporting any loneliness symptoms (i.e., UCLA loneliness score = 3) and reporting a low social support (i.e., OSSS-3 score < 9). Control variables were centered at mean according to their distribution in the sample.

To assess the mediating role of potential mediators (i.e., social support, loneliness, resilience, worsened economic situation, and unemployment) in the associations between age group and MDD, mediational analyses were performed using the Karlson-Holm-Breen (KHB) method (Breen et al., 2013), which divides the total effect of a variable into a direct and an indirect (i.e., mediational) effect. The mediation models' outcome was MDD at T2 and the models were adjusted for sex, educational level, partner status, province of residence, general health, mediating factors at T1 (except from resilience), and MDD at T1. The KHB "disentangle" option was applied to have a more detailed description of the mediational effects, as it shows how much of the difference between the total and the indirect effect is contributed by each mediator.

Stata statistical software was used to execute all the analyses.

3. Results

The overall characteristics of the study sample and the specific characteristics of those participants with major depressive disorder (MDD) before (T1) and during the pandemic (T2) are shown in Table 1. The sample consisted of a nearly balanced proportion of females and males in both waves. The best represented age group was those between 45 and 64 years (30 % at T1), followed by those between 30 and 44 years (28 % at T1). The other two age groups (18-29 and 65+ years) represented around 21 % of the sample each. Slightly more than half of the sample had a higher-secondary (29 %) or tertiary (24 %) education level at T1, and 53 % were married or with a civil partner. The sample was almost equally distributed between Barcelona (52 %) and Madrid (48 %) and presented a mean general health of 74.8 out of 100. At baseline, 3.4 % of the study sample reported MDD and during the pandemic the MDD prevalence increased to 9.5 %. Participants with MDD at T2 were younger, mainly from Madrid province, with a higher educational level, better general health, and lower social support, when compared to participants with MDD at T1.

Table 2 reports the mixed-model results showing a statistically significant interaction between age group and time point (T1 vs. T2) with MDD risk as the outcome. This interaction reveals that the MDD risk of the younger age groups (18–29 and 30–44 years) between T1 and T2 increased in a statistically significantly manner, while MDD odds remained stable among older age groups (45–64 and 65+ years). Fig. 1 represents the probability of having MDD according to the age group and time point. Among the younger age cohorts (18–29 and 30-44 years), the probability of having MDD increased from 0.04 (95 % CI 0.002–0.09) to 0.25 (95 % CI 0.12–0.39), and from 0.02 (95 % CI −0.001–0.03) to 0.11 (95 % CI 0.04–0.17), respectively.

Fig. 2 shows probabilities for low social support, not being lonely, low resilience, worsened economic situation, and unemployment by age

Table 1
Characteristics of the whole study sample and of individuals with major depressive disorder (MDD) at T1 (pre-pandemic) and T2 (during the pandemic).

Characteristic	Total sample T1 (N = 1880)	Total sample T2 (N = 1103)	MDD at T1 (n = 68, 3.36 %)	MDD at T2 (n = 87, 9.50 %)
Sex, n(%)				
Male	817 (47.74)	437 (46.92)	22 (36.78)	28 (41.10)
Female	1063 (52.26)	666 (53.08)	46 (63.22)	59 (58.90)
Age, n(%)				
18-29	203 (21.49)	111 (17.97)	6 (18.29)	18 (27.00)
30-44	263 (27.61)	163 (25.64)	5 (15.11)	18 (30.72)
45-64	750 (30.43)	525 (38.38)	32 (44.54)	38 (34.25)
65+	664 (20.47)	304 (18.02)	25 (22.07)	13 (8.03)
Education, n(%)				
Less than primary	262 (8.76)	98 (6.23)	14 (12.07)	8 (7.06)
Primary	508 (21.10)	282 (20.93)	24 (30.76)	16 (14.59)
Lower-secondary	283 (17.50)	172 (16.45)	9 (19.05)	18 (23.49)
Higher-secondary	453 (29.12)	294 (30.90)	12 (19.89)	32 (35.81)
Tertiary	374 (23.52)	257 (25.49)	9 (18.23)	13 (19.04)
Partner status, n(%)				
Not married/cohabiting	307 (25.89)	181 (24.77)	10 (24.61)	21 (31.69)
Married/civil partner	1100 (52.80)	639 (52.66)	37 (43.55)	42 (42.48)
Cohabiting	80 (6.62)	62 (8.11)	2 (5.71)	7 (10.81)
Separated/divorced	182 (8.14)	110 (7.94)	8 (16.66)	11 (10.56)
Widowed	211 (6.56)	111 (6.52)	11 (9.47)	6 (4.46)
Province of residence, n(%)				
Barcelona	976 (52.33)	547 (49.86)	54 (82.25)	39 (46.46)
Madrid	904 (47.67)	556 (50.14)	14 (17.75)	48 (53.54)
Health (0–100), mean(SD)	74.84 (0.50)	74.01 (0.62)	50.09 (2.61)	65.72 (2.49)
Social support, n(%)				
Low	154 (7.86)	70 (7.25)	4 (6.22)	13 (12.18)
Moderate	617 (34.31)	397 (41.65)	23 (36.83)	42 (51.77)
High	1037 (57.82)	523 (51.09)	39 (56.95)	28 (36.05)
Loneliness (3-9), mean(SD)	3.67 (0.04)	3.80 (0.05)	5.91 (0.36)	5.42 (0.22)
Resilience, n(%)				
Low	–	164 (15.42)	–	47 (55.58)
Normal/high	–	939 (84.58)	–	40 (44.42)
Worsened economic situation, n(%)				
No	–	767 (65.16)	–	42 (45.82)
Yes	–	331 (34.84)	–	45 (54.18)
Unemployment, n(%)				
No	–	920 (79.28)	–	65 (69.84)
Yes	–	179 (20.72)	–	22 (30.16)

Unweighted frequencies and weighted percentages are displayed for categorical variables, and weighted means with standard deviation (SD) for continuous variables. Some variables did not include all cases due to missing values.

Table 2
Mixed logistic regression model of the association between age group and major depressive disorder (MDD) at T1 (before the pandemic) and T2 (during the pandemic).

	MDD odds ratio (95 % CI)
Time point	
T1 (pre-pandemic)	Ref.
T2 (pandemic)	1.48 (0.72, 3.05)
Age (years)	
65+	Ref.
45–64	2.04 (1.08, 3.86)*
30–44	1.55 (0.52, 4.65)
18–29	4.57 (1.47, 14.21)**
Time × age[a]	
T1 × 65+	Ref.
T2 × 45-64	1.22 (0.50, 2.95)
T2 × 30-44	5.12 (1.40, 18.75)*
T2 × 18-29	4.94 (1.43, 17.05)*
Intercept	0.44 (0.05, 4.32)

[a] Interaction term. 95 % CI: confidence interval. Ref. = category of reference (Odds Ratio = 1.00). Model adjusted for sex, educational level, partner status, province of residence, and health.
* $p < 0.05$.
** $p < 0.01$.

group. The younger groups (18–29 and 30–44 years) demonstrate a higher probability of being lonely, having low social support, and presenting low resilience. They were more likely to have a worsened economic situation and unemployment due to the COVID-19 pandemic. These potential mediation variables were included in the mediation models alone and with different variables to test all possible combinations. Table 3 presents the combination of variables accounting for the highest mediation percentage, which included loneliness (12.0 %), low resilience (10.7 %), and worsened economic situation (13.9 %), together explaining 36.6 % of the association between age group and risk for MDD during the COVID-19 pandemic.

4. Discussion

To the best of our knowledge, this is the first study to examine the association between age and changes in MDD risk before and during the COVID-19 pandemic, as well as potential mediating factors in the association based on longitudinal data. Our results confirm the increase in depression during the pandemic when compared with pre-pandemic data among young adults (18–44 years) and specifically, among the youngest (18–29 years). Regarding the studied potential mediating variables (i.e., social support, loneliness, resilience, worse economic situation, and unemployment), the younger population had a higher probability of having worse outcomes. More than one third of the relationship of being younger and having a higher probability of MDD during the pandemic was explained by loneliness, worsened economic situation, and resilience, which are modifiable factors that could be targeted to reduce MDD among this vulnerable age-group.

In line with our results, several studies have found young adults to be at higher risk of depression during pandemic (Beutel et al., 2021; Morin et al., 2021; Nwachukwu et al., 2020; Varma et al., 2021). Bu et al. (2020) examined the loneliness trajectories and predictors during the COVID-19 pandemic and found that the odds of being in a higher loneliness cluster were greater in an inverse dose-response pattern with age, i.e. younger adults were at higher risk of loneliness compared to older adults, which was also confirmed by other studies (Varga et al., 2021). Loneliness is a well-known predictor of mental health disorders, but it has usually been reported and studied among old-age populations. Our results indicate that loneliness explained part of the association between younger age and higher MDD, which underlines the necessity of

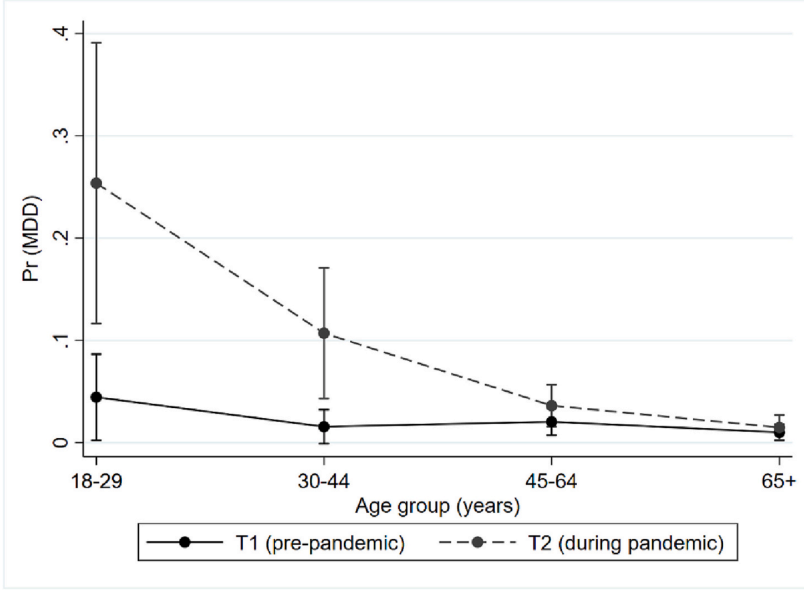

Fig. 1. Probability of having major depressive disorder (MDD) by age group and time point.
NOTE: Predicted margins from mixed model of Table 2. Control variables were centered at mean according to their distribution in the study sample

a deeper evaluation of potential interventions targeting feelings of loneliness among young adults. Conversely, social support was not a significant mediator variable in the association between age group and MDD, which could be explained by the fact that the pandemic has had a greater impact on subjective factors of social relationships like loneliness, rather than on objective factors such as the available social support. In addition, previous studies have reported that loneliness is a mediating variable in the association between social support and mental health (Gabarrell-Pascuet et al., 2022; Santini et al., 2016) and a recent meta-analysis on the association of social support and loneliness with mental health during the pandemic, found that social support had a weak association with depressive symptoms, while the association with loneliness was moderate (Gabarrell-Pascuet et al., 2023). Therefore, when it comes to mental health, social relationships in an objective sense might not be as important as the perception one has of them.

Resilience results are also coherent with prior studies done during the pandemic (Ran et al., 2020). Resilience acts as a protective factor for depression and is usually stronger among older adults, who in our sample had lower probabilities of having low resilience. In contrast, younger adults had a higher probability of having low resilience, which mediated part of the association between age and MDD risk, so younger adults were more prone to report MDD. Resilience is dynamic and can be trained, so interventions promoting the development of resilience among youth might prevent the long-term mental health effects of the COVID-19 pandemic and future hazards.

Older adults were less affected by the economic impact of the pandemic and had more means to deal with them. In Spain, the official retirement age is 67, so most of the sample of the 65+ age group was retired, and consequently less affected by the layoffs. On the other hand, the higher unemployment due to the COVID-19 pandemic and worsened economic situation among younger adults might be explained by the fact that they usually work in more vulnerable sectors, such as tourism, catering, services, trade, and manufacture, with seasonal or temporary contracts, and are hired by private companies or small businesses, which were more vulnerable during the pandemic (Injuve, 2020b). Moreover, young people and short-term workers benefited less during the pandemic from the temporary work suspension, known as ERTE in Spain. The rates of re-entry into active employment of those affected by ERTE were lower for young people. Worsened economic situation due to the pandemic explains the association between age and MDD, while unemployment does not. This could be explained by young people having financial struggles despite being employed, as they might have kept their jobs but with lowered financial benefits (e.g., reduction in both their working hours and their salaries) (Arce, 2021). Moreover, the progressive delay in the age of emancipation and the fall in the rate of home ownership among young people in Spain have left many young adults economically dependent on their parents' employment situation. Finally, we must also bear in mind that financial hardships, in addition to fostering depressive symptoms, can prevent accessibility to adequate mental health care.

Finally, it is important to bear in mind that interventions to target these modifiable factors in practice are not simple to currently apply and even less so in contexts such as the pandemic. However, successful initiatives have been carried out in these contexts. In the case of addressing loneliness, there are many psychosocial interventions that have shown to be effective in reducing feelings of loneliness (Veronese et al., 2021), and some of them could be feasible in a pandemic context through telematic means (Hickin et al., 2021). Regarding resilience, there have been promising online interventions to increase psychological resilience in response to the pandemic (Wang et al., 2021; Zhang et al., 2022). Currently, psychological care in Spain is suffering from an overflow, so public health measures to increase the number of visits each person receives and the professional-to-patient ratio are needed to improve mental health care and compensate the saturation of these services (Ballescà et al., 2022). In addition, it is important that policies consider the social complexity that influences mental health, offering shared strategies outside the strictly health field, such as from social services, employment offices, or educational centres, focusing also on the socio-economic effects of the pandemic. It is necessary to assess the cost-utility of these interventions and strategies in order to evaluate which aspects should be prioritized.

The high rates of depression during the COVID-19 pandemic among young adults, together with its expected long-term consequences, highlight the need for understanding the potential factors that may have

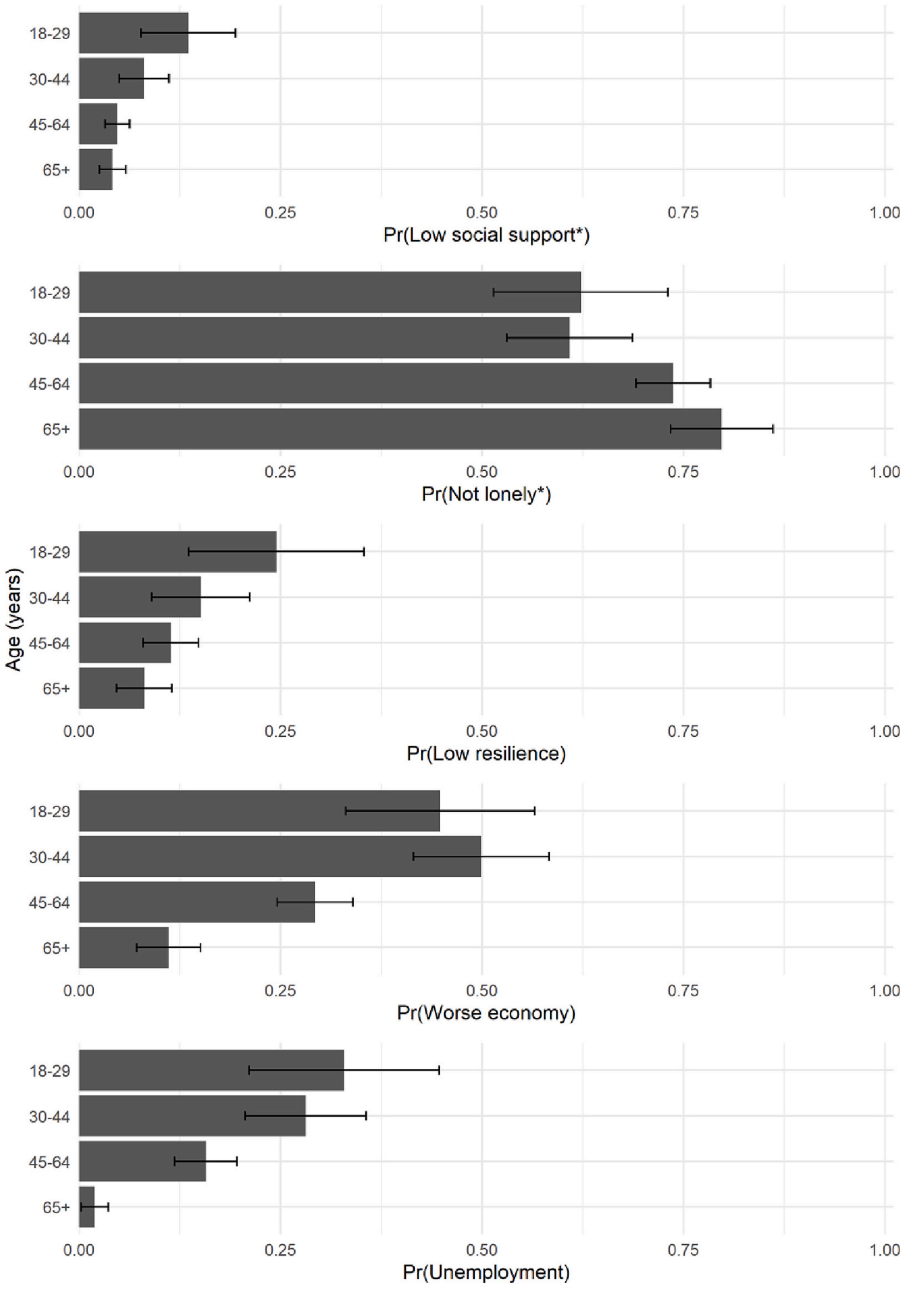

Fig. 2. Probabilities of potential risk factors for MDD by age group.
Probabilities with 95 % confidence interval obtained through margins calculation from logistic regression models. In the case of social support and loneliness, ordered logistic regression models were constructed and the probabilities of not reporting any loneliness symptoms (i.e., UCLA loneliness score = 3) and reporting a low social support (i.e., OSSS-3 score < 9) were calculated. All models were adjusted for sex, educational level, partner status, province of residence, health, and loneliness and social support at T1. Probabilities were calculated with covariates centered at mean according to their distribution in the study sample.

contributed to the increase. The present study was intended to contribute to improved understanding of their role and influence, together with the identification of vulnerable age-groups, which can help in the design and implementation of public health strategies and psychological and social interventions that directly address these mediating factors.

