



OPEN Nationwide longitudinal study reveals impact of both national restriction levels and genetic risk factors on loneliness during the COVID-19 pandemic

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The impact of social restrictions during the COVID-19 pandemic on social isolation and loneliness has been widely debated, yet little attention has been given to identifying particularly vulnerable groups. In this study, we analysed data from 8,042 participants of the Danish Blood Donor Study (DBDS) through a prospective design with multiple follow-ups, integrating genetic, health, and socioeconomic information to identify distinct loneliness trajectories during the pandemic. Using the 3-item UCLA Loneliness Scale (UCLA-3), we found that self-reported loneliness increased in parallel with social restriction index, with women being particularly affected. We identified three distinct loneliness trajectories: high loneliness, pandemic loneliness, and low loneliness. Individuals in the high and pandemic loneliness trajectories both had higher polygenic scores (PGS) for loneliness and for the personality trait neuroticism compared to the low loneliness trajectory. The high loneliness trajectory was additionally associated with high PGS for psychiatric disorders and low PGS for the personality trait extraversion in addition to a higher proportion of pre-pandemic psychiatric disorder diagnoses. In contrast, the pandemic loneliness trajectory was linked to low PGS for the personality traits agreeableness and conscientiousness, as well as higher PGS for religious participation. These findings highlight the need for tailored interventions targeting individuals with poor mental well-being.

Loneliness is a feeling that arises when the quantity and quality of the available social relations do not match an individual's social needs¹. High levels of loneliness have been associated with several adverse outcomes including poor physical health², low sleep quality³, low cognitive ability⁴ and poor mental health⁵, indicating that loneliness could both contribute to development and worsening of disease as well as being a marker of poor health generally.

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Recent research has increasingly pointed to the heritable nature of loneliness with genetic factors accounting for a considerable portion of the variance in experienced loneliness^{6,7}. Polygenic scores (PGS), which aggregate the effects of numerous genetic variants associated with a trait have shown potential in predicting susceptibility to loneliness. This genetic predisposition also exhibits pleiotropy, sharing genetic architecture with other psychological traits and health conditions, which underscores the complex interplay between genetics and environmental factors in the manifestation of loneliness^{8,9}.

In addition to PGS's numerous other individual characteristics such as prior psychiatric disorders, personality traits (i.e. the 'big five': openness, conscientiousness, extraversion, agreeableness, and neuroticism), sex, and year of birth have previously been associated with loneliness^{6–14}. Furthermore, macro-level factors which impact how individual characteristics are distributed at a societal level or even internationally, have been shown to impact levels of loneliness^{15–17}. For example, implementation of social restrictions during the COVID-19 pandemic impacted social norms and behaviours¹⁸, and individuals are likely to have been impacted differently as a result of personal characteristics.

An increasing amount of research is focusing on the impacts the COVID-19 pandemic had on loneliness^{19–21}. This mainly stems from government enforced lockdowns, which included prohibiting social gatherings. These lockdowns would have imposed strains on individuals' social networks and relationships leading to concerns about general physical and mental wellbeing during and after the pandemic^{22,23}. Most of the studies conducted, including a study of Danish blood donors²⁴, have reported a general increase in loneliness during the pandemic²⁵, although some studies reported stable levels of loneliness during the pandemic^{26,27}. However, efforts to identify specific patterns (trajectories) of loneliness to more efficiently characterise sub-groups of individuals vulnerable to experiencing loneliness are very sparse. This impacts our ability to effectively intervene against loneliness, address potential long-term consequences, and direct strategies towards individuals prone to experiencing loneliness. Hence, identifiers of distinct loneliness vulnerability profiles are needed.

The primary aim of this study was to identify distinct trajectories of loneliness during the COVID-19 pandemic and characterise their profiles using genetic, health and socioeconomic data.

Methods

Study population and design

The present study was based on a sample of 8,042 participants from the Danish Blood Donor Study (DBDS). The DBDS is an ongoing nationwide prospective cohort study that is described in further detail elsewhere²⁸. During the COVID-19 pandemic, questionnaires were sent to DBDS participants to monitor health and wellbeing including loneliness during different stages of the pandemic. Participants in the present study all reported their prospective level of loneliness at three timepoints during the pandemic (December 2020, August 2021, and May 2022) as well as their retrospective pre-pandemic level of loneliness (December 2020). They all had available genetic information for calculation of PGS, were classified as having European ancestry (see appendix—Supplementary Methods 1 for description of ancestry classification) and were genetically unrelated to other study participants (king-cut-off < 0.084 for study participants) (Fig. 1) (see appendix—Supplementary Methods 2 for description of relatedness analysis).

