Vaccine 45 (2025) 126591

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Mental illness and antibody responses after COVID-19 vaccination in a prospective population-based study in Catalonia

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ARTICLE INFO

Keywords:
COVID-19 vaccine
mood affective disorders
depression
IgG
IgA
genetics

ABSTRACT

Background

Mental illnesses have been overlooked as a potential factor influencing antibody responses to COVID-19 vaccine. Associations between mental disorders and antibody response might vary by specific disorders, depend on the long-term course of the illness and relate to psychotropic treatment.

Methods: The association between mental illness diagnoses (mood affective disorders, anxiety disorders, other) over ten years and psychotropic drug prescription based on electronic health records with antibody levels (IgG and IgA) post COVID-19 vaccination was assessed in 939 vaccinated adults from Catalonia, Spain. We employed linear regression models to assess associations between specific mental illnesses and psychotropic drugs with antibody levels, correcting for demographics, comorbidities and lifestyle factors. In a genotyped subset ($n = 247$) we assessed the effect of polygenic risk scores (PRS) for mental illnesses and performed a two-sample mendelian randomization (MR) analysis to examine causality between mental illness and antibody responses.

Results: Mood affective disorders were associated with lower IgG to receptor binding domain (RBD) [percentage change = −26.37 (95 % CI, −42.00, −6.54)]. Diagnosis of anxiety disorders was not associated with the outcome. The group of other diagnoses (mainly including insomnia and nicotine dependence) were associated with lower IgG RBD levels [percentage change: -21.53 (95 % CI, −35.38, −4.71)] and recent onset cases (≤5 years ago) showed greater decline in antibody levels. Participants on second-generation antipsychotics and multiple classes of psychotropic drugs in the last 6 months exhibited lower antibody levels. In the genotyped population, higher genetic liability (higher PRS) to schizophrenia was associated with lower IgG RBD levels [percentage change = −35.49 (95 % CI, −56.55, −4.23)]. MR analysis revealed a causal relationship between major depression genetic instrumental variables and lower IgG RBD and S levels.

Conclusions: These findings raise concerns about the efficacy of COVID-19 vaccines and potentially of other vaccines as well, in individuals with mood affective disorders, current/recent insomnia and nicotine dependence and people on multiple psychotropic drugs. Whether these associations are translated into increased risk for breakthrough infections and immune mediated long-term sequels of the SARS-CoV-2 infection warrants further investigation

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https://doi.org/10.1016/j.vaccine.2024.126591
Received 9 April 2024; Received in revised form 22 October 2024; Accepted 3 December 2024
Available online 12 December 2024

1. Introduction

Concerns about the efficacy of COVID-19 vaccines in individuals with mental illness exist. Nishimi et al. observed higher incidence of breakthrough infections in COVID-19 vaccinated people with psychiatric conditions independent of other factors such as medical comorbidities and smoking, suggesting that immunologic mechanisms could explain the association [1]. In two prior studies, one from our group, presence of mental health diseases was recognised as a risk factor for lower IgG responses to COVID-19 vaccines [2,3]. Nonetheless, both studies are limited by the self-reported nature of data on mental illness [4]. Moreover, associations might be disorder specific and depend on the severity and long-term course of the disease. These aspects along with treatment information can be efficiently captured by electronic health records (EHR) and facilitate a thorough understanding of these associations using real-patient longitudinal data [5].

Several pathways connect mental illness with blunted responses to vaccines. First, anti-psychotic drugs are often prescribed to people with mental illness, some of which exhibit anti-inflammatory and immunomodulatory actions that may impact antibody responses following vaccination [6,7]. Second, having a mental illness is associated with a specific lifestyle profile characterized by sleep disturbances, physical inactivity, smoking and alcohol drinking that are known risk factors for poor immune response [8,9]. Studies that consider all these relevant variables are scarce. Third, there might be shared genetic factors that contribute both to mental illness and immune response. There is emerging evidence on shared genetic aetiology between schizophrenia and peripheral immune factors and immune-mediated diseases, but less is known on other mental illness and vaccine induced immune responses [10,11]. Fourth, the brain communicates with the immune system through neuroendocrine hormones and the innervation of lymphoid organs by the sympathetic nervous system [12]. Mental health diseases may affect these neuro-immune connections and subsequently adequate and balanced responses to immune triggers. Given the bi-directional relationship between brain and the immune system [13] identifying causality appears challenging. Mendelian randomization (MR) could facilitate this, as it is a valuable method for exploring causal relationships among a wide range of traits using summary statistics from genome wide association studies (GWAS), under specific assumptions.

The present study sought to investigate the association between mental illness and antibody responses after COVID-19 vaccination, using a prospective design in a population based study of middle-aged adults in Catalonia. Specifically, the study aimed: to differentiate associations according to specific diagnoses, the chronicity and the severity of the mental illnesses as noted in the EHR up to 10 years prior to serological testing; to investigate the independent effect of psychotropic drugs; to assess the polygenic liability to mental illness, and to apply MR to appraise causality in the relationship between mental illness and vaccine responses.

2. Materials and methods

2.1. Study design

This analysis uses longitudinally collected data from 939 participants of the COVICAT Study (COVID-19 cohort in Catalonia) who provided a blood sample in 2021 for SARS-CoV-2 serology and were COVID-19 vaccinated (at least one dose) at the time of sampling. All individuals of this analysis are members of the GCAT (Genomes for Life cohort in Catalonia, www.genomesforlife.org), a study started in 2014 that includes middle-aged (40–65 years old at baseline) residents of Catalonia regularly followed-up [last pre-pandemic follow-up, 2018–2019 (n = 9308)] [14]. During the pandemic, GCAT-eligible participants were contacted just after the strict first confinement period in 2020 and almost a year later in 2021. Participants were contacted via email or telephone and asked to respond to a questionnaire and to provide a blood sample in the 2020 and 2021 follow-up [2]. Ethical approval was obtained by the ethics committees at the Hospital Universitari Germans Trias i Pujol (CEI no PI-13-020)(CEI no. PI-20-182) and the Parc de Salut Mar (CEIM-PS MAR, no. 2020/9307/I). All participants provided informed consent.