4.1. Limitations and strengths

The strengths of this study include its large sample size and heterogeneity, including good stratification across all major socio-demographic groups. Moreover, the study was based on pre-pandemic and during-pandemic assessments of the same population, using the same questionnaires, which enables the comparability of various factors. The study controls for the main confounding factors and assesses the study variables with a range of validated scales. Nevertheless, these results must be interpreted in light of several limitations. First, our data are based on self-reported measurements, so reporting or recall bias could be present, particularly in the COVID-19 pandemic context, which could distort participants' perceptions and increase the chances for these

Table 3
Association between age groups and major depressive disorder (MDD) at T2, with loneliness, resilience, and economic situation at T2 as mediators (KHB method).

	Coefficient (95 % CI)	% Mediated
Mediation model		
Total	−0.80 (−1.27, −0.32)***	
Direct	−0.51 (−0.97, −0.05)*	
Indirect:	−0.29 (−0.46, −0.12)***	36.55 %
Loneliness	−0.10 (−0.17, −0.03)	11.96 %
Resilience	−0.09 (−0.19, 0.02)	10.67 %
Economic situation	−0.11 (−0.21, −0.01)	13.93 %

CI: confidence interval. All models were adjusted for sex, educational level, partner status, province of residence, health, and MDD and loneliness at T1.
* $p < 0.05$.
*** $p < 0.001$.

biases. However, in our study recall periods were short and well-defined, which minimizes recall bias. The main study outcome (MDD) was measured with the CIDI 3.0 by lay interviewers who received a specific training (Lara et al., 2022) and, although they often lack clinical experience, the outcome screening was done by researchers according to an algorithm combining criteria based on the ICD-10. Moreover, a previous study found no evidence for systematic bias in the diagnostic threshold for depression by the CIDI 3.0 (Haro et al., 2006). Second, the pre-pandemic data were collected through face-to-face interviews, while the pandemic data were collected through telephone interviews due to the restrictions that prevented in-person contacts. This methodological difference could also be linked to differences regarding social desirability bias. Third, socioeconomic factors were measured with single-item and non-validated direct questions, which limit the reliability of these constructs; nonetheless the assessed constructs were unidimensional and clearly defined, overcoming part of the bias that could be associated with single-item measures. Moreover, several articles about the impact of the COVID-19 pandemic on mental health used similar measures to assess changes in financial or employment situation due to the pandemic (Codagnone et al., 2020; Zajacova et al., 2020), which allows comparability between studies. Fourth, our study population was from the two largest provinces of Spain, leaving out participants from rural areas that have been found to be protective against feelings of loneliness during the pandemic (Bu et al., 2020); this could have been an additional factor to consider in our analysis. Finally, the generalizability of our results is limited to the period between 2019 and the initial months of the pandemic in Spain. Future longitudinal studies with longer follow-up periods in Spain (e.g., it is planned to reinterview the cohort of the present study in 2023) and from other countries should investigate to what extent the detected differences remain in the medium and long term and whether they occur in other countries that applied different policies to control the pandemic, with different cultural perceptions, and socioeconomic conditions.

5. Conclusions

The results of our study show that loneliness has been an important explanatory factor for the increase in mental health problems among young adults during the pandemic. The younger population has also been affected by the socioeconomic consequences of the pandemic to a greater extent and have shown lower psychological resilience to stressors. Over the coming months and years, we will assess whether the impact of the pandemic on mental health remains, and we will study the need and possibility of implementing strategies focused on the detected risk factors.

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CRediT authorship contribution statement

Aina Gabarrell-Pascuet: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Tibor V. Varga:** Methodology, Formal analysis, Writing – review & editing. **María Victoria Moneta:** Data curation. **José Luis Ayuso-Mateos:** Project administration, Funding acquisition. **Elvira Lara:** Writing – review & editing, Funding acquisition, Project administration. **Beatriz Olaya:** Project administration, Funding acquisition. **Josep Maria Haro:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Joan Domènech-Abella:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Supervision, Project administration.

Conflict of interest

The authors declare no conflict of interests.

Data availability statement

Data will be made available upon request made to the corresponding author.

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Article III

The association of age with depression, anxiety, and posttraumatic stress symptoms during the COVID-19 pandemic in Spain: the role of loneliness and prepandemic mental disorder

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The Association of Age With Depression, Anxiety, and Posttraumatic Stress Symptoms During the COVID-19 Pandemic in Spain: The Role of Loneliness and Prepandemic Mental Disorder

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ABSTRACT

Objective: Older adults may be at lower risk of common mental disorders than younger adults during the coronavirus disease 2019 (COVID-19) pandemic. Previous research has shown shown differences by age in psychosocial well-being during the pandemic and have highlighted the moderating effect of prepandemic mental disorders on that association. In this line, we examined the association of age with self-reported symptoms of loneliness, depression, anxiety, and posttraumatic stress, as well as potential roles of loneliness symptoms and prepandemic mental disorders on the association between age and mental disorder symptoms.

Methods: Cross-sectional data of 2000 adults in Spain interviewed by telephone during the COVID-19 pandemic (February–March 2021) were analyzed. Depression, anxiety, and posttraumatic stress were measured with the eight-item Patient Health Questionnaire, the seven-item Generalized Anxiety Disorder Scale, and the four-item checklist for *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition), respectively. Loneliness was measured with the three-item University of California at Los Angeles Loneliness Scale. Several regression models were constructed to assess factors related to loneliness and mental disorders.

Results: According to cutoff points used, 12.4% of participants revealed depression, 11.9% revealed anxiety, and 11.6% revealed posttraumatic stress. Age was negatively related to mental disorder symptoms and loneliness. Loneliness was associated with higher levels of mental disorder symptoms. This association was stronger in younger adults without prepandemic mental disorders and in older adults with them. The association between age and loneliness was stronger in those with prepandemic mental disorders. Loneliness mediated the association of age with mental disorder symptoms.

Conclusions: Interventions focused on loneliness could alleviate the impact of the COVID-19 pandemic on mental health.

Key words: loneliness, age, major depressive disorder, generalized anxiety disorder, posttraumatic stress disorder.

INTRODUCTION

The effect of socially disruptive measures on social connectedness and mental health in the context of the coronavirus disease 2019 (COVID-19) pandemic is a research priority (1–3). Social distancing measures, lockdowns, and quarantines, despite their effectiveness in stopping the spread of the virus, have been related to adverse effects such as loneliness, anxiety, and depression (4). Posttraumatic stress disorder (PTSD) may also increase as a result of the COVID-19 pandemic because the population may be exposed to trauma (particularly health care workers and other hospital staff, COVID-19 patients and their close contacts, older people, individuals who reside in high COVID-19 prevalence areas, etc.) by being at increased risk of infection or severe illness, or because of the loss of family members and friends due to COVID-19 (5).

Loneliness is an unpleasant feeling that occurs when available social support is perceived as deficient in a quantitative or qualitative sense (6). According to the European Social Survey data, in 2018 the prevalence of frequent loneliness was 5.2% in Northern Europe, 6.6% in Western Europe, 8.9% in Southern Europe, and 10.8% in Eastern Europe (7). In addition, according to several

COVID-19 = coronavirus disease 2019, **GAD** = generalized anxiety disorder, **MDD** = major depressive disorder, **PCL5** = PTSD Checklist for DSM-5, **PHQ** = Patient Health Questionnaire Depression Scale, **PTSD** = posttraumatic stress disorder

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researchers, loneliness has increased during the COVID-19 pandemic (8,9) and has been shown to be related to physical and mental health, including depression, anxiety, and PTSD (10–12).

Several systematic reviews have examined the prevalence of mental health problems during the COVID-19 pandemic. Although all of these studies consistently report an increase in the prevalence of mental health problems during the COVID-19 pandemic, the differences in the measures used make comparison among them difficult, with wide variation being reported. Specifically, the reported prevalence of depression ranges from 16% to 34% (13,14), anxiety from 15% to 40% (13,14), and PTSD from 21% to 33% (15,16). In a study conducted in Spain during the COVID pandemic, 18.7%, 21.6%, and 15.8% of the sample reported depressive, anxiety, and PTSD symptoms, respectively (17).

Depression and loneliness are generally more common among older adults, whereas the prevalence of anxiety does not vary substantially among age groups (18,19). However, in the context of the COVID-19 pandemic, being an older adult could be a protective factor for these conditions (17,20). This may be explained by the fact that social support, defined as the instrumental, informational, and emotional support provided by a social network that includes family, friends, and neighbors (21), might well have remained stable during the pandemic, whereas the frequency and variety of face-to-face interactions decreased because of the public health and social measures put in place to stop the spread of COVID-19. Younger adults have a greater need for frequent social interaction than older adults, as a consequence of a reorganization of goals in life that occurs gradually across adulthood (22), so these measures could have affected young adults to a greater extent, causing them to feel loneliness more frequently (23). This may have contributed to the higher prevalence of mental disorders (e.g., depression, anxiety, and PTSD) and loneliness reported during the COVID-19 pandemic (17,20). Therefore, loneliness could play a mediating role in the association between age and mental health.

It should be noted that the association between loneliness and mental disorder symptoms could also be moderated by age because older adults have more effective emotional regulation, and this could lead to greater resilience regarding mental health problems associated with loneliness (24,25). In addition, recent research has shown that people with prepandemic mental disorders experienced more psychological distress and anxiety compared with people who had no psychiatric diagnosis (26), and that low levels of social support in particular increased the symptoms of preexisting mental disorder diagnoses (27). Therefore, prepandemic mental disorders could have a moderating effect on the association of loneliness with mental disorder symptoms.

To date, however, there is a lack of information about the mediating or moderating effects of loneliness and prepandemic mental health on the association between age and mental disorders. Given this, and using data from a population-based sample of 2000 Spanish adult individuals who participated in a telephone interview during the COVID-19 pandemic (February–March 2021), the present study aimed to examine whether a) age is negatively related to mental disorder symptoms (depression, anxiety, and posttraumatic stress) during the pandemic, b) loneliness has a moderating and mediating effect on that association, and c) these mediating and moderating effects could vary depending on the existence of prepandemic mental disorders.

METHODS

Study Design

This was a cross-sectional study using data from the first follow-up assessment (February–March 2021) of participants in the MIND/COVID general population study (www.mindcovid.org). A nationally representative sample from the adult general population in Spain was obtained at the end of the first wave of the COVID-19 pandemic (June 2020). The sample was drawn from a dual-frame random digit dialing telephone survey, including both landlines and mobile telephones. First, a sample of Spanish mobile telephone numbers was generated through an automated system. Subsequently, landline numbers were selected from an internal database developed and maintained by the survey company to ensure that all geographical areas were represented in the required proportion. Up to seven calls at different times of day were attempted to each number. The distribution of the interviews was planned according to quotas proportional to the Spanish population in terms of age group, sex, and region of residence. Noninstitutionalized Spanish adults (18 years or older) with access to a landline or mobile telephone and with no Spanish language barrier were eligible to participate. Further details about sampling are reported elsewhere (28). Professional interviewers from the experienced survey company IPSOS carried out computer-assisted telephone interviews. Participants in the baseline survey (n = 3500) were invited to respond to a follow-up survey, of whom n = 2000 responded (Response rate = 57.1%); their responses were analyzed for the present study.

Ethics Statement

Ethical approval was provided by Parc Sanitari Sant Joan de Déu, Barcelona, Spain (PIC 86-20), and by the Parc de Salut Mar Clinical Research Ethics Committee (protocol 2020/9203/I). Once a potential participant was fully informed about the objectives and procedures of the study, oral consent was obtained to proceed with the interview.

Measurements

Loneliness and Age

Age was assessed as a continuous variable (18–90), whereas loneliness was assessed with the three-item University of California at Los Angeles Loneliness Scale, which has a satisfactory degree of reliability and has both concurrent and discriminant validity (29). It contains three items ranging from 1 to 3. The total sum score range is therefore from 3 to 9, with higher scores indicating a greater degree of loneliness. Previous researchers used a cutoff of 6 to distinguish frequent loneliness (30). The three-item University of California at Los Angeles Loneliness Scale showed acceptable internal consistency (Cronbach α = .71) for the study sample.

Mental Disorder Symptoms (Depression, Anxiety, PTSD)

Symptoms of depression were measured using the eight-item Patient Health Questionnaire Depression Scale (PHQ-8) (31). The PHQ-8 contains eight items, with a total score ranging from 0 to 24, where each item is scored from 0 to 3 (0, not at all; 1, several days; 2, more than half of the days; 3, nearly every day). A PHQ-8 score of ≥10 is an established cutoff for detecting major depressive disorder (MDD) and has been previously tested in a large population, yielding a prevalence of depression similar to that defined by the diagnostic algorithm (31). The eight items of the PHQ-8 scale showed good internal consistency (Cronbach α = .85) in the present study sample. According to a recent systematic review, the PHQ-8 score is very similar to the widely used PHQ-9 score and allows for the reduction of items in large questionnaires. The correlation between PHQ-8 and PHQ-9 scores was 0.996, and the cutoff point of 10 optimized sensitivity (86%) and specificity (86%) for PHQ-8 (32).

The Generalized Anxiety Disorder Scale (33) was used to measure anxiety symptoms. This measure has seven items, with items scored 0 to 3, and a total score of 21. A cutoff of 10 is optimal for screening for potential generalized anxiety disorder (GAD), and for optimized sensitivity (89%) and specificity (82%) (33). The seven items of the Generalized Anxiety Disorder Scale showed good internal consistency (Cronbach $\alpha = .87$) for the study sample.

PTSD was assessed using the four-item version of the PTSD Checklist for *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (PCL5) (34). It offers a scale from 0 to 16 that generates cutoffs for screening close to those of the full PCL5. A cutoff of 7 optimized sensitivity (95%) and specificity (97%) for a conservative definition of PTSD (34). The four items of the PCL5 scale showed acceptable internal consistency (Cronbach $\alpha = .78$) for the study sample. The existence of prepandemic lifetime mental disorders was assessed using a checklist based on the Composite International Diagnostic Interview (35) that screens for depression, bipolar disorder, anxiety, panic attacks, alcohol and drug use problems, and 'other' mental disorders.

Control Variables

The control variables were selected based on previous studies that used as covariates sociodemographic variables such as sex and marital status, physical and mental health-related variables, and socioeconomic indicators, because these had a statistically significant relationship with depression during the COVID-19 pandemic (17).

Sociodemographic control variables included sex, marital status (never married, married or cohabiting, separated/divorced, or widowed), and education level (primary, secondary low, secondary high, and tertiary). We also included employment situation during the pandemic (mainly working outside home, mainly working at home, retired/disability, unemployed, or student), loss of income due to the COVID-19 pandemic (no, yes), and living situation (alone, with one person, with two or more people).

We assessed COVID-19 infection status by asking whether the respondent had been hospitalized for COVID-19 infection and/or had a positive COVID-19 test result or medical diagnosis of COVID-19 not requiring hospitalization. Pain or discomfort was assessed through an item from the European Quality of Life 5-Dimension 5-Level questionnaire (36). Participants were asked to indicate their pain or discomfort level at the time of the interview through five categories: none, low, moderate, high, or extreme.

Statistical Analysis

The data were adjusted with poststratification weights to restore distribution of the adult general population of Spain according to age group, sex, and geographic area, to compensate for survey nonresponse. Descriptive analyses included weighted proportions and unweighted frequencies for categorical variables (including prevalence of loneliness and mental disorders) and weighted means and standard deviation for continuous variables (i.e., symptoms of loneliness and mental disorders). Zero-order correlations for the key variables (i.e., symptoms of MDD, GAD, PTSD, loneliness, and age) were also calculated.

To examine the association of age groups with symptoms of MDD, GAD, PTSD, and loneliness, several Tobit regression models were constructed. We constructed unadjusted and adjusted models. Unadjusted models tested the association of age and the remaining covariates (sex, education, marital status, employment situation, loss of income due to the pandemic, living situation, pain or discomfort, prepandemic mental disorders, and COVID-19 diagnosis status) with loneliness and mental disorder symptoms (MDD, GAD, and PTSD) as outcomes. Those control variables that predicted the outcomes ($p < .20$) in the unadjusted models were included in the adjusted models (37). Furthermore, Tobit regression models were constructed to explore potential interactions among age, loneliness, and prepandemic mental disorders. Interactions including these three variables were statistically significant with MDD, GAD, and PTSD as outcome and were therefore included in the adjusted models. None of the potential interactions were statistically significant with loneliness as outcome.