Exposure

Polygenic scores (PGS) for the following traits were calculated and included as identifiers of potential distinct loneliness trajectories: loneliness, all 'big five' personality traits, religious participation, schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorder, and attention deficit hyperactivity disorder (see appendix—Supplementary Methods 3 for a detailed description of PGS calculation).

Covariates

Social restriction index

The social restriction levels in place at the time of data collection (December 2020, August 2021, and May 2022) were obtained using the Oxford Coronavirus Government Response Tracker (OxCGRT), which has been described in length elsewhere²⁹. For each of the time points, we used the mean OxCGRT restriction level in Denmark over the three months prior to the respective time point.

Demographic factors

Information on sex and year of birth was obtained from the Danish civil registration system that holds this information for all individuals alive in Denmark on April 2, 1968 and onwards³⁰. In addition, employment status (full time employment, part time employment, self employed, student, unemployed, retired and other) and cohabitation status denoting if an individual lived alone were obtained from questionnaire responses in December 2020.

Pre-pandemic psychiatric disorders

Any pre-pandemic (i.e., before 01 Jan 2020) psychiatric disorder were defined according to the 10th revision of the international classification of diseases (ICD-10), using the entire F-chapter. Information on psychiatric disorders was obtained from the Danish national patient registry, holding information on psychiatric disorders diagnosed at a psychiatric hospital department in Denmark since 1995³¹. In addition, prescriptions of psychotropic medication (Anatomical Therapeutic Chemical [ATC] classification codes N05A, N05B, N06A, and N06AB) redeemed from Danish pharmacies were included to describe psychiatric disorders treated in a primary care setting. The Danish prescription register contains information on all redeemed prescriptions at Danish pharmacies since 1995^{32,33}.