2.2. Mental health diagnoses

We used ICD10 diagnoses registered directly by healthcare professionals or converted from ICD-9 registries [15] since 2010 to define people with i) mood (affective) disorders (ICD10 F30-F39), ii) anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (hereafter referred as “anxiety disorders”) (ICD10 F40-F48) and iii) other mental health diagnoses except the aforementioned (ICD10: F01-F09, F10-F19, F20-F29, F50-F59, F60-F69, F70-F79, F80-F89, F90-F98, F99) (hereafter referred as “other mental health disorders”) (Table S1). The latest group is quite heterogeneous and mainly includes cases of insomnia and nicotine dependence. For mood and anxiety disorders, these broad groups were decided, because diagnostic switches may exist between the diagnoses included in each group and may represent a more informative approach [16]. The onset of a mental health diagnosis was defined as the date of clinical contact in which a specific diagnosis was first documented for the time period 2010–2021. We defined people as having a recent (first diagnosis within the last 5 years which includes the period of the pandemic) or an older onset (first diagnosis >5 years ago). The number of visits within the specific registered diagnoses throughout the study period was calculated to create an estimate of the severity (burden) of the mental illness [17]. Diagnoses within 6 months were considered as one event/visit because readmissions occur or are even scheduled as part of the same event. We based information on the exposure on questionnaires administered in 2020 and 2021 follow-up for 43 individuals with serological data but missing information from EHR. All 43 self-reported no current or prior mental health disorders, and therefore were categorized as having no mental illness.

2.3. Psychotropic drugs

We considered all psychotropic drugs dispensed at the pharmacy grouped by Anatomical Therapeutic Chemical (ATC) code. Based on pharmacokinetics, we considered drugs prescribed the last 6 months and at least 30 days prior to serological testing. Medications were grouped by pharmacologic class: antidepressants, antiepileptics, anxiolytics, mood stabilizers, benzodiazepines and second-generation antipsychotics (table S2). Though antiepileptics receive initial indications for the treatment of epilepsy, currently the majority of them are used to treat pain and psychiatric disorders [18]. We also evaluated effects related to polypharmacy, referring to the prescription of medications from ≥2 of the aforementioned classes.

2.4. Serology

Primary outcomes of interest were IgG and IgA responses (MFI, median fluorescence intensity) against a panel of three Wuhan SARS-CoV-2 spike antigens: the S full length protein and the receptor binding domain (RBD) found in S and the sub-region S2 [19,20]. The antibody levels were measured by high-throughput multiplex quantitative suspension array technology in blood samples collected in 2021 after COVID-19 vaccine administration began in Spain. Antibody responses against the N-antigen were also measured but were not considered as outcomes since the available vaccines did not contain or produce N-antigen. Assay performance was previously established as of 100 % specificity and 95.78 % sensitivity for seropositivity 14 days after symptoms onset [21].

2.5. Statistical analysis: observational estimates

We applied linear regression models to assess the association between mental health variables and the log10-transformed antibody levels, and results were expressed as percentage change in the geometric mean and 95 % confidence intervals (CIs). We examined the effect of previous diagnosis of mood disorders, anxiety disorders and other mental health disorders with reference group participants with none mental health diagnosis (n = 568). We considered the following potential confounders: age (continuous), gender (male, female), highest attained educational level (primary or less, secondary, university), time since last vaccination (<31, 31–60, 61–90, 91–120, >120 days), type of vaccine (BNT162b2, mRNA-1273, ChAdOx1 nCoV-19), number of doses, chronic diseases [a disease in the last 6 months that required visit to the doctor or medical treatment, including cardiovascular (hypertension, heart attack, angina pectoris), respiratory (asthma, chronic obstructive pulmonary disease), diabetes, kidney, immune-related (autoimmune diseases, HIV, or other immunodeficiency), digestive, or gynecological diseases, as well as cancer] and evidence of previous SARS-CoV-2 infection [20,22]. In a separate model, estimates were also adjusted for factors that have been associated with response to COVID-19 vaccine or other vaccines [2,9] and may be different in people with mental health disorders, including current smoking (no, yes), current alcohol consumption (no, yes daily, yes occasionally), physical activity according to International Physical Activity Questionnaire scoring (low, moderate, high) and current sleep duration (<6 h, 6–8 h, ≥9 h). When information on covariates was missing in 2021 (n = 4 for smoking, n = 4 for alcohol, n = 12 for physical activity, n = 6 for sleep duration) we used responses in 2020 questionnaires. Similar models were build to examine the effect of prescription of psychotropic drugs the last 6 months on antibody levels and estimates were also adjusted for ever being diagnosed with a mental health disease (yes, no). Reference group was the participants never prescribed psychotropic drugs during the study period 2010–2021 (n = 511).

Given that vaccination responses might partially be age and gender specific and dependent on history of SARS-CoV-2 infection we tested for interaction by these characteristics. Moreover, an interaction term between vaccine type (mRNA, non-mRNA) and psychotropic drugs was included in the corresponding models as suggested in the literature [23]. We performed all aforementioned statistical analyses using Stata/SE (version 16; StataCorp LLC.).

2.6. Genetic data

Genotypic information was accessible for 247 individuals of the present analysis. Overall, genotypes were available from a subsample of the GCAT cohort that included unrelated participants with Iberian ethnicity, determined by self-described ethnicity and PC analysis. A detailed description of the genotyping quality control and imputation procedures has been provided previously [24].