Tobit models produce theoretically continuous values with a normal distribution using the highest possibility estimates for censored values and a standard linear model for the rest of the values (38). We considered the lowest levels of the four outcome scales (MDD, GAD, PTSD, and loneliness) as censored values because lower values included more than half of the sample. The effect on the uncensored latent dependent variables is shown by the Tobit regression coefficients with their 95% confidence intervals.

To clarify the associations of age with mental disorders and loneliness, as well as the moderating effects of loneliness and prepandemic mental disorders on the association between age and mental disorders, estimated means for MDD, GAD, PTSD, and loneliness depending on age were calculated through margins (39), based on the adjusted Tobit regression models. In the case of models with mental disorders as outcomes, results were stratified by loneliness level and prepandemic mental disorder to clarify the effect of the interaction terms. In all cases, control variables were centered by taking the real proportion in the sample into account.

To assess the mediating role of loneliness in the associations between age and mental disorder symptoms among participants with and without previous mental disorder, separately, mediational analysis was performed using the KHB command (40–42). This breaks down the total effect of a variable into direct and indirect (i.e., mediational) effects. This method also allows for the calculation of the mediated percentage, which is interpreted as the percentage of the main association that can be explained by the mediator.

All reported p values were based on a two-sided test, where the level of statistical significance was set at $p < .05$. Stata version SE 13 (43) was used to analyze the survey data.

RESULTS

The sociodemographic characteristics of the study sample are presented in Table 1. The percentages of participants reporting symptom levels equal to or above the cutoff point for MDD, GAD, PTSD, and frequent loneliness were 12.4%, 11.9%, 11.6%, and 13.1%, respectively.

Table 2 reports the zero-order correlations for the variables of interest. Correlations among mental disorder symptoms ranged from 0.63 to 0.76, correlations of loneliness with mental disorders ranged from 0.42 to 0.45, and correlations between age and the remaining variables ranged from −0.16 to −0.17. In all cases, the correlations were statistically significant ($p < .001$).

Table 3 shows the coefficients of the unadjusted Tobit regression models of the associations of the control variables, with symptoms of mental disorders and loneliness as the outcomes. Risk factors for depression were younger age, female sex, being unmarried, being unemployed, being a student, having loss of income due to the pandemic, poor physical health, prepandemic mental disorder, and feeling lonely. These were also risk factors for anxiety and PTSD, with the addition, respectively, of living with more than one person and having an education level higher than primary. Risk factors for loneliness were younger age, female sex, being unmarried, living alone, not working outside, having loss of income due to the pandemic, poor physical health, and prepandemic mental disorder.

Table 4 shows the coefficients of the adjusted Tobit regression models, with the covariates predicting the outcomes in unadjusted models ($p < .20$) (37) and the statistically significant interaction

TABLE 1. Characteristics of the Study Sample (n = 2000)

	Freq. (%) or Mean [SD]
Age, y	
Range: 18–90	49.7 [16.4]
Sex	
Male	890 (48.5)
Female	1110 (51.5)
Marital status	
Never married	629 (33.3)
Married	1087 (52.0)
Divorced/separated	185 (8.5)
Widowed	99 (6.2)
Education	
Primary	115 (6.6)
Secondary low	620 (30.8)
Secondary high	379 (18.4)
Tertiary	886 (44.2)
Living situation	
Living alone	264 (14.8)
Living with 1 person	667 (35.1)
Living with 2 or more people	1053 (50.1)
Employment situation	
Mainly working outside home	751 (35.2)
Mainly working at home	290 (13.8)
Retired/disability	506 (29.7)
Unemployed	397 (18.6)
Student	45 (2.7)
Loss of income due to pandemic	
No	1499 (76.3)
Yes	496 (23.7)
Pain or discomfort	
None	1152 (58.1)
Low	498 (24.5)
Moderate	264 (13.1)
High	67 (3.3)
Extreme	19 (1.0)
COVID-19 (test positive or diagnosed)	
No	1943 (97.3)
Yes	57 (2.7)
Prepandemic mental disorder	
No	1303 (65.9)
Yes	697 (34.1)
MDD	
Range: 0–24	4.3 [4.7]
≥10	261 (12.4)
GAD	
Range: 0–21	4.1 [4.4]
≥10	245 (11.9)
PTSD	
Range: 0–16	2.4 [2.9]
≥7	238 (11.6)
Loneliness	
Range: 3–9	3.9 [1.4]
≥6	263 (13.1)

MDD = major depressive disorder; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder.

Unweighted frequencies (Freq.) and weighted proportions for categorical variables (%) and weighted mean with standard deviation (SD) for continuous variables are displayed.

terms. Most risk factors found in the unadjusted models remained as statistically significant except for sex with loneliness as outcome, marital status with all outcomes, being a student with all mental disorder symptoms as outcomes, being unemployed in the GAD and PTSD models, and loss of income due to the pandemic in all models. The three models with mental disorders as outcome showed significant interaction terms including age, loneliness, and prepandemic mental disorder.

Figure 1 shows predicted means of symptoms of mental disorders and loneliness, depending on age and stratified by prepandemic mental disorder. In the case of symptoms of mental disorder results, models were also stratified by loneliness level to clarify the effect of interaction terms. Age was negatively related to mental disorder symptoms and loneliness. Loneliness was associated with higher levels of mental disorder symptoms. This association was stronger in younger adults without prepandemic mental disorders and in older adults with them. The association between age and loneliness was stronger in those with prepandemic mental disorders.

The results of the mediation analyses stratified by prepandemic mental disorder are shown in Table 5. The association between age and mental disorder symptoms was mediated by loneliness in both participants with (21.4% for MDD, 21.6% for GAD, and 21.6% for PTSD) and without (19.4% for MDD, 16.1% for GAD, and 20.0% for PTSD) prepandemic mental disorders.

DISCUSSION

To the best of our knowledge, this is one of the few studies to examine older age as a protective factor for loneliness, and the role of loneliness and prepandemic mental disorder in the association of

TABLE 2. Correlations for Variables of Interest

	MDD	GAD	PTSD	Loneliness	Age
MDD	1				
GAD	0.763*	1			
PTSD	0.631*	0.683*	1		
Loneliness	0.448*	0.416*	0.445*	1	
Age	−0.163*	−0.173*	−0.168*	−0.113*	1

MDD = major depressive disorder; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder.

* $p < .001$.

TABLE 3. Unadjusted Tobit Regression Models of Factors Related to Symptoms of Loneliness and Mental Disorders

	Depression (0–24)	Anxiety (0–21)	PTSD (0–16)	Loneliness (3–9)
Age, y				
Range: 18–90	−0.07 (−0.09 to −0.05)***	−0.07 (−0.09 to −0.05)***	−0.06 (−0.07 to −0.04)***	−0.03 (−0.03 to −0.02)***
Sex				
Male	Ref.	Ref.	Ref.	Ref.
Female	2.04 (1.50 to 2.58)***	1.31 (0.81 to 1.82)***	1.02 (0.61 to 1.42)***	0.38 (0.11 to 0.66)**
Marital status				
Never married	Ref.	Ref.	Ref.	Ref.
Married	−1.60 (−2.19 to −1.01)***	−1.29 (−1.84 to −0.74)***	−1.12 (−1.56 to −0.68)***	−1.15 (−1.44 to −0.87)***
Divorced/separated	−0.90 (−1.94 to 0.13)	−0.95 (−1.89 to −0.00)*	−0.44 (−1.23 to 0.35)	−0.13 (−0.62 to 0.36)
Widowed	−1.46 (−2.77 to −0.16)*	−1.90 (−3.22 to −0.57)**	−1.22 (−2.21 to −0.22)*	−0.19 (−0.76 to 0.38)
Education				
Primary	Ref.	Ref.	Ref.	Ref.
Secondary low	0.57 (−0.72 to 1.87)	0.26 (−0.95 to 1.46)	1.68 (0.75 to 2.61)***	0.26 (−0.40 to 0.93)
Secondary high	−0.05 (−1.39 to 1.30)	−0.11 (−1.35 to 1.14)	1.47 (0.50 to 2.43)**	0.01 (−0.69 to 0.70)
Tertiary	0.01 (−1.24 to 1.26)	−0.32 (−1.49 to 0.85)	1.39 (0.48 to 2.29)**	0.37 (−0.27 to 1.02)
Living situation				
Living alone	Ref.	Ref.	Ref.	Ref.
Living with 1 person	−0.34 (−1.18 to 0.51)	0.14 (−0.71 to 0.98)	−0.12 (−0.82 to 0.57)	−1.17 (−1.58 to −0.77)***
Living with >1 people	0.28 (−0.53 to 1.09)	1.04 (0.23 to 1.86)*	0.46 (−0.20 to 1.11)	−1.12 (−1.49 to −0.75)***
Employment situation				
Working outside	Ref.	Ref.	Ref.	Ref.
Working at home	−0.02 (−0.77 to 0.72)	−0.24 (−0.94 to 0.45)	0.00 (−0.59 to 0.60)	0.66 (0.28 to 1.04)**
Retired/disability	−0.53 (−1.22 to 0.16)	−1.04 (−1.70 to −0.39)**	−0.61 (−1.13 to −0.08)*	0.12 (−0.23 to 0.48)
Unemployed	1.71 (0.94 to 2.49)***	1.35 (0.64 to 2.06)***	0.66 (0.12 to 1.21)*	0.57 (0.19 to 0.94)**
Student	2.71 (0.97 to 4.45)**	1.94 (0.36 to 3.52)*	1.42 (0.20 to 2.64)*	1.39 (0.69 to 2.08)***
Loss of income due to pandemic				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.75 (1.11 to 2.40)***	1.65 (1.06 to 2.24)***	1.14 (0.68 to 1.61)***	0.52 (0.22 to 0.82)**
Pain/discomfort				
None	Ref.	Ref.	Ref.	Ref.
Low	1.94 (1.30 to 2.58)***	1.24 (0.65 to 1.82)***	0.83 (0.36 to 1.29)**	0.50 (0.19 to 0.82)**
Moderate	3.24 (2.47 to 4.01)***	2.45 (1.67 to 3.24)***	2.01 (1.41 to 2.61)***	0.93 (0.53 to 1.34)***
High	5.31 (3.38 to 7.24)***	3.85 (2.25 to 5.45)***	3.08 (1.93 to 4.23)***	1.28 (0.49 to 2.07)**
Extreme	6.95 (3.65 to 10.25)***	5.30 (2.56 to 8.05)***	1.23 (−1.30 to 3.77)	2.01 (0.69 to 3.32)**
COVID positive				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.34 (−0.23 to 2.91)	−0.10 (−1.72 to 1.52)	−0.58 (−1.91 to 0.75)	−0.03 (−0.94 to 0.88)
Prepandemic MD				
No	Ref.	Ref.	Ref.	Ref.
Yes	3.52 (2.98 to 4.07)***	3.19 (2.67 to 3.71)***	2.22 (1.81 to 2.63)***	1.32 (1.05 to 1.59)***
Loneliness	1.86 (1.67 to 2.05)***	1.63 (1.44 to 1.81)***	1.28 (1.14 to 1.42)***	—

PTSD = posttraumatic stress disorder; Ref. = category of reference; MD = mental disorder.

Unstandardized coefficients with 95% confidence interval are displayed.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

age with MDD, GAD, and PTSD symptoms during the COVID-19 pandemic in a population-based sample. In line with our hypothesis, younger age was related to higher levels of loneliness, MDD, GAD, and PTSD, whereas loneliness has a mediating effect on the association between age and mental disorders and also a moderating effect in that association, which varies depending on the presence or absence of a prepandemic mental disorder.

TABLE 4. Adjusted Tobit Regression Models of Factors Related to Symptoms of Loneliness and Mental Disorders

	Depression (0–24)	Anxiety (0–21)	PTSD (0–16)	Loneliness (3–9)
Intercept	5.19 (1.38 to 8.99)	5.04 (1.11 to 8.97)	0.79 (−2.30 to 3.87)	5.48 (4.78 to 6.18)
Age, y				
Range: 18–90	−0.17 (−0.25 to −0.083)***	−0.16 (−0.24 to −0.07)***	−0.11 (−0.17 to −0.05)***	−0.04 (−0.05 to −0.03)***
Sex				
Male	Ref.	Ref.	Ref.	Ref.
Female	1.18 (0.73 to 1.64)***	0.67 (0.23 to 1.11)**	0.59 (0.24 to 0.94)**	0.21 (−0.04 to 0.46)
Marital status				
Never married	Ref.	Ref.	Ref.	Ref.
Married	0.08 (−0.49 to 0.66)	0.08 (−0.52 to 0.69)	0.04 (−0.45 to 0.53)	−0.22 (−0.57 to 0.12)
Divorced/separated	−0.54 (−1.48 to 0.39)	−0.32 (−1.22 to 0.58)	0.18 (−0.53 to 0.90)	0.16 (−0.34 to 0.67)
Widowed	0.07 (−1.07 to 1.21)	0.10 (−1.15 to 1.36)	0.49 (−0.45 to 1.43)	0.30 (−0.32 to 0.92)
Education				
Primary	—	—	Ref.	—
Secondary low	—	—	0.92 (0.10 to 1.73)*	—
Secondary high	—	—	0.96 (0.10 to 1.81)*	—
Tertiary	—	—	0.76 (−0.06 to 1.58)	—
Living situation				
Living alone	—	Ref.	Ref.	Ref.
Living with 1 person	—	0.85 (0.04 to 1.67)*	0.65 (0.01 to 1.30)*	−0.94 (−1.36 to −0.53)***
Living with >1 people	—	1.12 (0.25 to 1.99)*	0.76 (0.08 to 1.45)*	−1.21 (−1.63 to −0.78)***
Employment situation				
Working outside	Ref.	Ref.	Ref.	Ref.
Working at home	−0.30 (−0.93 to 0.34)	−0.51 (−1.12 to 0.11)	−0.18 (−0.71 to 0.35)	0.61 (0.26 to 0.97)**
Retired/disability	0.32 (−0.42 to 1.05)	−0.01 (−0.72 to 0.71)	0.30 (−0.29 to 0.90)	0.53 (0.12 to 0.95)*
Unemployed	0.74 (0.07 to 1.41)*	0.51 (−0.13 to 1.15)	0.06 (−0.42 to 0.54)	0.42 (0.05 to 0.78)*
Student	0.01 (−1.48 to 1.50)	−0.17 (−1.64 to 1.29)	−0.47 (−1.65 to 0.71)	0.62 (−0.01 to 1.25)
Loss of income due to pandemic				
Not	Ref.	Ref.	Ref.	Ref.
Yes	0.53 to (−0.04 to 1.10)	0.49 (−0.054 to 1.04)	0.28 (−0.14 to 0.71)	0.24 (−0.05 to 0.54)
Pain/discomfort				
None	Ref.	Ref.	Ref.	Ref.
Low	1.60 (1.05 to 2.15)***	1.02 (0.51 to 1.53)***	0.64 (0.22 to 1.05)**	0.65 (0.35 to 0.96)***
Moderate	2.71 (1.99 to 3.43)***	2.08 (1.35 to 2.81)***	1.76 (1.17 to 2.34)***	1.00 (0.60 to 1.40)***
High	4.01 (2.28 to 5.73)***	2.74 (1.27 to 4.21)***	2.24 (1.26 to 3.22)***	1.12 (0.33 to 1.91)**
Extreme	5.43 (2.64 to 8.23)***	3.86 (0.73 to 7.00)*	0.02 (−2.15 to 2.18)	2.17 (0.87 to 3.46)**
COVID positive				
No	Ref.	—	Ref.	—
Yes	0.94 (−0.41 to 2.30)	—	−0.58 (−1.91 to 0.75)	—

Continued on next page

TABLE 4. *(Continued)*

	Depression (0–24)	Anxiety (0–21)	PTSD (0–16)	Loneliness (3–9)
Prepandemic MD				
No	Ref.	Ref.	Ref.	Ref.
Yes	−10.55 (−15.43 to −5.66)***	−10.54 (−15.30 to −5.77)***	−7.38 (−11.05 to −3.70)***	0.86 (0.60 to 1.12)***
Loneliness	0.43 (−0.44 to 1.29)	0.18 (−0.65 to 1.02)	0.56 (−0.06 to 1.18)	—
Interactions				
Age × loneliness × prepandemic MD	−0.04 (−0.06 to −0.02)**	−0.04 (−0.07 to −0.02)***	−0.03 (−0.05 to −0.01)**	—
Age × loneliness	0.02 (0.01 to 0.04)*	0.023 (0.01 to 0.042)*	0.01 (−0.00 to 0.03)	—
Age × prepandemic MD	0.17 (0.08 to 0.27)**	0.17 (0.07 to 0.27)**	0.14 (0.06 to 0.21)***	—
Loneliness × prepandemic MD	2.02 (0.85 to 3.19)**	2.16 (1.05 to 3.27)***	1.37 (0.52 to 2.21)**	—

PTSD = posttraumatic stress disorder; Ref. = category of reference; MD = mental disorder. (—) Covariates with a p value >.2 in unadjusted model were not included in adjusted model.