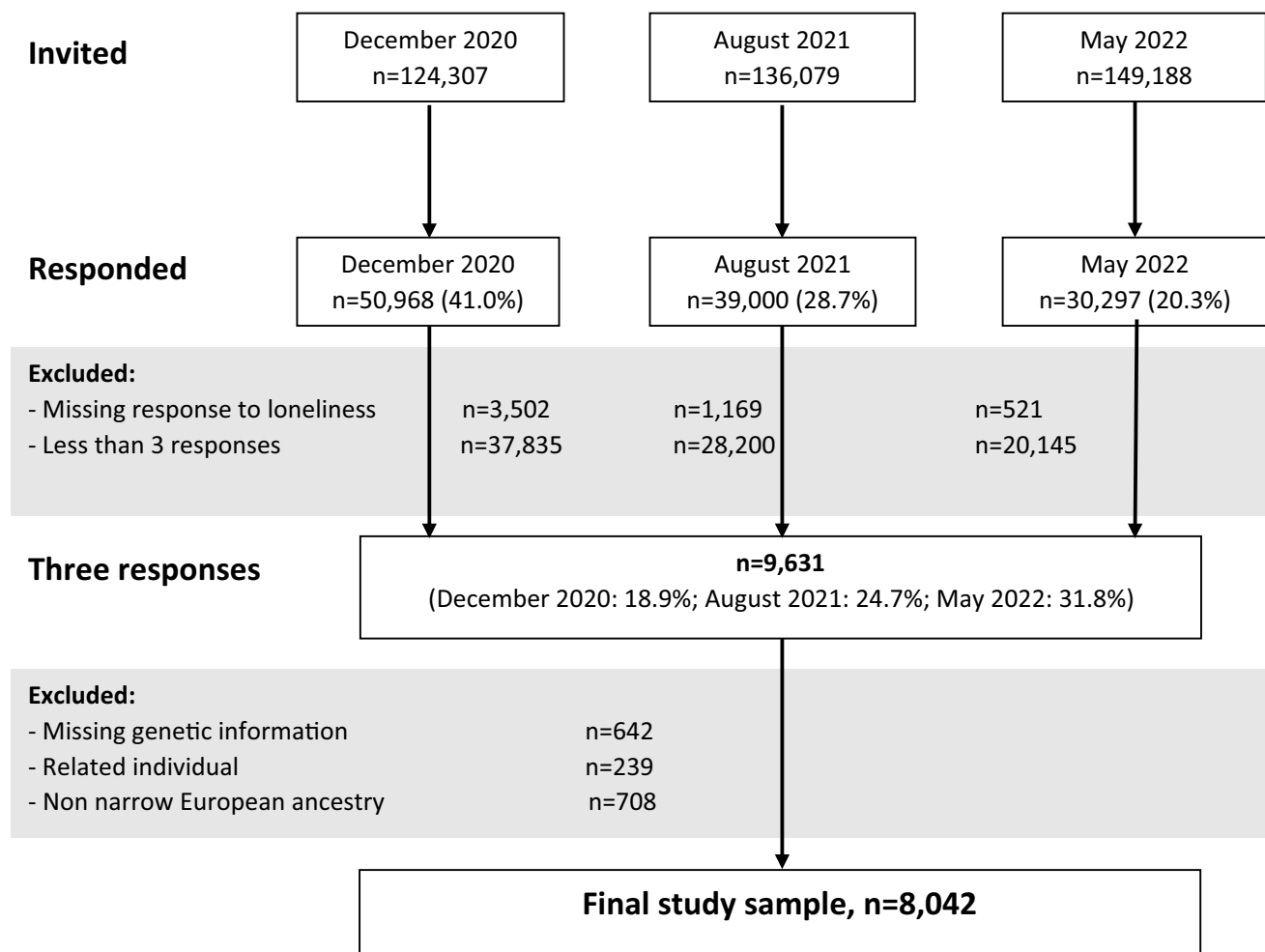


Fig. 1. selection of the study sample.

Outcome

Loneliness

Levels of loneliness were measured with the University of California, Los Angeles Loneliness Scale in its three-item form (UCLA-3). This scale has been described in greater detail elsewhere^{34–36}, but briefly, UCLA-3 is a shortened version of the revised UCLA loneliness scale (R-UCLA). R-UCLA has been translated into Danish with high reliability and validity and correlates highly with UCLA-3, indicating that UCLA-3 is a high-quality measure of loneliness. Each of the three items in UCLA-3 is rated on a scale from 1–3, resulting in a combined loneliness score ranging from 3–9, with 9 indicating the highest level of loneliness. Scores above 6 are normally regarded as an indicator of loneliness³⁷.

Statistical analyses

Cluster analysis

K-means cluster analysis was used to identify distinct loneliness trajectories over time by grouping individuals based on their repeated loneliness scores, revealing different pathways of loneliness experience during the COVID-19 pandemic. To select the appropriate K number we used the between and within cluster sum of squares ratio for each K. This metric both measures the degree of within cluster compactness and the amount of separation between clusters. When evaluating these values we used the elbow method, which indicated the point at which the between and within-cluster sum of squares ratio diminished. Based on this K=3 was selected as the appropriate number of clusters (*high loneliness*, *pandemic loneliness* and *low loneliness*. See results.). To check the stability of trajectories for K=3, and to ensure robustness against local minima, the clustering process was repeated 100 times, each with a unique random initialization, ensuring a unique starting point for each run. This was done to reduce the likelihood of the results being influenced by unfortunate initial centroid placements, which can lead to suboptimal clustering due to the algorithm's susceptibility to local minima. Each iteration used nstart=10, which initializes the centroids 10 times per run and selects the best solution based on within-cluster sum of squares (WCSS).

WCSS is a measure of the compactness of clusters, calculated as the sum of squared distances between each data point and its cluster centroid. The 100 clustering runs were ranked based on WCSS values. The ten runs

with the lowest WCSS were classified as the "best runs," while the ten runs with the highest WCSS were classified as the "worst runs." For both groups, within-cluster variances were compared to evaluate clustering quality and stability. The best runs had a mean WCSS of 28,391.63, while the worst runs had a slightly higher mean WCSS of 28,399.47, indicating a marginal difference in clustering compactness. The minimal difference between the best and worst runs suggested that the k-means algorithm consistently converged to near-optimal solutions. Only 146 individuals (1.8% of total individuals) had alternative clustering assignments between the best and worst runs in terms of WCSS. Clustering was identical for the ten best runs, reflecting a measure of robustness in the clustering process. K-means analysis was performed in rstudio with cluster analysis and metrics processed using the fpc and cluster packages^{38,39}.

Descriptive statistics

Descriptive characteristics of the study were calculated for all study participants and for identified trajectories (Table 1). This included count and percentages of decade of birth, each sex, cohabitation status, employment status and prevalence of any pre-pandemic psychiatric disorder and redeemed prescriptions of psychotropic medication.

Polygenic profiles

Polygenic profiles of the three identified trajectories were assessed in multinomial logistic regression models where the trajectories *high loneliness* and *pandemic loneliness* were compared with the trajectory *low loneliness*. A total of 12 multinomial regression models were created, using an indicator variable for trajectory (*high loneliness*, *pandemic loneliness*, or *low loneliness*) as the dependent variable and each PGS as the independent variable adjusted for the first ten principal components (see appendix Supplementary Methods 3 for detailed description of principal components calculation).