2.7. Polygenic risk scores (PRS) analysis

Summary statistics from large-scale GWAS from European-descent individuals on mental health disorders were used for major depressive disorder [25], bipolar disorder [26], anxiety disorders (based on the factor scores models that involved larger sample size) [27], and schizophrenia [28]. These were used to compute the disease specific PRS using PRScs [29] a Bayesian regression framework which enables continuous shrinkage priors on SNP effects to infer their posterior mean effects. PRS for each individual were then computed by multiplying the number of risk alleles by the PRSs inferred weights for each variant, and summing across the genome using PLINK1.9 [30]. Raw PRS were converted into standardized z-scores to make results comparable across analyses and then participants were allocated to quartiles [1st quartile (Q1), the lowest PRS for the specific disorder; 4th quartile (Q4), the highest PRS for the specific disorder]. For the PRS analyses, we employed linear regression models for the log10-transformed IgG levels with mental illness PRS in quartiles as the independent variable, and results were expressed as percentage change in the geometric mean and 95 % confidence intervals (CIs). Estimates were adjusted for age (continuous), gender, educational level (university, secondary, primary or less), type of vaccine (BNT162b2, mRNA-1273, ChAdOx1 nCoV-19), number of vaccine doses, time since last vaccine (<31 days, 31–60 days, 61–90 days, 91–120 days, >120 days), evidence of previous infection and the first ten principal components of ancestry.

2.8. Two-sample MR analysis

We assessed the causal associations between selected mental health disorders and IgG levels against RBD, S and S2 antigens using the aforementioned summary statistics from GWAS on mental health disorders (major depressive disorder, bipolar disorder, anxiety disorders and schizophrenia) and the GWAS for antibody levels conducted in our study sample. We conducted a GWAS for IgG levels using PLINK (version 2.0), since there was no available GWAS of COVID-19 vaccine induced antibody responses. Antibody levels were rank-based inverse normal transformed, and linear regression models were used, assuming an additive genetic model and including age and gender as covariates, as well as the first ten principal components of ancestry to control the potential population stratification. Manhattan plot, lead variants and gene annotations were obtained using the GWASLab python toolkit. Lead variants were defined using sliding windows of 500 kb and a suggestive significance threshold 1e-5. Detailed information about the GWAS can be found in table S3.

Independent significant genetic instruments with a $p \leq 5 \times 10^{-8}$ were identified by linkage disequilibrium (LD) clumping the summary statistics using and LD R2 threshold of 0.001 and a 10 Mb clumping window. For each exposure-outcome combination, the variants were harmonized, filtering out variants with mismatched alleles and ambiguous palindromic variants. We used fixed-effects Inverse Variance Weighted, maximum likelihood, MR-Egger regression, weighted median, and weighted mode to estimate the causal effect. Sensitivity analysis for significant associations was carried out using MR-PRESSO global test to assess the heterogeneity, and MR-Egger intercept, to assess the presence of pleiotropy. All MR analyses were conducted using the TwoSampleMR (v0.5.7) R package with R v4.3.0 [31].

3. Results

The study population comprised 939 individuals with EHR data since 2010 and serological data post-vaccination (see flow chart for exclusions, Fig. S1) of which 124 (13.2 %) had a previous diagnosis of mood disorders, 217 (23.1 %) of anxiety disorders, 189 (20.1 %) of other mental health disorders and 568 did not have a diagnosis of mental health illness. There were 31 participants diagnosed with mood, anxiety and other mental health disorders. Characteristics of the study population are presented in Table 1.

3.1. Mental health diagnoses and antibody responses to COVID-19 vaccination

Being diagnosed with a mood disorder was associated with 26 % decrease in IgG RBD levels [percentage change = −26.37 (95 % CI: −42.00, −6.54)] (Fig. 1). Time related analysis revealed decrease in all anti-spike IgG levels for people with onset of mood disorders >5 years ago versus those with none mental heath diagnosis; for RBD, percentage change: -33.60 (95 % CI: −49.17, −13.52); for S, percentage change: -23.68 (95 % CI: −38.73, −4.91); and for S2, percentage change: −17.47 (−29.85, −2.91) (Fig. 1).

Also, being diagnosed with other mental health disorders was associated with lower IgG RBD levels [percentage change: -21.53 (95 % CI:

Table 1
Characteristics (n, %) of the study population stratified on groups without diagnosis and with a diagnosis of mood-affective disorders, anxiety disorders or other mental disorders since 2010 among vaccinated participants in 2021 of the COVICAT cohort.

	no diagnosis	Mood disorders	Anxiety disorders	Other mental disorders
Characteristic	n = 568	*n* = 124	*n* = 217	*n* = 189
Age, mean (SD)	57.6 (6.9)	58.8 (6.7)	56.7 (7.3)	57.5 (6.7)
Gender				
Male	262 (46.1)	31 (25.0)	69 (31.8)	75 (39.7)
Female	306 (53.9)	93 (75.0)	148 (68.2)	114 (60.3)
Educational level				
Primary or less	41 (7.2)	13 (10.5)	33 (15.2)	27 (14.3)
Secondary	226 (39.8)	61 (49.2)	94 (43.3)	82 (43.4)
University	301 (53.0)	50 (40.3)	90 (41.5)	80 (42.3)
Type of vaccine				
BNT162b2	260 (45.8)	46 (37.1)	98 (45.2)	87 (46)
mRNA-1273	67 (11.8)	16 (12.9)	25 (11.5)	24 (12.7)
ChAdOx1 nCoV-19	241 (42.4)	62 (50.0)	94 (43.3)	78 (41.3)
Evidence of infection at time of serology				
No	374 (65.8)	90 (72.6)	154 (71.0)	126 (66.7)
Yes	194 (34.2)	34 (27.4)	63 (29.0)	63 (33.3)
Long COVID-19				
No	526 (92.6)	112 (90.3)	194 (89.4)	177 (93.7)
Yes	42 (7.4)	12 (9.7)	23 (10.6)	12 (6.3)
Chronic diseases				
No	404 (71.1)	50 (40.3)	116 (53.5)	101 (53.4)
Yes	164 (28.9)	74 (59.7)	101 (46.5)	88 (46.6)
Current smoking				
No	514 (90.8)	111 (89.5)	191 (88.4)	134 (71.7)
Yes	52 (9.2)	13 (10.5)	25 (11.6)	53 (28.3)
Current alcohol consumption				
No	126 (22.3)	43 (34.7)	63 (29.2)	43 (23.0)
Yes, daily	66 (11.7)	16 (12.9)	25 (11.6)	34 (18.2)
Yes, occasionally	374 (66.1)	65 (52.4)	128 (59.3)	110 (58.8)
Physical Activity				
Low	77 (13.7)	27 (22.7)	48 (22.5)	37 (20.3)
Moderate	277 (49.2)	62 (52.1)	101 (47.4)	75 (41.2)
High	209 (37.1)	30 (25.2)	64 (30.0)	70 (38.5)
Current sleep duration				
<6 h per day	41 (7.3)	18 (14.5)	28 (13)	25 (13.4)
6–8 h per day	516 (91.5)	95 (76.6)	176 (81.5)	152 (81.3)
≥9 h per day	7 (1.2)	11 (8.9)	12 (5.6)	10 (5.3)
Psychotropic medication				
none-never	401 70.6)	13 (10.5)	43 (19.8)	73 (38.6)
yes >6 months ago	139 (24.5)	43 (34.7)	100 (46.1)	65 (34.4)
yes from 1 to 2 classes the last 6 months	28 (4.9)	50 (40.3)	61 (28.1)	42 (22.2)
yes from 3 to 4 classes the last 6 months	0 (0.0)	18 (14.5)	13 (6.0)	9 (4.8)