Unstandardized coefficients with 95% confidence interval are displayed.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

The fact that older people are less prone to loneliness and mental disorders is in contrast with previously reported global estimates (18,19). This could be due to the COVID-19 pandemic particularly affecting the mental health of younger adults. These results are consistent with the socioemotional selectivity theory, according to which the psychosocial well-being of younger adults depends on frequent social relationships to a greater extent than it does among older adults (22). Therefore, the socially disruptive measures in the context of the pandemic would affect younger adults more severely, which in turn could explain the observed increase in loneliness and subsequent mental disorders among this age group (8,9). The mediating effect of loneliness on the association between age and mental disorders was limited, which means that other mediating factors should be taken into account to improve understanding of older age as a protective factor for mental disorders during the COVID-19 pandemic. In this line, previous research suggests that older adults are more resilient than younger adults, including their use of problem-solving strategies to cope with adversity (44). In addition, the public health and social measures put in place to stop the spread of COVID-19 may have had a stronger negative effect on the finances of younger adults because the jobs most affected by the pandemic are usually held by young people (e.g., in restaurants, hotels, and other services) (45).

In accordance with our hypothesis, the negative association between age and loneliness was stronger in participants with prepandemic mental disorders. Previous research found that the impact of the COVID-19 pandemic on psychosocial well-being was stronger among them (26). According to our results, this impact could be higher still among younger adults. Among participants without prepandemic mental disorders, the impact of loneliness on mental health was stronger in younger adults, which could be explained by the greater psychological resilience of older adults in moderating that association (24,25). In contrast, among participants with prepandemic mental disorders, the impact of loneliness on mental disorders was stronger in older adults. Future studies with longitudinal data should test this particular impact of loneliness depending on age and the existence of previous mental disorders, as well as potential causal factors such as changes in psychological resilience.

Although most research on loneliness has focused on the elderly, the results of the present study are in line with those showing that loneliness can be an important mental health problem for younger adults as well (46). Therefore, a life course perspective is important in addressing the role of the social network and loneliness at each developmental stage, together with the development of age-appropriate interventions to improve the mental health of the population (47).

In the present study, we found a strong multimorbidity between symptoms of MDD, GAD, and PTSD, which were also strongly related to prepandemic mental disorders, as well as pain or physical discomfort; these are relations that have been widely recognized (48). In line with previous studies, being unemployed was related to depression and loneliness (49,50). Living alone was found to be related to feeling alone, although these are two distinct conditions with different impacts on public health (51). In the context of the COVID-19 pandemic, our results are in line with those of other authors who found associations between working mainly outside home and lower likelihood of loneliness (52). In contrast, some of the associations that we tested and that are widely

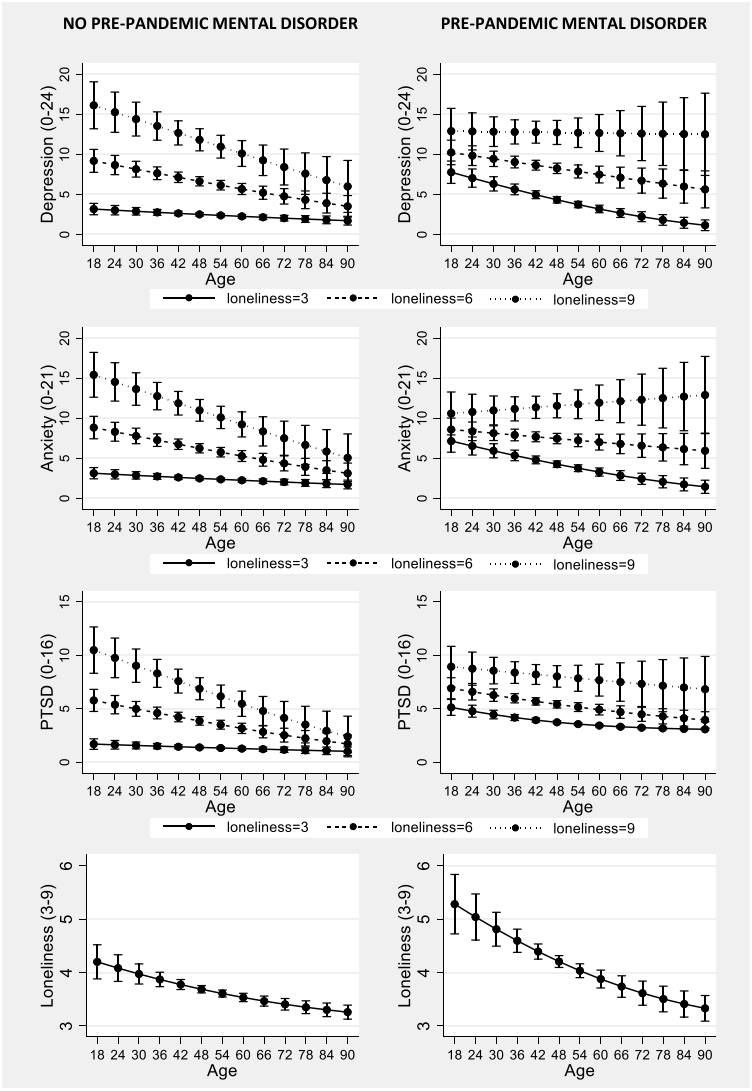

FIGURE 1. Predicted means (95% CI) for loneliness and mental disorder symptoms depending on age, loneliness, and prepandemic mental disorder, All models were adjusted for sex, marital status, education level, pain or discomfort, and COVID status. PTSD = posttraumatic stress disorder; CI = confidence interval.

recognized have not been found to be protective factors for mental health in the present study, such as being married or having a high level of education in Western countries (49,53). In the case of being married, some studies have detected an increase in marital problems and sexist violence during confinement (54), which could partly explain our results, whereas in the case of educational level, we found no explanations for the results obtained in the reviewed literature beyond the need to take into account the different indicators available to understand the impact of socioeconomic status on mental health (50).

The observed prevalence rates for MDD, GAD, and PTSD was 12.4%, 11.9%, and 11.6%, respectively, lower than the lowest pooled values reported by previous meta-analyses carried during the COVID-19 pandemic in which the prevalence rates were 15%, 16%, and 21%, respectively (13,15). Our figures were also lower than the prevalence reported by a study of Spanish adults (18.7%, 21.6%, and 15.8%, respectively) (17) using similar measurement tools. However, comparability with the study by González-Sanguino et al. (17) is limited because their study was not population based and also had a high proportion of female participants (75%). The lower prevalence observed in our study may also be due to the different phases of the pandemic in which the studies were carried out. The study by González-Sanguino et al. was carried at the initial stage of the COVID-19 pandemic (from March 21 to 28, 2020), when the population was locked down at home, while our study was carried out in February to March

TABLE 5. Tobit Regression Analyses of the Association of Age With Mental Disorder Symptoms and Loneliness as Mediator (KHB Method)

Dependent Variables:	Independent Variable: Age Groups	% Mediated
No prepandemic mental disorder		
Depression		
Total	−0.07 (−0.09 to −0.05)***	
Direct	−0.06 (−0.08 to −0.04)***	
Indirect	−0.01 (−0.02 to −0.01)***	19.4
Anxiety		
Total	−0.08 (−0.10 to −0.06)***	
Direct	−0.07 (−0.09 to −0.05)***	
Indirect	−0.01 (−0.02 to −0.01)***	16.1
PTSD		
Total	−0.05 (−0.07 to −0.03)***	
Direct	−0.04 (−0.06 to −0.02)***	
Indirect	−0.01 (−0.01 to −0.01)***	20.0
Prepandemic mental disorder		
Depression		
Total	−0.11 (−0.15 to −0.08)***	
Direct	−0.09 (−0.12 to −0.05)***	
Indirect	−0.02 (−0.04 to −0.01)**	21.4
Anxiety		
Total	−0.10 (−0.14 to −0.07)***	
Direct	−0.08 (−0.11 to −0.05)***	
Indirect	−0.02 (−0.04 to −0.01)**	21.6
PTSD		
Total	−0.09 (−0.11 to −0.06)***	
Direct	−0.07 (−0.09 to −0.04)***	
Indirect	−0.02 (−0.03 to −0.01)**	21.6

PTSD = posttraumatic stress disorder.

All models were adjusted for sex, marital status, education level, pain or discomfort, and COVID status. Coefficients with 95% confidence interval are displayed. Percentage mediated is considered statistically significant when indirect effect is $p < .05$.

** $p < .01$.

*** $p < .001$.

2021, when the de-escalation plan had already started and the lockdown was about to end. The somewhat more relaxed COVID-19 management measures in place at the time of ours study could have allowed for an improvement in the mental health and psychosocial well-being of the population. Future studies analyzing the trajectory of mental health throughout the pandemic may serve to confirm or refute our suggestions.

Strengths and Limitations of the Study

The strengths of our study include the use of a large nationally representative sample of Spanish adults from a variety of socioeconomic backgrounds, and the ability to control for confounding factors. However, several limitations of our study deserve consideration. First, because participants were not asked about loneliness in the baseline survey, we were limited to analyzing the follow-up data and carrying out a cross-sectional design, which precludes interpreting the described associations as causal. However, we used prepandemic mental disorders as an adjusting variable, mental disorder symptoms during the pandemic as the dependent variable, and age as the independent variable, which, considered as year of birth, is a time-invariant variable. Moreover, according to previous research, the association between loneliness and mental disorders is stronger with loneliness as cause (10), which is consistent with the mediation models that were constructed. Nevertheless, future studies should use longitudinal data to reinforce our findings (55). Second, our data are based on self-reporting, which may result in recall or reporting bias. Nevertheless, in our study, recall periods were short and well defined, which should minimize recall bias. Finally, there are other factors related to social networks, such as objective measures of social isolation, that could add information to the present study. Future studies with longitudinal data, taking into account distinct phases of the pandemic, in different settings and countries, and focused on several characteristics of social life, are needed to replicate our findings concerning the associations within social relationships and mental health among younger adults in pandemic contexts.

CONCLUSIONS

Our results suggest the need to address feelings of loneliness among general populations to promote mental health in the context of the COVID-19 pandemic. Moreover, the consequences of socially disruptive measures associated with the pandemic could include the mental health of younger adults to a greater extent because of their social needs being particularly unmet, which in turn would increase the risk for loneliness and consequent mental disorders. Therefore, age-appropriate interventions focused on each developmental stage would be an effective strategy to address the consequences of the COVID-19 pandemic in loneliness and mental health.

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Article IV

Loneliness during the last phase of the COVID-19 pandemic in Spain: A longitudinal study of group-based trajectories, risk factors, and consequences in mental health

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Loneliness during the last phase of the COVID-19 pandemic in Spain: A longitudinal study of group-based trajectories, risk factors, and consequences in mental health

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ABSTRACT

Introduction: The present study aims to investigate the courses of loneliness following a national state of emergency including a curfew due to a rise in COVID-19 cases, associated risk factors, and the effect of loneliness on symptoms of depression and anxiety.

Methods: Data of 2,000 adults in Spain which were interviewed by telephone at the first follow-up of the MINDCOVID project (February–March 2021) and of whom 953 were interviewed nine months later (November-December 2021) were analyzed. Group-based trajectories and mixed models were constructed.

Results: Three courses of loneliness were detected: (1) invariant low loneliness (42.6%), (2) decreasing medium loneliness (51.5%), and (3) fairly invariant high loneliness (5.9%). Loneliness courses were associated with the severity and variability of symptoms of depression and anxiety. In contrast to the majority of pre-pandemic studies, younger adults more frequently reported loneliness compared to middle-aged and, particularly, older individuals. Other risk factors for loneliness were being female, being unmarried, and, notably, having pre-pandemic mental disorders.

Conclusions: Future studies should validate whether the newly observed loneliness patterns across age groups persist and assess the evolution of loneliness courses and their impact on mental health, with particular attention given to young adults and individuals with pre-existing mental disorders.

1. Introduction

The effects of socially restrictive measures on mental health in the context of the COVID-19 pandemic as well as their consequences in the medium and long term are a research priority (Galea et al., 2020; Tyrrell and Williams, 2020; Williams et al., 2020). Social distancing measures, lockdowns, and quarantines to stop the spread of the coronavirus have been related with adverse effects on socioeconomic circumstances as well as on social relationships and loneliness, which, in turn, have been related to increases in depression and anxiety symptoms (Domènech-Abella et al., 2018; Leigh-Hunt et al., 2017; Liu et al., 2020).

Loneliness is an unpleasant feeling which occurs as a consequence of a discrepancy between desired and real social relationships in a quantitative or qualitative sense (Perlman and Peplau, 1981). In 2018, the prevalence of loneliness in the European Union was 5.2% in Northern Europe, 6.6% in Western Europe, 8.9% in Southern Europe, and 10.8% in Eastern Europe. Levels of loneliness have increased during the COVID-19 pandemic in Europe (Baarck et al., 2022; Ernst et al., 2022).

Poor health and financial status, and being divorced or widowed, are strongly associated with loneliness, both in the pandemic and pre-

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pandemic periods as well as being female, particularly in samples of older adults, which typically reported a prevalence higher than younger adults before the pandemic (Surkalim et al., 2022). However, some studies shown that younger adults have been the most affected by social distancing measures and reported loneliness more frequently (Gabarrell-Pascuet et al., 2023a; 2023b).

Depression and anxiety are two frequent and highly comorbid mental disorders. Like loneliness, some of their main predictors are female gender, low socioeconomic status, being divorced or widowed, a lack or loss of close social contacts, poor health status, and a clinical history of mental disorders (Domènech-Abella et al., 2018; Prince et al., 2007). During the COVID-19 pandemic, researchers have focused on living situation and being a young adult as risk factors for both mental disorders (Domènech-Abella et al., 2021; Gambin et al., 2021).

There is no consensus about the possible increase in mental disorders during the COVID-19 pandemic in European countries. Studies with general populations in the United Kingdom and the Czech Republic reported increased depression and anxiety symptoms from before to during the pandemic (Pierce et al., 2020; Winkler et al., 2020), whereas according to a study with a Norwegian population the prevalence of these mental disorders remained stable (Knudsen et al., 2021). Several systematic reviews during the pandemic period reported pooled prevalence of depression and anxiety symptoms in the general population. However, differing measurement tools makes comparison among them difficult, ranging the reported prevalence of depression and anxiety from 16% to 34% (Cénat et al., 2021; Necho et al., 2021), and from 15% to 40% (Cénat et al., 2021; Necho et al., 2021), respectively. A systematic review of general population studies in Spain found pooled prevalence rates of 20% and 22% (Zhang et al., 2022).

A cross-sectional study, with a nationally representative sample from the adult general population in Spain (MINDCOVID project; www.mindcovid.org) interviewed during February-March 2021 (i.e., during a imposed national curfew part of a declared state of emergency due to a new rise in COVID-19 cases), reported a prevalence of depression, anxiety, and loneliness of 12.4%, 11.9%, and 13.1%, respectively (Gabarrell-Pascuet et al., 2023a). These prevalence of depression and anxiety in Spain are lower than the pooled prevalence from that systematic review (Zhang et al., 2022). However, these differences could be partially explained by limitations in the representativeness of the sample, since just 10% of the studies on mental health during the COVID-19 pandemic used random sampling methods to recruit participants (Nieto et al., 2020). As in previous research on the COVID-19 pandemic, age was negatively related with mental disorder symptoms and loneliness significantly mediated the association of age with mental disorder symptoms (Gabarrell-Pascuet et al., 2023a).

While we have information on changes in loneliness and mental health from before to during the pandemic in Spain, which has allowed us to detect that the pandemic has modified the patterns of loneliness' distribution by age group and evaluate the association between loneliness and mental health as well as the impact of several sociodemographic and socioeconomic risk factors in that association (Gabarrell-Pascuet et al., 2023a; 2023b), we do not have information on whether these changes have persisted at the end of the pandemic. The present study analyzed a sample of 2000 adult residents of Spain who were interviewed during the last state of emergency in Spain (February-March 2021), of which 953 were re-interviewed after the state of emergency had ended (November-December 2021). This allows us to assess courses of loneliness, characteristics of individuals in each loneliness course, and their impact on mental health. This information enables us to understand the impact of the pandemic on loneliness and mental health in the post-pandemic period and identify aspects to consider in order to mitigate this impact. The hypotheses we propose are: (1) there are different patterns of loneliness courses, (2) younger individuals with pre-pandemic mental disorders and other risk factors such as being unmarried, having a low level of education, and being female are more likely to report unfavorable loneliness courses, and (3) loneliness courses are associated with the severity and variability of symptoms of depression and anxiety.

2. Methods

2.1. Study design

This was a prospective cohort study using data from the MIND/COVID general population study (www.mindcovid.org). A nationally representative sample from the adult general population in Spain (aged 18 or older) was obtained in June 2020 through a dual-frame random digit dialing (DFRDD) telephone survey, including both landlines and mobile telephones. . Participants in the baseline survey (n = 3500) during the initial phase of the pandemic, were invited to respond to the first (Time 1, February-March 2021) and second (Time 2, November-December 2021) follow-up surveys.