			Loneliness trajectories					
All participants			Low loneliness		High loneliness		Pandemic loneliness	
n	8042		4463		1024		2555	
YOB								
Before 1950	813	10.10% (9.5%-10.8%)	520	11.70% (10.7%-12.6%)	69	6.70% (5.2%-8.3%)	224	8.80% (7.7%-9.9%)
1950s	2128	26.50% (25.5%-27.4%)	1328	29.80% (28.4%-31.1%)	206	20.10% (17.7%-22.6%)	594	23.20% (21.6%-24.9%)
1960s	2337	29.10% (28.1%-30.1%)	1359	30.50% (29.1%-31.8%)	224	21.90% (19.3%-24.4%)	754	29.50% (27.7%-31.3%)
1970s	1417	17.60% (16.8%-18.5%)	725	16.20% (15.2%-17.3%)	205	20.00% (17.6%-22.5%)	487	19.10% (17.5%-20.6%)
1980s	807	10.00% (9.4%-10.7%)	363	8.10% (7.3%-8.9%)	165	16.10% (13.9%-18.4%)	279	10.90% (9.7%-12.1%)
After 1989	540	6.70% (6.2%-7.3%)	168	3.80% (3.2%-4.3%)	155	15.10% (12.9%-17.3%)	217	8.50% (7.4%-9.6%)
Sex								
Male	3825	47.60% (46.5%-48.7%)	2345	52.50% (51.1%-54.0%)	373	36.40% (33.5%-39.4%)	1107	43.30% (41.4%-45.2%)
Female	4217	52.40% (51.3%-53.5%)	2118	47.50% (46.0%-48.9%)	651	63.60% (60.6%-66.5%)	1448	56.70% (54.8%-58.6%)
Live alone								
Yes	2709	33.70% (32.7%-34.7%)	1381	30.90% (29.6%-32.3%)	490	47.90% (44.8%-50.9%)	838	32.80% (31.0%-34.6%)
No	5333	66.30% (65.3%-67.3%)	3082	69.10% (67.7%-70.4%)	534	52.10% (49.1%-55.2%)	1717	67.20% (65.4%-69.0%)
Pre-pandemic psychiatric diagnosis	483	6.00% (3.9%-5.1%)	222	5.00% (4.3%-5.6%)	112	10.90% (9.0%-12.8%)	149	5.80% (4.9%-6.7%)
Pre-pandemic psychotropic medication	381	4.7% (5.5%-6.5%)	202	4.5% (3.9%-5.1%)	65	6.3% (4.9%-7.8%)	114	4.5% (3.7%-5.3%)
Pre-pandemic employment category								
Full time	4854	60.4% (59.3%-61.4%)	2622	58.8% (57.3%-60.2%)	627	61.2% (58.2%-64.2%)	1605	62.8% (60.9%-64.7%)
Part time	652	8.1% (7.5%-8.7%)	366	8.2% (7.4%-9.0%)	75	7.3% (5.7%-8.9%)	211	8.3% (7.2%-9.3%)
Self employed	306	3.8% (3.3%-4.2%)	208	4.7% (4.0%-5.3%)	27	2.6% (1.7%-3.6%)	71	2.8% (2.1%-3.4%)
Student	274	3.4% (3.0%-3.8%)	80	1.8% (1.4%-2.2%)	86	8.4% (6.7%-10.0%)	108	4.2% (3.4%-5.0%)
Unemployed	125	1.6% (1.3%-1.8%)	57	1.3% (0.9%-1.6%)	33	3.2% (2.1%-4.3%)	35	1.4% (0.9%-1.8%)
Retired	1622	20.2% (19.3%-21.0%)	1007	22.6% (21.3%-23.8%)	152	14.8% (12.7%-17.0%)	463	18.1% (16.6%-19.6%)
Other	209	2.6% (2.3%-2.9%)	123	2.8% (2.3%-3.2%)	24	2.3% (1.4%-3.3%)	62	2.4% (1.8%-3.0%)

Table 1. Characteristics of the study population and the three distinct loneliness trajectories.

Relationship with depression

To investigate the relationship between symptoms of depression and loneliness, depression scores for individuals in our study were obtained at four time points during the pandemic (May 2020, December 2020, August 2021, and May 2022). Symptoms of depression were estimated using the Patient Health Questionnaire-9 instrument (PHQ-9). PHQ-9 is a standardised, validated, multi-purpose instrument used for screening, diagnosis and measurement of depression. PHQ-9 contains nine questions that are rated on a scale from 0–3, resulting in an overall score of 0–27, with 27 indicating the highest level of depression symptoms. PHQ-9 has been described in depth elsewhere⁴⁰. The correlation between depression scores and loneliness was calculated in the entire study sample and for each response timepoint, using Pearson correlation coefficients. For identified loneliness trajectories mean depression scores were calculated for each time point.