−35.38, −4.71)] (Fig. 1). A recent onset of other mental health disorders (≤5 years) showed larger decreases in antibody levels, being statistically significant for IgG RBD responses [percentage change: -38.35 (95 % CI: −55.78, −14.05)] (Fig. 1). In this group, both recent onset of insomnia/sleep disorders and dependence disorders were associated with lower IgG RBD levels (table S4).

The aforementioned effect sizes were robust to correction for smoking, alcohol consumption, physical activity and sleep duration (table S5). Number of visits was not found to differentiate the associations (table S6). Overall, anxiety disorders were not associated with IgG levels (Fig. 1). No associations were observed for IgA (table S7). There was no evidence for effect modification of the associations by gender, age and infection (table S8).

3.2. Psychotropic drugs and antibody responses to COVID-19 vaccination

Prescription of second-generation antipsychotic drugs the last 6 months before serology was associated with 64 % decrease in IgG RBD levels [percentage change = −64.64 (95 % CI: −84.24, −20.63)] and 53 % decrease in IgG S levels [percentage change = −53.27 (95 % CI: −75.84, −9.63)] compared to those who have never been prescribed psychotropic drugs (Table 2). When we investigated the effect of polypharmacy, people who were prescribed ≥3 classes of psychotropic drugs the last 6 months presented lower IgG RBD [percentage change = −46.61 (95 % CI: −68.83, −8.53)] and S levels [percentage change = −39.80 (95 % CI: −61.08, −6.89)] (Table 2) and lower IgA S levels [percentage change = −52.12 (95 % CI: −75.94, −4.72)] (table S9) compared to the reference group.

We further tested for effect modification of the associations by vaccine type, infection, age and gender. People on antidepressants and antiepileptics presented lower IgG S2 levels [percentage change = −34.82 (95 % CI: −50.37, −14.39) -51.28 (95 % CI: −69.42, −22.38), respectively] when vaccinated with non-mRNA vaccines (table S10) and when they were ≥ 60 years of age [−33.65 (95 % CI: −49.53, −12.77) and −51.56 (95 % CI: −68.31, −25.95), respectively] (table S11). Participants on second-generation antipsychotics presented lower IgG RBD, S and S2 levels following vaccination when they have been previously infected and a similar pattern was observed for benzodiazepines and mood stabilizers (table S10). Overall, prescription of ≥3 drug categories of psychotropics was associated with lower IgG S [percentage change = −72.21 (95 % CI: −86.24, −43.87)] and IgG S2 [percentage change = −61.72 (95 % CI: −77.64, −34.47)] among previously infected participants (table S10). No differences were observed between men and women (table S11).

3.3. PRS based analyses

For the analyses using PRS for major depressive disorder, bipolar disorder, anxiety and schizophrenia, we observed that participants in the highest quartile of the score for schizophrenia had lower IgG RBD levels [percentage change = −35.49 (95 % CI: −56.55, −4.23)] compared to those in the lowest quartile (Table 3). No associations were observed for IgA (Table S12).

3.4. GWAS for antibody responses to COVID-19 vaccination

GWAS analyses on antibody responses to COVID-19 vaccination revealed a genome-wide significant association for IgG S2 levels in an intron of gene *CNBD1 (Cyclic Nucleotide Binding Domain Containing)* (fig. S2). At a less stringent level of statistical significance ($p \leq$1e-5) we identified 38 lead SNPs in IgG S, 41 lead SNPs in IgG S2 and, 39 in IgG RBD. Out of these, two genetic signals close to genes *TBC1D5* and *NPIPA8* surpassed the suggestive significance level in all three IgG measurements. IgG RBD and IgG S share 19 genes mapped to genetic signals and IgG S and IgG S2 share 5 genes (fig. S3).