In the baseline of the MINDCOVID survey, a total of 138,656 numbers were sampled, with a final split of 71% mobile and 29% landline telephones. Out of these numbers, 45,002 were non-eligible, including 43,120 non-existing numbers, 984 enterprise numbers, 444 numbers of individuals with Spanish language barriers, 268 fax numbers, and 186 numbers belonging to a quota, of which 8 were already completed. Additionally, 72,428 numbers had unknown eligibility, meaning that no contact was made after the seven attempted calls, resulting in a cooperation rate of 16.5%. During the COVID-19 lockdown in Spain, a total of 3500 people were interviewed in the baseline survey. Unlike the baseline, in the follow-up questionnaires, answers about loneliness were included, and the responses from participants in the follow-ups were analyzed in the present study. A total of 2000 participants were included in the first follow-up (Time 1), of whom 959 responded in the second follow-up (Time 2) and were included in the present study.

3. Ethics statement

Ethical approval was provided by Parc Sanitari Sant Joan de Déu, Barcelona, Spain (PIC 86–20) and by the Parc de Salut Mar Clinical Research Ethics Committee (protocol 2020/9203/I). Once a potential participant was fully informed about the objectives and procedures of the study, oral consent was obtained to proceed with the interview.

4. Measurements

4.1. Loneliness

Loneliness was assessed with the three-item UCLA Loneliness Scale (Hughes et al., 2004). It contains three items ranging from 1 to 3. The total sum score range is from 3 to 9, with higher scores indicating a greater degree of loneliness. The 3-item UCLA Loneliness Scale showed acceptable internal consistency for the study sample since Cronbach's alpha had values of 0.71 and 0.78 in first and second follow-ups, respectively.

4.2. Depression and anxiety symptoms

Symptoms of depression were measured using the eight-item Patient Health Questionnaire Depression Scale (PHQ-8) (Kroenke et al., 2009). The PHQ-8 contains 8 items ranging from 0 to 3, with a total score ranging from 0 to 24, where higher values indicate greater depressive symptoms. A PHQ-8 score of $\geq$ 10 is an established cut-off for screening major depressive disorder (MDD) (Kroenke et al., 2009). The 8 items of the PHQ-8 scale showed a good internal consistency in the present study sample with Cronbach's alpha of 0.85 and 0.83 in first and second follow-ups, respectively.

The seven-item Generalized Anxiety Disorder Scale (GAD-7) (Spitzer et al., 2006) was used to measure anxiety symptoms. This measure has 7

items, scored 0–3, and a total score of 21. Higher scores indicate greater anxiety symptoms. A cut-off of 10 is optimal for screening for potential generalized anxiety disorder (GAD) (Spitzer et al., 2006). The 7 items of the GAD-7 scale showed good internal consistency with Cronbach's alpha = 0.87 in both follow-ups.

4.3. Risk factors

Risk factors were selected based on previous studies which used as covariates sociodemographic variables such as gender, age, marital status, pre-pandemic mental health-related variables, and socioeconomic indicators, since these variables had a statistically significant relationship with mental disorders during the COVID-19 pandemic (Domènech-Abella et al., 2021; Gambin et al., 2021).

Sociodemographic control variables included age group (18–34, 34–49, 50–64, 65+), sex, partner status (married or cohabiting/single, widowed, separated or divorced), and education level (primary, secondary, and tertiary). We also included loss of income due to the COVID-19 pandemic (no, yes).

The existence of pre-pandemic lifetime mental disorders was assessed retrospectively using a checklist based on the Composite International Diagnostic Interview (CIDI) (Kessler and Ustün, 2004) that screens for depression and anxiety mental disorders.

4. Statistical analysis

To restore the bias arising from attrition in the follow-up surveys, we applied inverse probability weights (IPW). These were obtained as the inverse of the probability of completing each follow-up survey according to observed characteristics from previous surveys, estimated using a logistic regression models (Seaman et al., 2013). An initial list of variables to be incorporated in the logistic regression model included relevant variables from previous assessments that were shown in bivariate analysis to be related to the probability of completing a subsequent follow up survey. A reduced list of variables was further selected using lasso regularization, including sociodemographic (e.g. age, sex, education, marital status, reported financial problems due to the pandemic at baseline) health-related variables (e.g. presence of previous mental health problems), or perceived stress variables (interpersonal stress, stress related to own health) and relevant interactions among these variables. In addition, post-stratification adjustment to the weight was carried out in order to restore population distributions of the sample according to age, gender and region.

Descriptive analyses included weighted proportions and unweighted frequencies for categorical variables and weighted means and standard error for continuous variables (i.e., symptoms of loneliness and mental disorders.). Differences between Time 1 and Time 2 were evaluated with Student's *t*-test for means and Chi-squared test for proportions

The Stata version of the group-based trajectory model (GBTM) SAS procedure TRAJ (Jones and Nagin, 2007) was used to identify distinct subgroups of participants who followed similar loneliness trajectories. GBTM handles missing data by fitting the model using maximum likelihood estimation, and therefore handles missing data under the missing-at-random assumption (Nagin and Odgers, 2010). We modeled loneliness using a censored normal distribution since more than half of the participants reported the minimum level of loneliness scale, and the responses of the remaining participants were normally distributed along the scale (Nagin, 2005). Since we had two time points, trajectories were modeled as a linear function from Time 1 to Time 2. The Bayesian Information Criterion (BIC) was used to select the final number of trajectory groups. We tested models with 2, 3, and 4 trajectories considering that a positive change in the BIC of three or more is considered strong evidence that the model with an additional trajectory provides a better fit than the previous model (Jones et al., 2001) as well as smallest difference between the observed and expected proportion (missmatch) and a relative entropy closest to one (Mésidor et al., 2022). We also imposed the condition that models must have a class membership >5% and an average subsequent probability of belonging to a group >0.7, to ensure a high degree of confidence in class membership (Andruff et al., 2009). Chi-square tests were used to determine which baseline characteristics were associated with trajectory membership. Predictor variables used in these analyses included sex, age, partner status, education, losing income due to pandemic, and pre-pandemic mental disorder.

To provide a sound justification for employing hierarchical linear modeling (HLM) or mixed-effects regression in our data analysis, we conducted an assessment of unconditional models. These models were constructed without any predictors to effectively partition the data into level 2 units. The results from the unconditional models revealed significant random effects for ID variable. In the depression model, the estimated between person variance was 12.45 (SE = 0.67) and the ICC was 0.6. In the anxiety model, the estimated between-person variance was 11.72 (SE = 0.61), and the ICC was 0.62. This finding suggests the presence of variability among respondents and, thereby, supporting the utilization of mixed-effects models. By employing these models, we can appropriately account for the multilevel structure of the data and address temporal dependencies, which facilitates a more robust estimation of the effects of independent variables on the outcome variables.

Mixed-effects linear regression models for repeated measures were constructed to study the association of loneliness trajectories with depression and anxiety in Times 1 and 2, allowing inclusion of all available data. They are two-level random intercept models ("mixed" command in Stata) which were fitted through maximum likelihood and used loneliness trajectories as a fixed factor, time point (Time 1 or 2) as a within-participant repeated factor, and participant ID as a random factor. The models tested the interaction between loneliness trajectories and time points with depression and anxiety (at both Time 1 and Time 2) as the outcomes. Several unadjusted models were fitted to test the relationship of each potential risk factor with depression and anxiety (data not shown but available upon request). Those variables that predicted the outcome ($p<0.20$) (Mickey and Greenland, 1989) were introduced into adjusted models. The models were adjusted for sex, age group, partner status, education, losing income due to pandemic, and pre-pandemic mental disorder. Regression coefficients with 95% confidence interval (CI) were reported. To interpret our results, estimated means (with 95% CI) for depression and anxiety depending on loneliness trajectory and stratified by time point were calculated through margins (Williams, 2012). Control variables were centered at mean according to their distribution in the sample.

All reported p-values were based on a two-sided test, where the level of statistical significance was set at $p<0.05$. Stata version SE 13 (StataCorp, 2013) was used to analyze the survey data.

4. Results

The socio-demographic characteristics of the study sample are presented in Table 1. Means of symptoms of loneliness, depression, and anxiety significantly ($p<0.001$) decreased from Time 1 to Time 2.

Fig. 1 illustrates the trajectories of loneliness from Time 1 to Time 2. Through comparing goodness-of-fit among models with 2, 3, and 4 courses, three distinct courses were identified. Table 2 presents the goodness-of-fit indicators for these models. The BIC values for the models were −3742.6, −3726.1, and −3747.3, while the relative entropy values were 0.545, 0.713, and 0.706. These indicators suggest that the three-course model provides a better fit. Additionally, likelihood ratio tests were conducted, and the assumption of 3 courses nested in 4 courses was found to be statistically significant. However, considering the low Chi-squared value of the likelihood ratio test and the values of other indicators (BIC, Entropy) that penalize excessive complexity in the four-course model, the three-course model was selected.

Based on their characteristics, the three selected courses were labeled as follows: (1) "invariant low loneliness," (2) "decreasing

Table 1
Characteristics of the study sample.

Characteristic	T1 (N = 2000) N(%)	T2 (N = 953) N(%)	p-value
Sex			
• Male	890 (48.6)	442 (47.8)	p = 0.337
• Female	1110 (51.4)	511 (52.2)	
Age groups			
• 18–34	365 (22.0)	170 (21.6)	p = 0.580
• 35–49	616 (28.7)	273 (28.0)	
• 50–64	683 (25.8)	338 (27.0)	
• +65	336 (23.5)	172 (23.4)	
Partner status			
• Not married	921 (50.3)	420 (49.6)	p = 0.313
• Married	1079 (49.7)	533 (50.4)	
Education			
• Primary	115 (7.6)	42 (5.7)	p = 0.217
• Secondary	999 (52.8)	467 (54.5)	
• Tertiary	886 (39.6)	444 (39.8)	
Losing income			
• No	1337 (67.5)	647 (67.1)	p = 0.573
Yes	663 (32.5)	306 (32.9)	
Pre-pandemic mental disorder			
• No	1319 (65.7)	648 (66.5)	p = 0.270
• Yes	681 (34.3)	305 (33.5)	
	Mean(SE)	Mean(SE)	
Loneliness (3–9)	3.97 (0.03)	3.65 (0.05)	p<0.001
Depression (0–24)	4.48 (0.12)	3.38 (0.17)	p<0.001
Anxiety (0–21)	4.25 (0.11)	3.03 (0.14)	p<0.001

Note: Unweighted frequencies (N) with weighted percentages (%) and weighted means with standard error (SE) are reported. All differences between T1 and T2 were evaluated through T-tests for continuous variables and chi squared test for categorical variables. Continuous variables were repeated measures whereas remaining variables were reported at T1.

medium loneliness," and (3) "fairly invariant high loneliness." The observed proportions of participants in these courses were 0.525, 0.438, and 0.037, respectively, with mismatch values of −0.088, 0.072, and 0.016. The average subsequent probabilities of belonging to these groups were 0.83, 0.94, and 0.77 for participants in courses (1), (2), and (3), respectively.

Table 3 shows baseline characteristics by trajectory membership. Females, younger adults, those not married and not cohabiting, and those with any pre-pandemic mental disorder reported courses (2) and (3) more frequently. In addition, those with higher levels of education reported course (2) more frequently whereas those with lower levels of education reported course (3) in higher proportion.

Table 2
Goodness-of-fit indexes.

Courses	BIC	Entropy	Likelihood ratio test	
			chi2	p-value
2	−3742.63	0.545		
3	−3726.13	0.713	101.41	0.0000[1]
4	−3747.25	0.706	26.16	0.0035[2]

[1] Assumption: 2 courses nested in 3 courses.
[2] Assumption: 3 courses nested in 4 courses.

Table 4 reports the mixed-model fixed effects for depression and anxiety models. Females, younger adults, those married or cohabiting, those with a lower education level, those losing income due to pandemic, and those with a pre-pandemic mental disorder reported higher levels of depression and anxiety symptoms in unadjusted (not shown) and adjusted models. In both cases, a statistically significant interaction was found between loneliness courses and time point (Time 1 vs. Time 2) with depression and anxiety as the outcomes and adjusted for covariates. Interactions reveal that participants reported a statistically significant decrease in depression and anxiety symptoms from Time 1 to Time 2, except in the case of anxiety among those in the course "fairly invariant high loneliness" which reported a no significant decrease. In both cases the fairly invariant high loneliness course maintains a relatively low level of decrease which accentuated the disparity between the courses.

Table 5 reports the estimated means with 95% confidence intervals (CI) of depression and anxiety according to loneliness trajectory and time point as well as percentage decreases in depression and anxiety between time points. "Low invariant" course was related to lower levels of depressive and anxiety symptoms in Times 1 and 2, whereas "high fairly invariant" course was related to higher levels. "Medium decreasing" course was related to proportionally higher decreases in depressive and anxiety symptoms than "high fairly invariant" course.

5. Discussion

The present study detected 3 distinct courses of loneliness in the general adult population associated with the reduction of socially

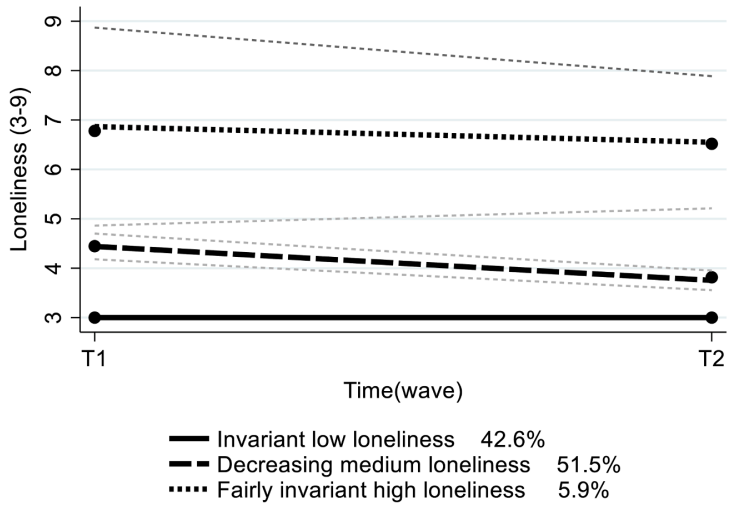

Fig. 1. Courses of loneliness from Time 1 (February–March 2021) to Time 2 (November–December 2021) and percentages of participants.
Note: Means of loneliness in Time 1 and Time 2 with 95% confidence interval (CI) as well as percentage of participants in every course are reported (N = 2000).

Table 3
Characteristics of participants by course of loneliness.

	Course 1 Low invariant Freq. (%)	Course 2 Medium decreasing Freq. (%)	Course 3 High fairly invariant Freq. (%)	p-value
Sex				
• Male	502 (54.7)	362 (41.9)	26 (3.5)	$p<0.01$
• Female	548 (48.0)	514 (47.4)	48 (4.6)	
Age groups				
• 18–34	135 (36.9)	206 (56.2)	24 (6.9)	$p<0.001$
• 35–49	322 (51.2)	269 (43.8)	25 (5.0)	
• 50–64	399 (58.1)	263 (38.8)	21 (3.1)	
• +65	194 (57.0)	138 (41.6)	4 (1.4)	
Partner status				
• Not married	385 (41.0)	478 (52.4)	58 (6.6)	$p<0.001$
• Married	665 (61.6)	398 (36.9)	16 (1.5)	
Education				
• Primary	71 (60.8)	38 (33.8)	6 (5.4)	$p<0.01$
• Secondary	546 (52.8)	408 (42.2)	45 (5.0)	
• Tertiary	433 (47.3)	430 (50.1)	23 (2.6)	
Losing income due to pandemic				
• No	720 (52.9)	572 (43.6)	45 (3.5)	$p = 0.167$
• Yes	330 (47.7)	304 (47.1)	29 (5.1)	
Prepandemic mental disorder				
• No	788 (58.6)	518 (40.4)	13 (1.0)	$p<0.001$
• Yes	262 (37.0)	358 (52.9)	61 (10.1)	

Note: Unweighted frequencies and weighted proportions are displayed. All differences were evaluated using $\chi 2$.

Table 4
Mixed linear regression models of factors related to depression and anxiety symptoms.

	Depression	Anxiety
Intercept	2.62 (1.75, 3.50)***	2.94 (2.07, 3.82)***
Sex		
• Male	Ref.	Ref.
• Female	1.21 (0.89, 1.53)***	0.89 (0.58, 1.21)***
Age groups		
• 18–34	Ref.	Ref.
• 35–49	−0.32 (−0.85, 0.22)	−0.23 (−0.76, 0.30)
• 50–64	−0.62 (−1.17, −0.07)*	−0.64 (−1.16, −0.12)*
• +65	−1.17 (−1.76, −0.59)***	−1.28 (−1.83, −0.73)***
Partner status		
• Not married	Ref.	Ref.
• Married	0.42 (0.06, 0.78)*	0.52 (0.16, 0.88)**
Education		
• Primary	Ref.	Ref.
• Secondary	−0.63 (−1.39, 0.12)	−0.87 (−1.64, −0.10)*
• Tertiary	−1.13 (−1.89, −0.38)**	−1.41 (−2.18, −0.63)***
Losing income		
• No	Ref.	Ref.
• Yes	0.46 (0.09, 0.83)*	0.43 (0.08, 0.79)*
Pre-pandemic mental disorder		
• No	Ref.	Ref.
• Yes	1.56 (1.18, 1.94)***	1.56 (1.18, 1.94)***
Courses of loneliness		
• 1. Invariant low	Ref.	Ref.
• 2. Decreasing medium	2.89 (2.50, 3.29)***	2.62 (2.24, 3.00)***
• 3. Fairly invariant high	7.36 (5.97, 8.75)***	5.69 (4.39, 7.00)***
Time		
• 1. February–March 2021	Ref.	Ref.
• 2. November-December 2021	−0.63 (−0.89, −0.37)***	−0.79 (−1.03, −0.56)***
Interaction: Course x Time		
• 1 × 1	Ref.	Ref.
• 2 × 2	−1.03 (−1.51, −0.55)***	−0.70 (−1.15, −0.25)**
• 3 × 2	−2.12 (−4.09, −0.15)*	−1.03 (−2.80, 0.74)

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

disruptive measures designed to stop the spread of the COVID-19 from the last state of alarm (T1) to a half year later in Spain (T2). Some 5.9% of the population reported "fairly invariant high loneliness", 51.5% "decreasing medium loneliness", and 42.6% "invariant low loneliness". Those with "fairly invariant high loneliness" reported higher levels of depression and anxiety symptoms and a proportionally lower decreases of these symptoms from T1 to T2 than remaining courses. Some 7% of younger adults reported "invariant high loneliness", double the figure

Table 5
Estimated means of depression and anxiety symptoms depending on course of loneliness and Time.

Loneliness course	Depression at T1 mean (95% CI)	Depression at T2 mean (95% CI)	% decrease
• Low invariant	2.62 (2.42, 2.83)	2.00 (1.76, 2.24)	23.66
• Medium decreasing	5.78 (5.47, 6.10)	4.13 (3.76, 4.49)	28.55
• High fairly invariant	11.21 (9.86, 12.56)	8.46 (6.72, 10.20)	24.53
Loneliness course	Anxiety at T1 mean (95% CI)	Anxiety at T2 mean (95% CI)	% decrease
• Low invariant	2.61 (2.41, 2.80)	1.81 (1.59, 2.04)	30.65
• Medium decreasing	5.45 (5.14, 5.76)	3.96 (3.59, 4.32)	27.34
• High fairly invariant	9.46 (8.20, 10.71)	7.63 (6.02, 9.25)	19.34

Estimated means from the logistic regression models of the Table 4. Covariates were centered at mean according to the distribution of the sample. CI: confidence interval.

for the middle-aged and 5 times more than for older adults. Younger adults also reported higher levels of depression and anxiety during the pandemic, particularly compared to older adults.

Being an older adult has previously been found to be a protective factor for mental disorder symptoms and loneliness during the COVID-19 pandemic, which has been explained by distinct relational necessities dependent on age (Gabarrell-Pascuet et al., 2023b). In line with the socioemotional selectivity theory, younger adults need more frequent and varied social relationships than older adults (Carstensen, 1993), and therefore they have suffered the socially disruptive measures to stop the pandemic greatly. Moreover, younger adults could be more affected by the socioeconomic consequences of the pandemic since they more frequently have poor labor conditions and jobs that were particularly affected by the pandemic, such as those in the hostelry and service sector (Kochhar and Barroso, 2020).

Apart from being a younger adult, we found that loneliness, depression, and anxiety symptoms were associated with being female, having a low education level, losing income during the pandemic, and having a pre-pandemic mental disorder. The impact of gender, previous mental disorders, and unfavorable socioeconomic circumstances on mental health and loneliness has previously been reported in research on the pandemic (Domènech-Abella et al., 2021; Gambin et al., 2021) and pre-pandemic periods (Domènech-Abella et al., 2018; 2018b). Moreover, in line with previous literature (Domènech-Abella et al., 2018; 2018b), being married has been found to be a protective factor for loneliness. However, in our sample, being married is also a risk factor for mental disorders symptoms during the pandemic, in line with what other researchers (Malesza and Kaczmarek, 2021; Msherghi et al., 2021) found and in contrast with research from the pre-pandemic period (Domènech-Abella et al., 2018; 2018b). This could be related to increases in gender violence during the pandemic (Mazza et al., 2020; Mittal and Singh, 2020).

The present study provides valuable insights into the trajectories of depression and its risk factors during the final stage of the pandemic. Interestingly, the majority of participants who reported loneliness were younger adults, which contrasts with the prevalence of loneliness observed before the pandemic. A recent meta-analysis based on pre-pandemic data from European countries revealed a consistent geographical pattern across all adult age groups. In Southern European countries, the rates of chronic loneliness were 5.4% (4.1% to 7.1%) for young adults and 15.7% (13.2% to 18.7%) for older adults (Surkalim et al., 2022). Our study's findings indicate a reversal of this pattern during the pandemic.

Furthermore, individuals with high levels of loneliness demonstrated a lower likelihood of improvement compared to those in the group with medium levels of loneliness, which could be attributed to the higher prevalence of chronic loneliness in the former group. Chronic loneliness is less responsive to changes in the individual's social environment and is closely associated with depressive symptoms and challenges in social cognition (Martín-María et al., 2021; Masi et al., 2011). On the other hand, individuals with medium levels of loneliness may have more transient and situational feelings of loneliness, which offer better prospects for improvement and are more responsive to changes in the social environment, such as the easing of mobility restrictions at the end of the pandemic period.

4.1. Strengths and limitations of the study

The strengths of our study include the use of a large, nationally representative sample of Spanish adults and longitudinal data that allowed us to evaluate changes from two timepoints that correspond with a decrease in the socially disruptive measures to stop the spread of COVID-19. However, several limitations of our study deserve consideration. First, since the association between loneliness and mental disorder symptoms is bidirectional, our statistical model did not include those with loneliness as an outcome. However, according to previous research, the association between loneliness and mental disorders is stronger with loneliness as the cause (Domènech-Abella et al., 2018). Second, our data are based on self-reporting, which may result in recall or reporting bias. Nevertheless, in our study, the recall periods were short and well-defined, which should minimize recall bias. Third, although the study used validated measures with acceptable internal consistencies, the measures of loneliness, depression, and anxiety are all short or screening measures, which reduces the information they can provide. Fourth, our study focused on a period of 6 months which prevents making predictions about medium- and long-term changes in the detected trajectories. Finally, the group-based trajectories models were constructed for two time points, and they could be not enough to detect all potential trajectories. Future studies should investigate whether risk factors, patterns of loneliness courses, and their impact on mental health remained over the medium and long terms.

5. Conclusions

The primary objective of the present study was to confirm that the COVID-19 pandemic has brought about modifications in loneliness distribution patterns across different age groups and to evaluate the courses of loneliness and their influence on mental health during the final stage of the pandemic. According to our results, younger adults constitute the minority in the invariant low loneliness course (36.9% vs. 57.0%), while they make up the majority in the decreasing medium loneliness course (56.2% vs. 41.6%) and the fairly invariant high loneliness course (6.9% vs. 1.4%) when compared to the older age group. Although both unfavorable courses display a decreasing trend and positively impact mental health improvement, the fairly invariant high loneliness course maintains a relatively low level of decrease. Consequently, its effect on alleviating symptoms of depression and anxiety is proportionally lower compared to the decreasing medium loneliness course, thus highlighting the disparity of the effect on mental health between these courses. Among remaining risk factors considered, the presence of a pre-pandemic mental disorder stands out. Participants with this condition are also in the majority in the decreasing medium loneliness course (52.9% vs. 40.4%) and the fairly invariant high loneliness course (10.1% vs. 1.0%).

Future studies should validate whether the newly observed loneliness patterns across age groups persist and assess the evolution of loneliness courses and their impact on mental health, with particular attention given to young adults and individuals with pre-existing mental disorders..

Contributors

The study design was made by JD-A, HG-M, AG-P, MF-N, PM, GV, BO, JA, and JMH. JD-A conducted the data analysis. JD-A, HG-M, and

AG-P drafted the article. JMH and JD-A supervised the data analysis and development of the paper. The paper was edited and reviewed by all the authors.

Data availability statement

Data will be made available upon request made to the corresponding author.

Declaration of Competing Interest

The authors declare that they have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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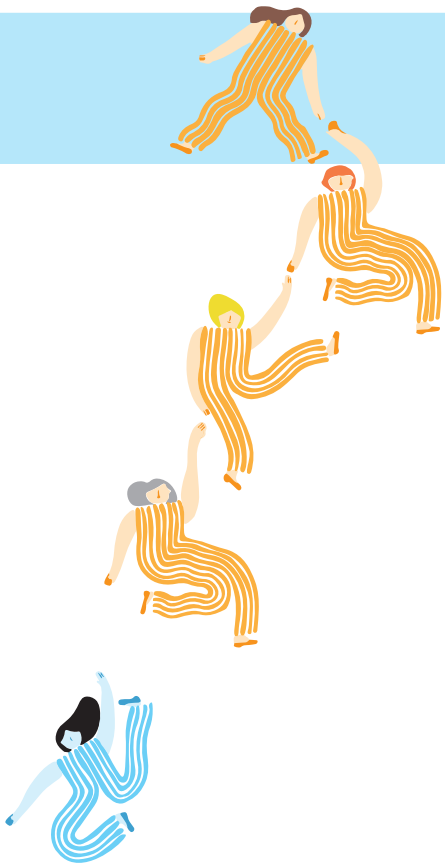
DISCUSSION



4.1. Summary and interpretation of findings

The results of the present thesis provide evidence on the role of subjective and objective aspects of social relationships on MDD, as well as the impact of the COVID-19 pandemic on this association. We used representative samples of the Spanish population and employed well-validated measures of loneliness and social support concerning the subjective and objective aspects of social relationships, respectively. First, we analysed potential moderating and mediating effects of these two constructs on the course of MDD (see Section 4.1.1). Furthermore, we examined changes in MDD risk during the pandemic according to age group (see Section 4.1.2). Based on our findings, loneliness significantly increases the risk of a worse MDD course and is one of the main mediating factors explaining a higher incidence of MDD among younger adults during the COVID-19 pandemic. While social support demonstrates a high capacity to reduce feelings of loneliness in individuals with depression, it does not represent a significant mediator explaining the higher incidence of MDD during the pandemic.

We also examined whether age and loneliness influenced the association between PPMD and depressive symptoms during the pandemic (see Section 4.1.3). As anticipated, younger individuals with PPMD reported higher levels of loneliness. However, contrary to our hypothesis, the impact of loneliness on depressive symptoms was lower in these cases.

Finally, we explored trajectories of loneliness during the pandemic (see Section 4.1.4). According to our results, approximately 6% of the

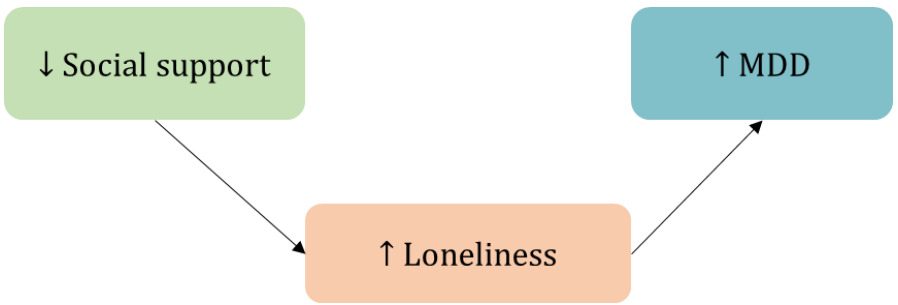
population maintained high levels of loneliness and depressive symptoms during the late stages of the pandemic.

4.1.1. Social support, loneliness, and the course of major depressive disorder

Our longitudinal study followed 404 adults over a 7-year period (2011 – 2018) of the 'Edad con Salud' 2011 cohort (292). In Article I we identified loneliness as a mediator between social support and MDD, therefore confirming that social support and loneliness not only influence MDD incidence, but also its course (Figure 9). Participants had MDD at baseline, and subsequent evaluations of MDD were conducted in two additional waves, spaced at intervals of 2-3 years. Thus, having MDD in the subsequent wave could be either due to a relapse following remission, a recurrence following recovery, or the persistence of a chronic course with an unremitting diagnosis of MDD.

Figure 9

Scheme of the mediation model of the association between social support and MDD course with loneliness as the mediator



Our results confirm previous literature that identifies loneliness and poor social support as risk factors for MDD incidence (293,294). Loneliness has been linked to depression onset (295), severity (296), and recovery (145). Lee et al. (296) published a study in which they also followed a cohort of individuals aged 50 years or over and found that higher levels of loneliness at baseline were associated with greater severity of depressive symptoms over a 12-year follow-up period, even after adjusting for related social factors, genetic predispositions, and other demographic and health-related variables. The study estimated that 11-18% of depression cases could potentially be prevented if loneliness was eliminated. Loneliness has also been reported before as a mediator in the psychological pathways between social support and depression (297,298), which is supported by our results. Thus, a substantial body of prior literature corroborates the risk effect of loneliness on depression. However, most studies primarily concentrate on the incidence of depression, underscoring the significance of our investigation, which delves into its effects on the course of MDD—an area notably sparse in existing literature.

The risk of recurrence following a first episode of MDD is estimated to be 3 to 6 times higher than the risk in the general population (299). Hardeveld et al. (300) review about predictors of recurrence of MDD found that the evidence for lack of social support as a predictor of MDD remission was still inconclusive. Studies including loneliness as a potential predictor have focussed on clinical cohorts (e.g., ambulatory patients) limiting generalizability (301,302). Nuyen et al. (303) using a representative sample of the general population, identified loneliness

as an adverse prognostic factor for the course of common mental disorders (CMD; i.e., mood, anxiety, and substance-use disorders), including MDD assessed with the CIDI. However, the study did not stratify the findings by each specific CMD. Consistent with our results, they found that when controlling for perceived social support at baseline in adults with CMD, the association between loneliness and subsequent persistent severe CMD disappeared. Van den Brink et al. (304) looked specifically at MDD course and reported that the predictive values of the effect of social support and loneliness on MDD course overlapped. These studies suggested concurring adverse effects of loneliness and perceived social support on the course of MDD, but could not disentangle the interwoven of these relationships. Therefore, our study provides novel understanding of the factors causally implicated in MDD course and opens a window of risk factors that can be targeted in prevention. According to our results, social support leads to subsequent loneliness, which in turn affects MDD course. A prompt identification and intervention of feelings of loneliness on individuals with MDD could improve their prognosis. Further, enhanced social support among adults with MDD could potentially mitigate feelings of loneliness, thus acting as a protective measure against the recurrence or persistence of MDD.

Previous studies have reported a longitudinal and bidirectional association of loneliness with depression (238,298,303), suggesting that depression may lead to greater social withdrawal, or alternatively, that social networks may be less inclined to maintain contact with individuals exhibiting MDD. Even so, our results did not support the

relation of MDD with subsequent feelings of loneliness or lower social support and therefore, we could not confirm this bidirectionality. Nevertheless, prior research has also indicated a unidirectional nature of these associations (242). Moreover, it has been suggested that the relationship between loneliness and depression is stronger when loneliness is considered as the origin (74,242), which is in line with our findings.

Loneliness has physical and cognitive health implications that may impede social interactions (127,295). Furthermore, as proposed by the ETL (155), the implicit hypervigilance of lonely individuals may induce further social withdrawal. Consequently, we would expect an association between loneliness and subsequent weaker social support, which was not found in our study. Perhaps conducting a longer-duration study could facilitate the observation of this association. Nonetheless, to the best of our knowledge, this association has mostly been reported in the direction of social support leading to loneliness (244), and in samples of the general population instead of individuals with MDD, which may be due to either limited analysis of the reverse direction in such population or non-publication of non-significant results.

Therefore, Article I provides new insights on the potential pathways of social support and loneliness on MDD. It also laid our groundwork to better understand the role of social relationships on MDD course and served as a starting point for the investigation of the impact of the COVID-19 pandemic on these factors, extending our focus to the general population across all age groups.

4.1.2. Age differences in MDD changes during the COVID-19 pandemic

At the beginning of the pandemic, scientific literature agreed that there had been a moderate increase in depressive symptoms, but most studies at that time were cross-sectional (272,305–307), showing a need for studies comparing the figures with pre-pandemic values. In Article II, using the 'Edad con Salud' 2019 cohort (292), we analysed a representative sample of the general population of 1,880 adults residing in the provinces of Barcelona and Madrid who were interviewed face-to-face in 2019 and during the COVID-19 lockdown in 2020 by telephone.

The prevalence of MDD before the pandemic in our study was slightly lower that the annual prevalence in Spain, which is 4.7% (4). In our study, the prevalence of MDD more than doubled, from 3.4% before the pandemic to 9.5% during the pandemic, confirming the peak at the beginning of the pandemic reported by previous literature. In Article II, MDD prevalence before the pandemic referred to the previous 12-months, while the measure during the pandemic referred to the previous 30 days, to cover specifically the pandemic period. Therefore, the shorter recall time could potentially underestimate this prevalence.