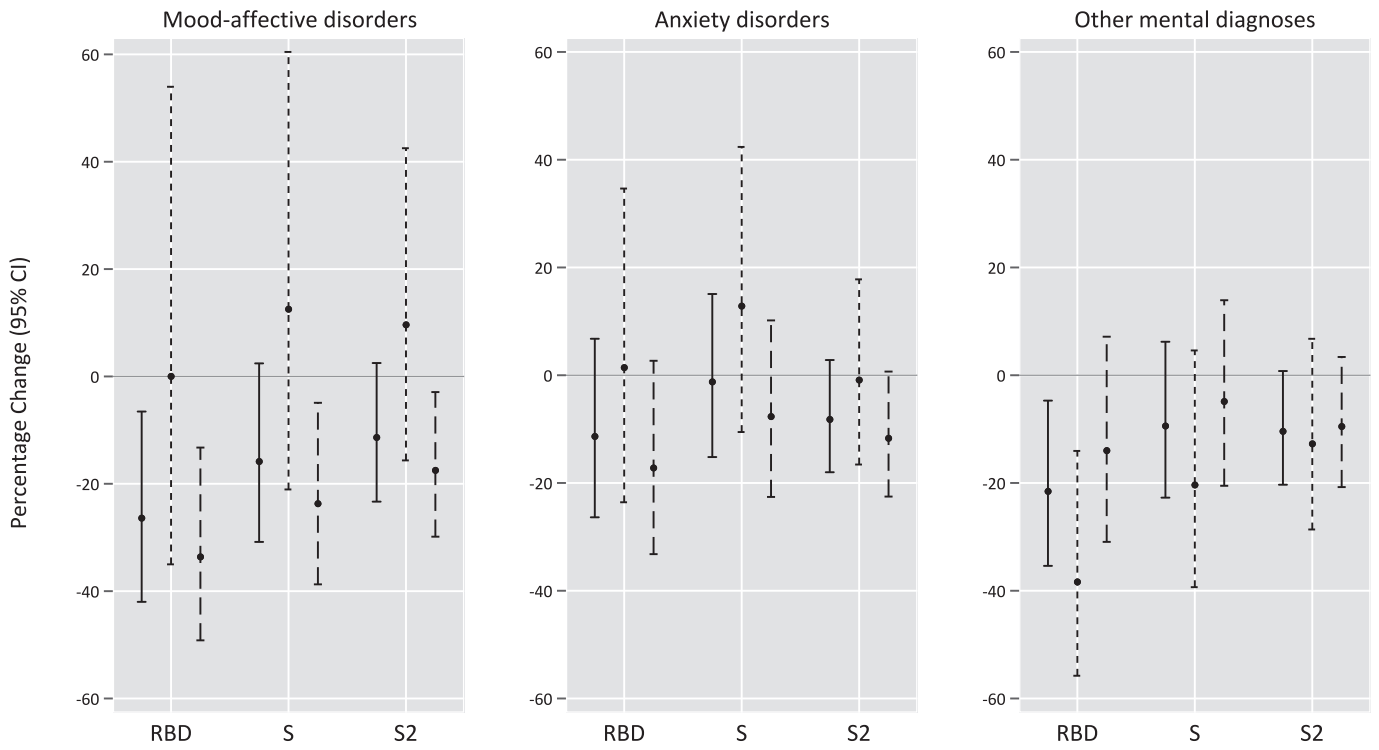

Fig. 1. Association of mental health diagnoses since 2010 with IgG levels against RBD, S and S2 antigens of SARS-CoV-2 among vaccinated participants in 2021 of the COVICAT cohort. The effect estimates are provided as percentage change with 95 % confidence intervals (CI) from linear regression for the log10 MFI (median fluorescence intensity). Estimates and CIs with solid line for ever having the specific diagnosis; with dot lines when first diagnosis was ≤5 years ago; and with dashed lines when first diagnosis was >5 years ago. Reference group is always people with none mental health diagnosis. All estimates are adjusted for age (continuous), gender, educational level (university, secondary, primary or less), type of vaccine (BNT162b2, mRNA-1273, ChAdOx1 nCoV-19), number of vaccine doses, time since last vaccine dose (<31 days, 31–60 days, 61–90 days, 91–120 days, >120 days), evidence of previous infection and chronic diseases (yes, no).

3.5. Two-sample MR analysis

Inverse Variance Weighted estimates revealed a detrimental causal association between major depression genetic instruments and IgG RBD and S levels (beta: −1.14, −1.16, −0.6, respectively). Maximum likelihood, MR-Egger regression, weighted median and weighted mode, suggested similar effects although only maximum likelihood reached the nominal significance threshold (Fig. 2). No significant evidence of directional pleiotropy was observed based on MR-Egger intercept test ($P_{RBD} = 0.88$; $P_S = 0.75$), neither increased heterogeneity according to Cohran Q ($P_{RBD} = 0.47$; $P_S = 0.46$). Results of bipolar disorder and schizophrenia genetic instruments with antibody responses can be found in table S12. For anxiety disorders, conducting a MR was not feasible due to the absence of significant hits in the GWAS.

4. Discussion

In this well-characterized cohort study, we integrated electronic health records for mental health diagnoses over 10 years, psychotropic drugs prescriptions and genetic data, with serological testing post COVID-19 vaccination and found that a diagnosis of mental health illness was associated with lower antibody responses to COVID-19 vaccines. This association was more pronounced for mood disorders, and a spectrum of other mental health diagnoses including mainly insomnia and nicotine dependence. MR analysis revealed detrimental causal association of major depression with IgG RBD and S responses but we acknowledge that MR has limited potency given the small number of participants with genetic data. We further showed that the use of second-generation antipsychotics and of multiple classes of psychotropic drugs, as well as higher genetic liability for schizophrenia were linked with reduced antibody responses. We discuss these findings in turn.

First, the disorder specific analysis allowed us to identify that particularly people with mood disorders developed lower IgG levels post vaccination. These associations remained after adjusting for lifestyle characteristics. Earlier research indicates that depression is associated with reduced immune response to other vaccination [32–35]. Older and not recent diagnoses of mood disorders exhibited lower responses suggesting that a prolonged state of these diseases induce effects on the immune system, or that time is needed upon emergence of the disorders to observe effects in the immune system. Our data do not allow us to disentangle between current and remitted cases of mood disorders. Nonetheless, depression, the most common diagnosis within the group of mood disorders, tends to persist over time upon diagnosis [36]. Although we assess associations prospectively, we cannot exclude that an immune dysregulation existed prior to the onset of the mental health disorder and that our findings might be related to the pathophysiology of these disorders [13]. The MR analysis provided evidence for a causal association between major depression and lower IgG RBD and S levels. Causal pathways may include: i) depression associated activity of the hypothalamic-pituitary-adrenocortical axis leading to hypercortisolaemia, which is well known to have a detrimental effect on B lymphocytes functions, including production of antibodies [37]; ii) chronic inflammation characterizing depressive disorders, which can disrupt the normal functioning of immune cells [38] and iii) a potentially “un-trained” immune system resulting in less effective immune responses to vaccines in people with depression as these people are lacking social interactions, which can limit their chances of exposure to various pathogens and decrease their immune system’s “training” [39,40]. Although the PRS-based analyses suggests that the genetic liability to major depression alone may not be sufficient to influence antibody responses, specific genetic factors related to depression may have a causal impact.