Moreover, our study confirmed a differential impact of the pandemic by age group on the probability of having MDD, when compared with pre-pandemic values. Among younger age cohorts the risk of having MDD, expressed in beta coefficients, increased significantly from 0.04 to 0.25 for those aged between 18 and 29 years, and from 0.02 to 0.11 for those aged 30 to 44 years, while MDD risk remained stable for older

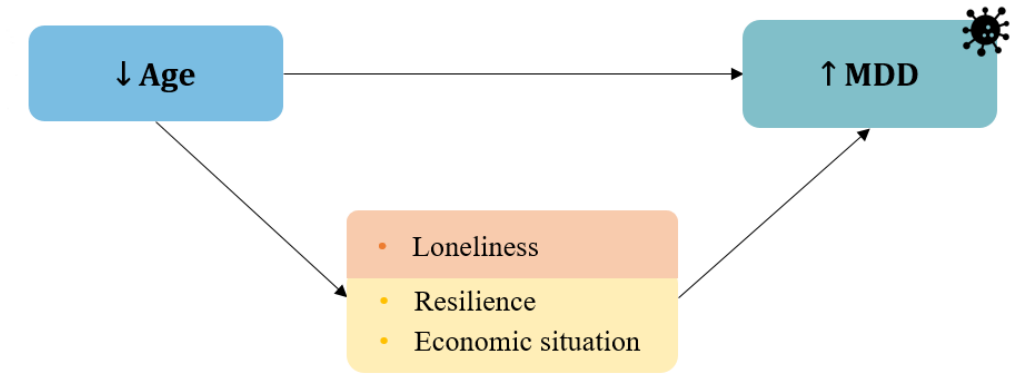
age groups. These results were confirmed in other countries by a systematic review of longitudinal studies about the global prevalence of MDD due to the pandemic (263)). This review also reported a higher increase in MDD prevalence due to COVID-19 among females, which was not observed in our study.

Mediating factors in the age - MDD association

We identified economic situation, loneliness, and resilience as potential variables explaining almost 40% of the increased risk of MDD in young people during the pandemic (Figure 10). Compared to pre-pandemic values, younger individuals (18 - 29 years) had higher odds of feeling lonely, having poor social support, low resilience, a worse economic situation, and unemployment due to the COVID-19 pandemic. Nonetheless, neither social support nor unemployment were significant mediators in the assessed relationship.

Figure 10

Scheme of the mediation model of the association between age and MDD



Previous studies had already reported that younger adults were a high-risk group for loneliness and lower social support (271,308–311). Age emerged as a protective factor against mental disorders and loneliness amid the pandemic. Middle-aged and older adults likely benefited from established, emotionally fulfilling relationships that may had remained relatively stable during the pandemic. Conversely, younger individuals, as suggested by the socioemotional selectivity theory (173,205), typically prioritize expanding their social networks, engaging in diverse interactions, and setting new life goals, aspects that were significantly disrupted by the pandemic's social restrictions. The pandemic deprived many students of the traditional opportunities for socializing, such as in-person classes and university activities, forcing them to remain isolated and impacting on their social development. For some, these disruptions may had occurred at a critical time in their lives, just as they were emancipating and establishing relationships beyond the family circle. The shift to online learning and potential job losses may have compelled some to return to their family homes. The forced and abrupt change to remote work disrupted habituated social relationships at work and increased social isolation and feelings of loneliness for some employees (312). It also increased time spent on social media (313), which could have had detrimental effects on young people, as limiting social media to approximately 30 minutes per day has been reported to decrease loneliness and depression (314). In addition, Cho et al. (315) found negative effects of social media use during the pandemic lockdown, particularly when it led to increased liability, where individuals felt obligated to provide support to others. This was

associated with negative cognitive appraisals and emotional responses. Nevertheless, the study also reported potential positive effects of social media use when it served as a source of social support, reducing feelings of anger, anxiety, and loneliness.

Interestingly, in our sample, although young people had a higher risk of having poor social support during the pandemic, it was not identified as a significant mediator in the relationship between age and MDD. This could be explained by the fact that the pandemic may have had a more significant effect on subjective factors of social relationships, such as loneliness, rather than on objective ones like social support, which may not have been as directly affected. In fact, Article I, with pre-pandemic data, indicates that loneliness is a mediator between social support and depression, suggesting that social support may influence depression through loneliness. Indeed, during the pandemic, social support was identified as a moderator in the relationship between loneliness and mental health (316).

Our results also align with studies focusing on resilience carried during the pandemic (290,316,317). Resilience involves adapting to changes and overcoming difficulties while maintaining high levels of functioning. It is acquired through strategies learned from effectively managing previous complex situations, which enhances individuals' ability to cope with future stressors and challenges. Research suggests that people accumulate resources over time to combat life’s challenges (318). Hence, people with life experience are likely to have acquired more resources to confront a pandemic, making them more resilient. Conversely, the pandemic and its associated adverse consequences

were overwhelming and highly stressful for many young people, who may have lacked sufficient resources and resilience.

In our study, younger adults were at higher risk of unemployment and a worse economic situation during the pandemic, which was also reported in other countries (319,320) and in Spain (277,321). Even before the pandemic, there was an escalating trend of labour precarity in Spain, characterized by increasing temporariness, underemployment, low remuneration, and diminished job security. This phenomenon disproportionately affected vulnerable groups, such as young individuals in the transitional phase of first entering to the formal workforce (321). Previous economic recessions had shown that the first to lose their jobs are workers with the most precarious occupations (322), facing young individuals a heightened economic vulnerability, with increased reliance on familial support, and exacerbated challenges in housing affordability. Moreover, young adults more frequently work in the service sector (323), which was forced to close during the lockdown and re-open later but with capacity limitations, thus requiring less staff. Additionally, young people benefitted less from the temporary work suspension, known as 'Expedientes de Regulación Temporal de Empleo' or 'ERTE' in Spain, with lower rates of re-entry into active employment compared to other age groups (277,323). Alternatively, older adults experienced less financial strain from the pandemic and had greater resources to cope with it. Middle-aged adults usually have more stable jobs and most individuals in the 65+ age group were already retired and thus not affected by layoffs. A worse economic situation mediated the association between age and MDD, while

unemployment was not a significant mediator. This may be due to young people facing financial struggles despite retaining employment, as they may have experienced reductions in working hours and salaries (324). Furthermore, the increasing delay in emancipation and the declining rate of home ownership among young people in Spain have left many individuals economically dependent on their parents' employment status. Finally, it's important to recognize that financial hardships not only contribute to depressive symptoms but also hinder access to adequate mental health care.

4.1.3. Pre-pandemic mental disorders, loneliness, and MDD during the pandemic

We conducted a cross-sectional study (Article III) with a representative sample of the Spanish population including 2,000 participants interviewed by telephone during the pandemic's last state of emergency (25/10 – 09/05/2021) as part of the second wave of the MINDCOVID study (325). We investigated whether the association between age, loneliness, and depression differed in individuals with and without PPMD, as some studies were beginning to suggest that it could be a key factor in understanding the various effects of the pandemic on the population's mental health.

In line with our previous studies, we found that age was negatively related with loneliness and depressive symptoms, showing that younger individuals were at higher risk of loneliness and MDD during the pandemic. Additionally, loneliness was identified as a mediator on

the association between age and MDD during the pandemic, confirming our results in a distinct yet equally representative sample of the general Spanish population.

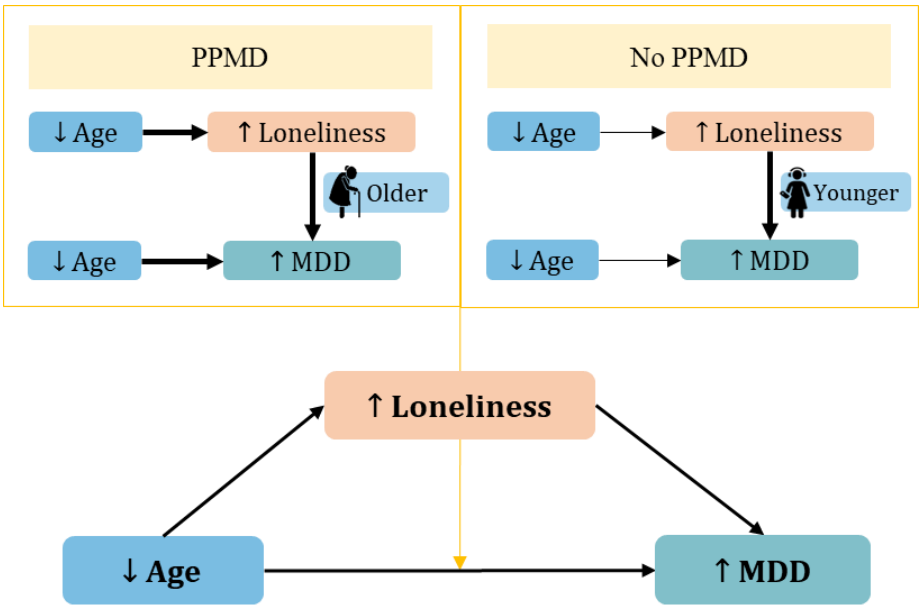
Moreover, loneliness was identified as a moderator on the association between age and depression depending on the presence or absence of PPMD. The main findings regarding the effects of PPMD were that both the relationship (i) between age and loneliness and (ii) between age and MDD are stronger in people with PPMD, and (iii) the relationship between loneliness and MDD is stronger in younger individuals without PPMD and in older individuals with PPMD (Figure 11).

The association between younger age and higher levels of loneliness was stronger in those with PPMD, suggesting an increased vulnerability of the young population with PPMD to loneliness. Previous studies have observed that people with mental disorders report more usually being lonely than individuals without them (145,301), but without specifying age differences. During the pandemic the same pattern was observed, with a study across four European countries reporting that between 20% and 50% of individuals with a prior history of mental illness experienced elevated levels of loneliness during the initial months of lockdown. Those younger than 30 years of age reported the highest levels of loneliness (310), although the combined effect of both characteristics was not studied.

Moreover, our findings showed that the association between younger age and a higher likelihood of MDD was stronger in individuals with PPMD. This could be explained by those having PPMD being at

Figure 11

Scheme of the moderation model of loneliness depending the presence/absence of PPMD on the association between age and MDD



Note. The thickness of the arrow indicates the magnitude of the association (e.g., the association between age and loneliness was stronger in individuals with PPMD (left) than in those without them (right)). PPMD = Pre-pandemic mental disorders; MDD = Major depressive disorder.

increased risk of worsening during the pandemic, potentially due to factors such as a higher susceptibility to COVID-19-related stressors (e.g., fears of danger, virus infection, and adverse economic consequences), as well as traumatic stress symptoms correlated with COVID-19 (326,327), all of which were linked to COVID-19-related stress and depression during the pandemic (328–330). Additionally, individuals with PPMD may have a heightened genetic and/or environmental vulnerability to mental health issues. They may also had

faced challenges such as poorer coping abilities, disruption of daily routines due to lockdowns and mobility restrictions (331–333), and interruption of their usual mental healthcare services, psychological treatments, and social support networks (334,335). These difficulties may have been exacerbated by already under-resourced and disorganized mental health systems, along with disruptions in services at the onset of the pandemic (336,337).

Despite several studies reporting no differences in the pandemic's impact on psychiatric patients compared to the general population (281,333,338), these studies did not stratify their results by age range or just distinguished two age groups (e.g., children vs adults; under 50 vs over 50 years) which can hinder detecting results by age. Moreover, individuals with PPMD generally exhibited higher levels of depression, loneliness, and COVID-related fear during the pandemic, making any changes in symptoms more impactful (326–328). These characteristics that made individuals with preexisting disorders more vulnerable to loneliness during the pandemic are also, in many cases, shared by the younger population, such as poorer economic conditions and lower resilience, as we have found in our studies.

Conversely, among those without PPMD, loneliness had a greater impact on mental health among younger adults, likely due to the factors detected and discussed previously regarding younger adults feeling more isolated due to the social restriction measures and lower resilience. However, among individuals with PPMD, loneliness had a stronger impact on older adults' mental health. Older adults with mental disorders already had reduced social circles and higher odds of

living with frailty or multimorbidity (339,340). The inability to access healthcare services during the pandemic, in addition to being subjected to stricter isolation measures due to their status as a vulnerable population (332), and the discontinuation of mental health therapy or dissatisfaction with virtual therapy (341,342), may had further contributed to a heightened sense of isolation within this population, thereby exacerbating feelings of loneliness and depressive symptomatology.

4.1.4. Trajectories of loneliness at the end of the pandemic

The COVID-19 pandemic and the measures taken to mitigate it have been linked to worsened mental health in both cross-sectional and longitudinal studies. Yet, it remains uncertain whether this signifies an adaptive reaction to a short-lived, unprecedented event or the onset of prolonged mental health issues that may last beyond the initial outbreak of the pandemic. To assess whether the changes in loneliness and MDD by age persisted after the states of emergency, we analysed the second and third waves of the MINDCOVID study (325) in Article IV. We used data of 2,000 participants who were interviewed between February and March 2021, during the last state of emergency in Spain, and 953 participants who were again interviewed between November and December 2021, when the state of emergency and the social restriction measures had ceased. Our study identified three distinct courses of loneliness: (i) ‘invariant low loneliness’ (42.6% of the sample), (ii) ‘decreasing medium loneliness’ (51.5%), and (iii) ‘fairly

invariant high loneliness' (5.9%). All courses presented an improvement in mental health (i.e., depressive and anxiety symptoms) after the release of the pandemic's social restriction measures, although such improvement was minimal for the 'fairly invariant high loneliness' course. This course had the higher loneliness scores and reported the higher levels of depressive symptoms. 7% of younger adults followed such course, which is double the proportion observed among middle-aged individuals and five times higher than that reported by older adults. Additionally, younger adults reported elevated levels of depression and anxiety throughout the pandemic, especially when compared to older adults. Other factors associated with unfavourable loneliness courses were being female, unmarried, having PPMD, or having a lower education level. These findings corroborate our prior research, underscoring the significance of younger age, loneliness, and PPMD as pivotal factors influencing MDD both during the pandemic and even after.

We conducted a study about chronic and transient loneliness in western countries (343), and found that out of the 10.6% of the sample who had loneliness, 5.6% was transient (53% of loneliness cases) and 5.0% was chronic (47% of loneliness cases). These agrees with previous population studies indicating that nearly 50% of loneliness cases are chronic (344,345). In our study, individuals experiencing loneliness were significantly predominant, representing a 57% of the total sample, a value much higher than the 5-20% loneliness prevalence usually reported in Europe (161). However, when we looked at the type of loneliness that participants exhibited, we observed that chronic

loneliness was similar to the percentages reported in previous studies (i.e., 5.9% of the sample pertained to the 'fairly invariant high loneliness' course), but transient loneliness was much higher (i.e., 51.5% in the 'medium decreasing loneliness' course). This suggests that the increase in loneliness is largely due to transient cases resulting from the pandemic, with both loneliness and depressive symptoms expected to diminish gradually over time. Nevertheless, those in the 'fairly invariant high loneliness' had a chronic loneliness course less responsive to changes in their social environment, which has previously been related with depressive symptoms and challenges in social cognition (346,347). Therefore, our research indicates that loneliness and depressive symptoms stemming from the COVID-19 pandemic were not solely an immediate reaction for some individuals (i.e., young people and individuals with PPMD), but could potentially imply the beginning of a persistent issue that extends beyond the pandemic.

Research about loneliness across the life span has reported mixed results regarding the relationship between age and loneliness. Some suggest a linear relationship in both directions (163,348,349), but most studies propose a complex non-linear relationship resembling a U-shaped distribution with higher prevalence of loneliness in adolescence and old age, and lower levels in middle-aged adults (166–169,350). A study distinguishing between loneliness types, found that emotional loneliness followed a U-shape distribution, while social loneliness was stable across adulthood and dropped in later stages of life (351). Our findings do not contradict these results, but they do suggest a more pronounced increase in loneliness among younger individuals, which

contrasts with a recent meta-analysis using pre-pandemic data that identified a consistent geographic pattern in Europe across age groups (161). According to this study, and as summarized in Table 1 (see Section 1.3), in Southern European countries, the pooled prevalence of loneliness among young adults was 5.4% (4.1% to 7.1%), while for older adults was 15.7% (13.2% to 18.7%). Thus, our findings suggest a reversal of this trend during the pandemic. Nevertheless, studies about loneliness across lifespan, although including huge representative samples, were mainly cross-sectional and a recent meta-analysis summarizing longitudinal studies attributed changes in loneliness to individual experiences, rather than age-related processes (352). Finally, our findings are in line with the data collected by the 'Observatory of Loneliness in Barcelona' in June 2020 (353), which indicate that 26.5% of young people in Barcelona aged 16 to 24 often or sometimes feel lonely, followed by adults aged 35 to 44 (20.7%) and individuals over 65 years old (18.7%).

Therefore, our findings suggest that the sociodemographic profile, particularly regarding age differences, of individuals experiencing loneliness has changed during the pandemic, and these changes have persisted beyond the cessation of restrictive measures. Subsequent research will be crucial to determine whether this shift persists.

4.2. Implications and psychosocial interventions

The COVID-19 pandemic has exposed and exacerbated problems that already existed before the pandemic related with the attention and care that mental health was receiving. Although the WHO had declared the prevention of mental disorders a priority due to its high prevalence and burden (354), it is estimated that governments spend an average of less than 2% of their overall health budgets on mental health (336). Moreover, it has been reported that recessions following economic crises are characterized by reductions in public funding for mental health care (355). Our mental health care system was saturated and overwhelmed during the pandemic, and although the Spanish government increased in 2021 the financial allocation to improve it and address the impact of COVID-19 (356), we still cannot determine if these measures are sufficient. Spain still lags behind compared to other European countries regarding the availability of healthcare professionals and infrastructures, as well as economic resources and appropriateness of mental healthcare. This is reflected by Spain being below the European average in the Headway 2023 – Mental Health Index, a multi-dimensional overview of the support provided by different countries to meet the mental healthcare needs of the population (357). We require a major investment in interventions, both at the clinical and community levels to prevent depressive symptoms from progressing to clinical depression and support the remission of those who have already recovered. An improvement of the social factors leading to MDD would alleviate the burden on the population.