Second, the group of other mental health diagnoses, particularly those with a recent onset, demonstrated reduced IgG levels after

Table 2
Association of psychotropic drug prescription the last 6 months before serology with IgG levels against RBD, S and S2 antigens of SARS-CoV-2 among vaccinated participants in 2021 of the COVICAT cohort.

		IgG RBD	IgG S	IgG S2
	n	Percentage change (95 % CI)	Percentage change (95 % CI)	Percentage change (95 % CI)
Antidepressants	77	−16.29 (−39.34, 15.53)	−19.50 (−38.25, 4.95)	−13.92 (−29.42, 4.98)
Antiepileptics	29	−15.22 (−45.62, 32.16)	−16.34 (−41.72, 20.12)	−21.46 (−40.26, 3.26)
Antipsychotics second generation	8	**−64.64 (−84.24, −20.63)**	**−53.27 (−75.84, −9.63)**	−30.91 (−57.83, 13.21)
Anxiolytics	3	−38.81 (−83.00, 120.22)	−24.83 (−73.55, 113.68)	−35.88 (−70.58, 39.77)
Benzodiazepines	86	−12.51 (−35.51, 18.69)	−9.65 (−29.32, 15.48)	−1.58 (−18.13, 18.33)
Mood stabilizers	12	−18.37 (−58.40, 60.20)	−18.99 (−53.31, 40.54)	−15.19 (−43.89, 28.19)
Polypharmacy				
None-never	511	reference	reference	reference
1–2 drug classes	123	0.80 (−21.04, 28.67)	−1.94 (−19.54, 19.51)	−4.59 (−17.97, 10.98)
3–4 drug classes	19	**−46.61 (−68.83, −8.53)**	**−39.80 (−61.08, −6.89)**	−28.02 (−48.41, 0.44)

The effect estimates are provided as percentage change with 95 % confidence intervals (CI) from linear regression for the log10 MFI (median fluorescence intensity). All estimates are adjusted for age (continuous), gender, educational level (university, secondary, primary or less), type of vaccine (BNT162b2, mRNA-1273, ChAdOx1 nCoV-19), number of vaccine doses, time since last vaccine dose (<31 days, 31–60 days, 61–90 days, 91–120 days, >120 days) evidence of previous infection and mental health disease (none, any). Reference group is always people never prescribed psychotropic drugs during the study period 2010–2021 ($n = 511$).

Table 3
Association of polygenic risk scores (PRS) for mental disorders in quartiles with IgG levels against RBD, S and S2 antigens of SARS-CoV-2 among vaccinated participants in 2021 of the COVICAT cohort.

		IgG RBD	IgG S	IgG S2
	n	Percentage change (95 % CI)	Percentage change (95 % CI)	Percentage change (95 % CI)
PRS for major depressive disorder				
Quartile 1	62	reference	reference	reference
Quartile 2	62	−7.15 (−36.89, 36.63)	−5.44 (−31.37, 30.31)	−1.86 (−23.99, 26.72)
Quartile 3	62	−20.49 (−45.63, 16.27)	−14.92 (−37.94, 16.64)	−5.79 (−26.74, 21.14)
Quartile 4	61	−8.54 (−37.89, 34.67)	0.41 (−27.17, 38.44)	9.54 (−15.20, 41.49)
PRS for bipolar disorder				
Quartile 1	62	reference	reference	reference
Quartile 2	62	15.21 (−21.65, 69.42)	5.07 (−23.71, 44.72)	−0.73 (−23.13, 28.19)
Quartile 3	62	22.24 (−17.50, 81.15)	13.83 (−17.88, 57.78)	−1.16 (−23.85, 28.30)
Quartile 4	61	−1.62 (−33.15, 44.78)	−6.58 (−32.22, 28.76)	−8.50 (−29.18, 18.23)
PRS for schizophrenia				
Quartile 1	62	reference	reference	reference
Quartile 2	62	−6.12 (−35.95, 37.60)	0.18 (−27.20, 37.85)	−2.96 (−24.77, 25,17)
Quartile 3	62	−19.41 (−45.53, 19.23)	−6.23 (−32.38, 30.04)	−13.16 (−33.10, 12.72)
Quartile 4	61	**−35.49 (−56.55, −4.23)**	−21.71 (−43.71, 8.89)	−16.83 (−36.07, 8.20)
PRS for anxiety				
Quartile 1	62	reference	reference	reference
Quartile 2	62	−11.10 (−40.09, 31.92)	−9.25 (−34.64, 26.00)	10.38 (−15.11, 43.52)
Quartile 3	62	8.41 (−26.05, 58.93)	7.29 (−21.94, 47.47)	14.54 (−11.20, 47.74)
Quartile 4	61	−24.99 (−48.78, 9.85)	−18.33 (−40.53, 12.16)	1.35 (−21.37, 30.63)

The effect estimates are provided as percentage change with 95 % confidence intervals (CI) from linear regression for the log10 MFI (median fluorescence intensity). All estimates are adjusted for age (continuous), gender, educational level (university, secondary, primary or less), type of vaccine (BNT162b2, mRNA-1273, ChAdOx1 nCoV-19), number of vaccine doses, time since last vaccine dose (<31 days, 31–60 days, 61–90 days, 91–120 days, >120 days), evidence of previous infection, chronic diseases (yes, no) and the first ten principal components of ancestry.

vaccination. This group includes mainly nicotine dependence and insomnia cases. It is well established the negative impact of smoking and sleep disturbances on our immune system [9]. Resolution of these risk factors might cause improvement in the immune function [41,42]. This might explain that the associations were evident in recent onset diagnoses. Given that we had almost no cases of schizophrenia and bipolar disorders in this population based study sample, we computed PRS for these diseases as "proxies" (similarly to Veeneman et al. [43]) and associated them with the antibody levels. Compared with individuals with low genetic risk, those with high genetic susceptibility to schizophrenia had lower IgG levels suggesting a shared genetic basis between them. Previous studies demonstrated a significant genetic overlap between schizophrenia and white blood cell counts, with lymphocytes showing the largest overlap, indicating an inherent systemic adaptive immune component in schizophrenia [11]. In UK biobank, PRS for schizophrenia was associated with immune-related parameters in peripheral blood but did not consider antibody responses [44]. To our knowledge, this is the first study to investigate the influence of polygenic risk for mental illness on antibody responses following vaccination.

Third, instead of correcting for use of psychotropic drugs in the analyses of mental illness, we tested their specific effect in the antibody responses. After restricting to a meaningful period of exposure based on pharmacokinetics, we observed that prescription of second-generation antipsychotics was negatively associated with IgG levels to COVID-19 vaccines irrespective of being diagnosed with a mental health disease. As these drugs were prescribed to only 8 people, caution is warranted in interpreting the results. In a preclinical model, May et al. showed that risperidone (an antipsychotic) prevented treated animals from mounting an antibody response following vaccination with pneumococcal polysaccharide vaccine (PPV-23) [45]. Polypharmacy, referring to psychotropic drugs, was also associated with reduced IgG and IgA responses to vaccination in our study. Trevisan et al. found that among 478 long-term care facility residents hyper-polypharmacy was associated with a steeper antibody decline after 6 months from the first COVID-19 vaccine dose than no polypharmacy, while no significant differences were observed at 12 months [46]. Our data indicated that there are likely to be interactions between psychotropic drugs and people's characteristics, which have not been adequately addressed, in prior studies. For example, we observed reduced antibody responses to vaccination among

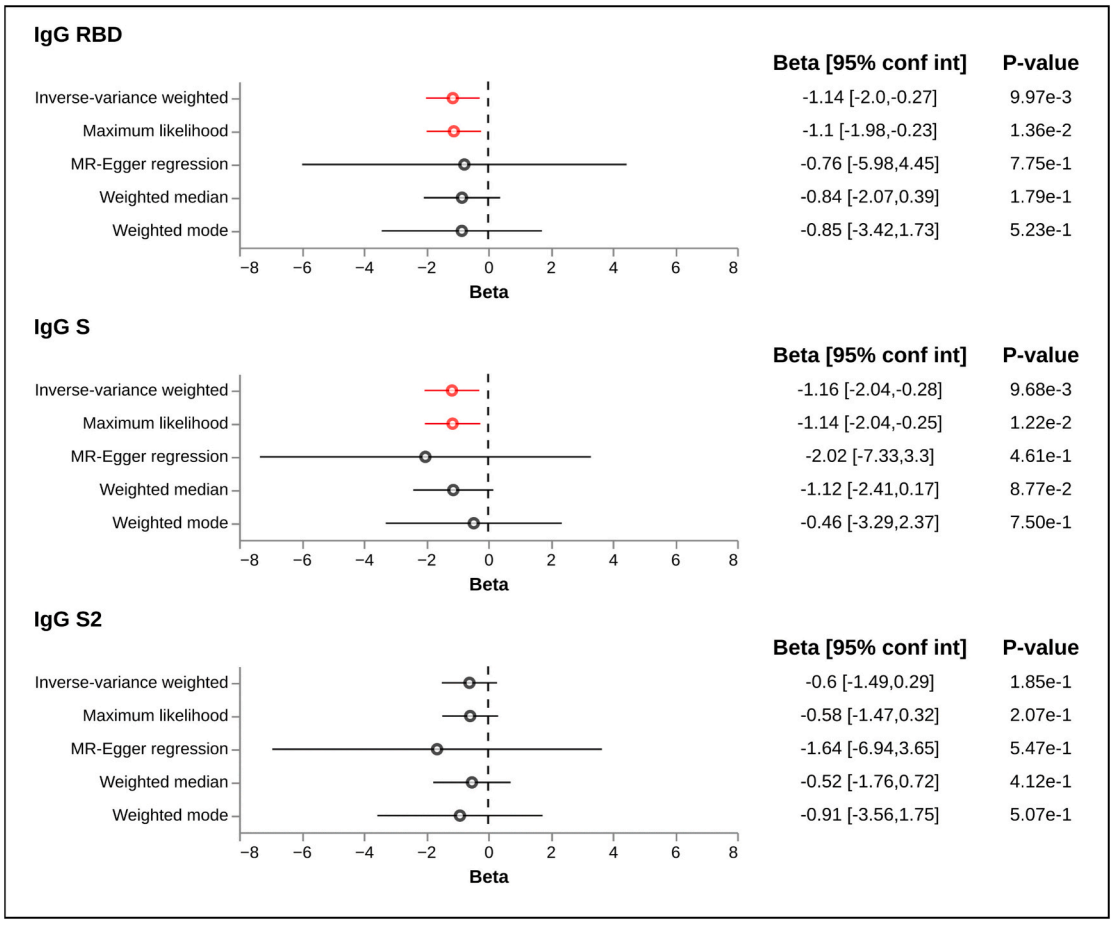

Fig. 2. Forest plots showing the results of the mendelian randomization depicting the causal relationship between major depressive disorder and IgG levels against RBD, S and S2 antigens of SARS-CoV-2 among vaccinated participants in 2021 of the COVICAT cohort.

people ≥60 years of age treated with antidepressants and antiepileptics probably related to immunosenescence [47]. Also, people on antipsychotics, benzodiazepines and mood stabilizers had lower antibody responses when previously infected. SARS-CoV-2 exploitation of host cytochrome P450 enzymes, might induce a lower drug metabolism, increasing drug levels in blood for antipsychotics and benzodiazepines explaining partly the stronger negative effect of those drugs on antibody responses among infected people [48]. Further antidepressants and antiepileptics were associated with lower antibody levels among people vaccinated with non-mRNA vaccines but the exact mechanism is unclear. A higher number of participants would likely clarify some of the trends observed here. Overall, psychotropic drugs have received less attention as a risk factor for reduced vaccine immunogenicity and efficacy and their interactions with COVID-19 vaccines should be carefully examined in vaccine trials [23,49].