The present study evidences the increased risk of MDD in young individuals (18 - 29 years) during the pandemic, partly explained by an increase in their feelings of loneliness. According to our results and regarding strategies to prevent depression, it is crucial to rebuild, enhance, and/or create social environments capable of mitigating the effects of the deterioration of social networks due to the pandemic, increasing social support and consequently reducing feelings of loneliness.

The effectiveness of interventions for loneliness has been shown to be moderately effective compared to control groups by several meta-analyses (347,358). One of the most powerful and highly cited meta-analyses in the field revealed that interventions on general population targeting maladaptative social cognition were the most effective (347). However, only 19 out of the 50 included studies evaluated interventions among adults with less than 60 years of age. A meta-analysis looking at interventions compatible with COVID-19 social distancing measures found that the most effective interventions were psychological therapies like mindfulness, lessons on friendship, robotic pets, and social facilitation software (359). Although this meta-analysis included all age groups, 51 out of the 58 included studies targeted older adults. Most meta-analyses to date on loneliness interventions are based on studies targeting the older population, thereby constraining the evidence available for younger populations. To our knowledge, only three meta-analyses have specifically been centred on the youth, but two also included samples of children and adolescents (age range: 3 - 25) (360,361), and the third one targeted a specific population (i.e.,

university students) (362). These meta-analyses results, together with results from studies on the general population, are in accordance with our findings, emphasizing that interventions that promote social support and increase social interaction, both virtually and in person, are associated with a reduction in the prevalence of loneliness (359,361–363). Additionally, in younger populations, psychoeducational interventions aimed at acquiring social and communicative skills have also proven effective (360,361), but only when accompanied by opportunities to enhance social connections (362).

The results of our research suggests that the type of loneliness (i.e., transient or chronic) should be considered when planning interventions. Surprisingly, to the best of our knowledge, no meta-analysis has explored yet this aspect as a potential source of the heterogeneity observed between intervention outcomes. Each form of loneliness is influenced by distinct risk factors and has varying impacts on health outcomes (344,345). Therefore, interventions should be tailored accordingly to effectively address the specific characteristics of each type of loneliness. Firstly, loneliness is a modifiable condition, and in many cases, especially when feelings of loneliness are transient, individuals may naturally desire to reconnect without the need for external intervention (154). Nevertheless, in some cases addressing transient loneliness may require interventions aimed at teaching emotion management and social skills, thereby facilitating effective coping with the experience, promoting successful reconnection, and preventing prolonged loneliness (364). In contrast, chronic loneliness, and its consequences, such as depression, tend to be more stable over

time and serve as risk factors for experiencing further relapses. Therefore, interventions targeting chronic loneliness should target the perceptual and cognitive biases that lead to heightened sensitivity to negative cues (152,238,365). This can be done through CBT, where individuals are encouraged to seek out evidence that challenges their perceptions of loneliness and enhances their sense of self-efficacy (152,347). The goal is to facilitate behavioural changes that promote greater social engagement and reduce feelings of loneliness (366). Additionally, we must consider that it is when we have poor social support that the relationship between loneliness and MDD is more robust, hence the delivery of these interventions through support groups or the promotion of social interaction will improve its effectiveness.

Finally, the findings of the present work also suggest that socioeconomic factors and psychological resilience could play a key role on the interplay of relationships between age, loneliness, and MDD. Consequently, we will now discuss some interventions that consider these variables.

DeTore et al. (367,368) performed a randomized clinical trial (RCT) of a resilience training intervention, designed to enhance emotional regulation, self-perception, and social interactions. The intervention showed promising results in increasing resilience and reducing feelings of loneliness (367) and depression (368), compared to the waitlist group. The 4-session program was aimed at young adults aged 18-25, particularly college students, exhibiting mild depressive symptoms and/or subclinical psychotic symptoms. The intervention was group-

based and employed techniques such as mindfulness, self-compassion, and mentalization through didactic material, experiential exercises, and group discussions.

Amidst the pandemic, Brog et al. (369) tested through a RCT an internet-based self-help intervention aimed at adults (mean age of 40 years) experiencing at least mild depressive symptoms and designed to enhance emotion regulation skills with CBT modules to address pandemic-related stress. Additionally, it included modules focusing on resilience strengthening and relaxation exercises. However, the intervention did not prove effective in reducing depressive symptoms nor loneliness, although it did show an increase in resilience. This intervention lacked a group-based aspect, which, according to our findings and as observed in DeTore's et al. RCT (367,368), would constitute a key element to reduce loneliness and depressive symptoms. In contrast, Brouzos's et al. RCT (370) of an online group intervention to mitigate the impact of the COVID-19 pandemic on the general population reported significant reductions in loneliness and depression, along with significant improvements in resilience. The contents of the intervention were based on positive psychology, and as Brog's et al. study (369), it included CBT components and aimed to promote participants' resilience and emotion regulation skills. These results further support that the group-oriented nature of the intervention could have promoted resilience and reduced loneliness through the provision of social support to participants. Furthermore, the findings of these interventions and the theoretical findings of the present thesis would suggest that targeting resilience and loneliness

during the pandemic might yield even greater outcomes in young individuals and those with PPMD.

We have been able to find interventions targeting loneliness and resilience in young populations with depressive symptoms, and although in the general adult population, interventions carried out online during COVID-19; however, none of them considered economic factors.

The economic situation of young individuals has emerged as a potential factor exacerbating loneliness and depressive symptoms during the pandemic. In general, direct economic interventions, such as money transfers, for example, have been heavily debated, and their success depends on economic context, gender, culture, and implementation type (371). They receive more support when the goal is more structural, such as welfare system policies in progressive economies that reduce disparities in mental health. Simpson's et al. review (372) indicates that policies aimed at expanding social security benefits are generally linked with improved mental health outcomes and reduced inequalities. Conversely, austerity-driven reductions in social security policies can adversely impact population mental health, particularly among more vulnerable societal groups who are also experiencing the disproportionate effects of the pandemic. In the Spanish context, the austerity policies implemented after 2008 financial crisis were associated with adverse outcomes on mental health (373,374). We also need to consider that economic struggles extend to housing payments, worsened by rising rental and purchase prices over the past decade in Spain. A quarter of young individuals in the city of Barcelona faced

housing payment challenges due to the COVID-19 pandemic (321). A review about the relationship between publicly subsidised housing and depression found varied evidence, contingent upon factors such as the type housing subsidy program, type of housing assistance, housing stability, and neighbourhood quality (375). Nevertheless, Reeves et al. (376) reported that reductions in housing assistance led to a higher prevalence of depressive symptoms in the United Kingdom (UK), so further research should explore its consequences. Considering the multitude of pathways through which poverty and financial strain affect social determinants of mental health, interventions and public health campaigns targeting population mental health enhancement should also tackle poverty. Neglecting this crucial aspect may significantly impede the effectiveness of these initiatives (377). Therefore, there is an urgent need for targeted policy interventions to mitigate youth unemployment, enhance labour market and housing opportunities, and address socio-economic disparities, ultimately fostering greater resilience and well-being among youth population.

4.3. Strengths & limitations

Although the strengths and limitations of the studies included in this thesis have been outlined in each of the published articles, we believe it is convenient to summarize the main strengths and weaknesses of this work.

Sample

One of the main strengths of this thesis lies in its utilization of data derived from large nationally-representative samples of the Spanish population, facilitating the generalizability of our findings within this context. To ensure good representation across major sociodemographic groups, post-stratifications corrections were applied to weights to restore the distribution of the adult general Spanish population according to age, sex, and geographic area, while also compensating for survey non-response.

Nevertheless, the sample used in the longitudinal study to investigate the relationship between age and MDD before and during the pandemic is a sample from the two largest provinces in Spain (Barcelona and Madrid), thereby restricting the generalizability of findings to these regions.

Study design

Three of the studies included in the present thesis employed longitudinal designs, except for one cross-sectional study (Article III). In the case of our study on the longitudinal association between social support, loneliness, and MDD in older adults (Article I), the sample had a lengthy 7-year follow-up period with three assessments. Then, our longitudinal examination of the association between age and MDD and potential mediators (Article II), studied the same sample before and during the pandemic, which provides rich data to assess the impact of the pandemic on this relationship. Finally, Article IV investigated

loneliness trajectories, conducting an initial assessment during the pandemic and a follow-up 9 months after, allowing for the exploration of changes following the end of the social restriction measures.

The predominant use of longitudinal designs across these studies enables the evaluation of the direction of relationships. However, it's important to acknowledge the limitations inherent to this approach, particularly the inability to adjust for all potential confounders that may influence exposures or outcomes, potentially introducing bias. Despite this limitation, our studies incorporated a comprehensive range of variables to adjust for the primary known confounders associated with each outcome, thereby enhancing the robustness of our analyses.

Variables

The assessment of variables in our studies relied predominantly on standardized questionnaires which have been previously validated in the Spanish context and in other countries, ensuring consistency and comparability across different samples and settings. However, the use of self-reported measures, despite being validated, introduces the possibility of report and recall bias. Report bias may affect the reliability of certain variables and influence the overall outcomes. To mitigate recall bias, we implemented short and well-defined recall periods. We acknowledge that self-reported measures may introduce more measurement error compared to clinical interviews, particularly in the case of assessing sensitive topics, such as mental health. Interviews were conducted by trained lay interviewers using structured diagnostic

interview techniques, both face-to-face and via telephone, with the latter potentially introducing more social desirability bias (378). However, the use of variables and tools previously validated and employed in other studies enhances the robustness of our findings, allowing for comparisons and contributing to the overall strength of our results.

Regarding the measures to assess MDD, depressive symptoms manifest along a spectrum, and measures of these symptoms capture the range of severity, thereby bolstering statistical power and reducing observer bias. However, structured instruments like the CIDI or PHQ-9 may force complex experiences into fixed-choice interview formats, potentially constraining the depth of exploration. Furthermore, our assessment of loneliness, through the 3-item UCLA scale, may have limitations in capturing nuances between emotional and social loneliness. Alternative scales, such as the De Jong Gierveld scale, although requiring more administration time due to their length, they have the potential to offer a more nuanced separation of these factors, facilitating comprehensive comparisons.

Finally, despite our efforts to incorporate key behavioural, material, and psychosocial factors as mediators, limitations persist in not including all potential variables outlined in the literature, which could have influenced our results, and residual confounding may exist due to unaccounted potential confounders, underscoring the need for cautious interpretation of our findings.

4.4. Future perspectives

Understanding the changes in populations particularly susceptible to loneliness because of the pandemic, and the necessity to determine whether the mental health effects on vulnerable individuals will persist after the pandemic, presents a challenge that demands the implementation of effective measures. The present study has identified loneliness, social support, resilience, and economic factors as modifiable variables that could serve as potential targets for preventing MDD and improving its course. Moreover, interventions need to be tailored according to age groups. We have observed that during the pandemic, and likely thereafter, young adults faced academic, familial, social, financial, and health-related challenges, highlighting the unique vulnerability of this demographic during a crucial period for their interpersonal development, education, and professional advancement. Nonetheless, future longitudinal studies with longer follow-up periods in Spain and other countries are needed to validate our findings over the long term and in diverse contexts. This is particularly important given the varying impacts of the economic and social crises resulting from the pandemic on different countries.

Paradoxically, despite the younger generation's heightened connectivity through online platforms during the pandemic, they experienced a disproportionate impact on loneliness. This implies that the social requirements of young people, which rely on a greater, more diverse, and frequent relationships (205,206), were not adequately met by the available online resources. Lee's et al. (379) meta-analysis

revealed that the excessive use of social media platforms was related with an elevated probability of experiencing depressive symptoms during the pandemic. Draženović's et al. review (380) reported the same association but identified a couple of studies that documented potential positive outcomes of social media use, such as offering support in managing stress and fostering a feeling of connection. Hence, it is imperative to incorporate online social relationships into the examination of social interactions and their impact on mental well-being. This necessitates the adaptation of existing theories to accommodate this increasingly prevalent mode of communication among younger adults, who, despite engaging in such interactions, have not been immune to experiencing heightened feelings of loneliness and depressive symptoms amidst the pandemic.

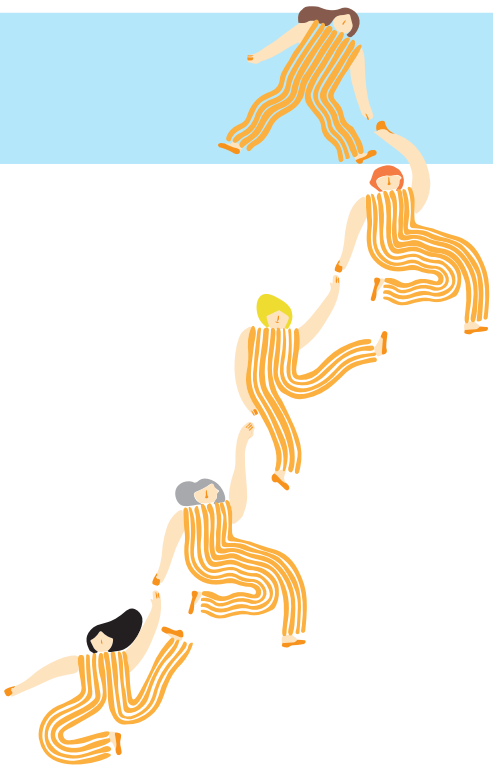
Additionally, improving accessibility to public psychological care is essential. The inadequacy of resources allocated to mental health care within the Spanish national healthcare system has promoted the growth of the private sector in this area of assistance. As a result, 8 out of every 10 psychiatric consultations are conducted within the private sector (381). Our findings indicate a heightened vulnerability among individuals with poorer economic circumstances, who may not have the means to afford private psychological services. This further widens the social gap and inequality in access to services, as only those who can afford it will be able to receive the necessary attention (381). In Spain, there are 6 clinical psychologists per 100,000 inhabitants in the public system, and the number of psychiatrists is less than half the average found in other European countries (381). This shortage means that an

appointment is not within reach for many patients who would need it. Moreover, once treated, sessions last only half an hour and are often spaced out over a month and a half. Additionally, individuals who do not access specialized psychological care services are treated by primary care physicians, who are already overwhelmed and lack the resources and time to address psychological issues. Faced with the impossibility of referring patients to therapy, they often end up prescribing anxiolytics, consuming tranquilizers one out of ten Spaniards (382). UK's national health system has designed a plan to implement social prescribing aiming to improve health outcomes and reduce healthcare workload (383–385). Social prescribing connects individuals to non-medical supports in the community. However, despite policy support, research on its implementation and impact remains limited and inconclusive (386), so further studies evaluating its impact are necessary to attract its implementation in other healthcare systems.

Interventions offering social support, targeting feelings of loneliness, and improving resilience among young adults, with a special focus on those with economic disadvantages, females, and those with PPMD, have important implications for public health planning and intervention strategies. Psychosocial interventions as described in the previous section, are non-pharmaceutical approaches that, unlike individual psychotherapy, can reach more people. Furthermore, these interventions promote the creation of new social support networks, which can serve as an accessible resource in the absence of formal mental health and social care services, fostering enduring supportive

relationships between individuals. Besides, within close relationships, support provision tends to be bidirectional, and research has shown that providing support is beneficial too for both physical and mental health outcomes (387–389). Consequently, social interventions benefits are not only for the individuals targeted by the intervention, but also extend its positive effects to the social connections formed as a result, expanding its impact beyond the initially targeted population.

CONCLUSIONS



Following the proposed hypotheses and based on the findings of the present thesis, we can conclude:

1. Individuals with poor social support and loneliness have a worse course of major depressive disorder.
2. Loneliness is as a mediator in the relationship between social support and major depressive disorder course.
3. Unlike older adults, the younger age groups had the higher risk of major depressive disorder during the COVID-19 pandemic compared to pre-pandemic levels.
4. The increased risk of major depressive disorder among the young was partly explained by younger adults experiencing increased loneliness, a worsened economic situation, and being less resilient during the pandemic.
5. Younger adults with pre-pandemic mental disorders were the most affected by loneliness during pandemic.
6. The impact of loneliness on depression during the pandemic was higher among younger adults without pre-pandemic mental disorders than among those with them.
7. Although the end of COVID-19's social restrictive measures meant a decrease in loneliness and therefore in depressive symptoms for many, some still maintained high levels of loneliness and depressive symptoms.
8. Being younger, with pre-pandemic mental disorders, and female were risk factors for experiencing chronic courses of loneliness after the pandemic.

These main findings suggest that public health agendas may benefit substantially by incorporating interventions to prevent and improve the course of major depressive disorder by targeting social support, loneliness, and resilience with a focus on vulnerable populations such as younger adults, those with financial strain, and those with a pre-existing psychiatric condition. More research on interventions on younger adults is imperative, as most interventions targeting loneliness have been tested in the elderly. And lastly, interventions need to be accompanied by public policies promoting structural economic changes targeting health inequality. Failure to implement structural changes following research and interventions may impede our capacity to effectively reach vulnerable populations and achieve enduring, sustainable impact.

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