This study is strengthened by its prospective design and the use of physician confirmed diagnoses and prescriptions from EHR, offering a longitudinal clinical picture of the population with more than ten years of observations. Considering that mental health disorders typically arise in early adulthood [50], it is anticipated that within our middle-aged population these disorders would have already become apparent. Using the genetic liability (PRS) to mental diseases, we were able to assess associations with schizophrenia and bipolar disorder, for which we had almost none diagnoses in our study sample. The use of well-validated serological assay detecting multiple vaccine-induced responses is another important strength of this study. These antibody levels predict vaccine efficacy [51]. Including both IgG and IgA is a strength of the study, as it enhances the understanding of how mental illness and psychotropic drugs impact specific immunological components. Reasons for not detecting large differences in IgA responses similar to those detected with IgG could be related to assessment of systemic and not mucosal IgA responses and that IgA responses decay faster than IgG responses. We acknowledge that including T cell-mediated responses, which are thought to provide protection against severe COVID-19, would provide us a better understanding of the immune associations of mental illness. The availability of extensive individual-level data on vaccination, lifestyle, socioeconomic status and comorbidities allows for extensive control of potential confounding and effect modification.

We recognise that EHR data may suffer from under−/over−/misdiagnosis. One concern is also related to the exposure heterogeneity, as even in the same diagnosis there are different subtypes e.g. related to clinical symptoms, severity of the disease, treatment responses or neurocognitive functions and biomarkers. At the same time, some people are experiencing more than one mental health issue. We plan to work on deep phenotyping of our population in the future. Regarding psychotropic drugs, we examined the effect of prescriptions and it was not possible to determine medication adherence from the available data. Moreover, owing to the restriction to a 6-month period of exposure to psychotropic drugs, we did no have the power to investigate the association between individual drugs such as lithium and the impact of duration and doses. Volunteer bias is always of concern especially for people with mental health disorders as they were less likely to participate in the study and donate a blood sample, which we expect would bias our results toward null. For example, compared to the entire cohort and the general population of Catalonia within the same age group, our study sample exhibited fewer mental health diagnoses (table S13). Although, we provide some evidence for a causality of the associations

through the MR, we cannot demonstrate the exact mechanisms and further studies are needed in this perspective. Additionally, we acknowledge that the limited sample size poses challenges in identifying strong and statistically robust genetic instruments.

5. Conclusions

Our data indicate that individuals with mood disorders are at risk of presenting lower antibody levels following COVID-19 vaccination. Similar effects may imply when examining responses to other vaccines. Given that the negative effects of mood disorders in our study population were not evident for recent onset diagnoses, it is likely that a potential window of opportunity for prevention may exist in the early stages of these disorders or even at their prodromal phase. Through the MR we provide evidence that major depression has causal effects in humoral vaccine responses. Psychotropic drugs, particularly antipsychotics and polypharmacy, were associated with lower antibody levels. These new findings may boost research examining the link of mental illnesses and their treatments with the immune system, and influence policies related to COVID-19 vaccine administration at the individual and population level.

Funding statement

This work was funded by Incentius a l'Avaluació de Centres CERCA (in_ CERCA); EIT HEALTH BP2020-20873-Certify.Health.; Fundació Privada Daniel Bravo Andreu; PID2019-110810RB-I00 grant (Spanish Ministry of Science & Innovation). Rocio Rubio had the support of the Health Department, Catalan Government (PERIS SLT017/20/000224). ISGlobal acknowledges support from the Spanish Ministry of Science and Innovation through the "Centro de Excelencia Severo Ochoa 2019-2023" Program (CEX2018-000806-S). ISGlobal and IGTP receive support from the Generalitat de Catalunya through the CERCA Program. GCAT was funded by Acción de Dinamización del ISCIII-MINECO and the Ministry of Health of the Generalitat of Catalunya (ADE 10/00026) and have additional suport by the Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR) (2017-SGR 529), National Grant PI18/01512 and VEIS project (001-P-001647) (co-funded by European Regional Development Fund (ERDF), "A way to build Europe"). This study was carried out using anonymized data provided by the Catalan Agency for Quality and Health Assessment, within the framework of the PADRIS Program. The funders had no role in the study design, data collection and analysis, interpretation of data, preparation of the manuscript, and decision to publish.

Data statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Protocol information will be available on reasonable request.

Ethical standards

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

CRediT authorship contribution statement

Marianna Karachaliou: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Ana Espinosa:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Xavier Farré:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Natalia Blay:** Writing – review & editing, Methodology, Data curation. **Gemma Castaño-Vinyals:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Data curation. **Susana Iraola-Guzmán:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Data curation. **Rocio Rubio:** Writing – review & editing, Validation, Methodology, Data curation. **Marta Vidal:** Writing – review & editing, Methodology, Investigation, Data curation. **Alfons Jiménez:** Writing – review & editing, Validation, Methodology, Data curation. **Marc Bañuls:** Writing – review & editing, Methodology, Investigation, Data curation. **Ruth Aguilar:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Data curation. **Judith Garcia-Aymerich:** Writing – review & editing, Supervision, Methodology, Funding acquisition. **Carlota Dobaño:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Data curation. **Manolis Kogevinas:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition. **Gemma Moncunill:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation. **Rafael de Cid:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the volunteers who participate in the cohort study and all the workers in different facilities of the Blood and Tissue Bank for sample collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.126591.

Data availability

Data will be made available on request.

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