Attrition analyses

Attrition was assessed by comparing the mean of all included PGSs between individuals with three questionnaire responses (included in the study) and individuals with less than three questionnaire responses.

Sensitivity analyses

Each of the multinomial models examining the association between PGS and loneliness trajectories were replicated including PGS for loneliness as a covariate.

Analyses were performed in RStudio Server 2023.12.1⁴¹ with a significance level of 0.05. All the analyses were exploratory with no critical hypothesis.

Results

Loneliness and social restriction index

In the entire study sample, there was a clear relation between the level of loneliness and social restriction index (Fig. 2a). This tendency was most pronounced among females who experienced higher levels of loneliness at all timepoints compared with males. The difference substantially increased when the social stringency index was at its highest (test of interaction OR = 1.22 [95% CI: 1.15–1.29]) (Fig. 2b).

Identification of distinct loneliness trajectories

Three distinct loneliness trajectories were identified in the study sample: *high loneliness* (n = 1024), *pandemic loneliness* (n = 2555) and *low loneliness* (n = 4463). The first trajectory, *high loneliness*, included individuals who had an elevated level of loneliness even before the COVID-19 pandemic. This trajectory also maintained the highest level of loneliness throughout the study period. The *high loneliness* trajectory appeared pandemic sensitive with mean loneliness levels exceeding 6 on UCLA-3, which has been used as a threshold for loneliness in other studies³⁷. The second trajectory, *pandemic loneliness*, was characterised by a relatively low level of both pre- and post-pandemic loneliness with a marked increase during the pandemic. Finally, the third trajectory, *low loneliness*, included individuals who had a stable low level of loneliness before, during and after the pandemic (Fig. 3a).

Characteristics of loneliness trajectories

Descriptive characteristics

Descriptive characteristics of the three identified trajectories are displayed in Table 1. The two loneliness trajectories (*high loneliness* and *pandemic loneliness*) were characterised by a large proportion of females (*high loneliness*: 63.3% [95% CI: 60.6%–66.5%] and *pandemic loneliness*: 56.2% [95% CI: 54.8%–58.6%] vs. *low loneliness*: 47.5% [95% CI: 46.0%–48.9%]). The *high loneliness* trajectory was distinguished from the other two trajectories (*pandemic loneliness* and *low loneliness*) by being younger (born after 1970: *high loneliness*: 51.3% vs. *pandemic loneliness*: 38.5% and *low loneliness*: 28.0%), more likely to live alone (*high loneliness*: 47.9% [95% CI: 44.8%–50.9%] vs. *pandemic loneliness*: 32.8% [95% CI: 31.0%–34.6%] and *low loneliness*: 30.9% [95% CI: 29.6%–32.3%]) and having almost double the prevalence of pre-pandemic psychiatric disorders (*high loneliness*: 10.9% [95% CI: 9.0%–12.8%] vs. *pandemic loneliness*: 5.8% [95% CI: 4.9%–6.7%] and *low loneliness*: 5.0% [95% CI: 4.3%–5.6%]) and increased redemption of psychotropic medication (*high loneliness*: 6.3% [95% CI: 4.9%–7.8%] vs. *pandemic loneliness*: 4.5% [95% CI: 3.7%–5.3%] and *low loneliness*: 4.7% [95% CI: 3.9%–5.1%]).

Polygenic profiles

The polygenic profiles of the trajectories are displayed in Fig. 3b where the two loneliness trajectories (*high loneliness* and *pandemic loneliness*) were compared with the trajectory *low loneliness*. High PGS for loneliness (*high loneliness*: OR = 1.19 [95% CI: 1.10–1.24], *pandemic loneliness*: OR = 1.06 [95% CI: 1.01–1.10]) and the 'big five' personality trait neuroticism (*high loneliness*: OR = 1.19 [95% CI: 1.11–1.25], *pandemic loneliness*: OR = 1.07 [95% CI: 1.02–1.11]) were associated with the loneliness trajectories. Low PGS for the 'big five' personality trait extraversion (OR = 0.90 [95% CI: 0.83–0.96]), and high PGS for psychiatric disorders (schizophrenia: OR = 1.07 [95% CI: 1.00–1.14], major depressive disorder: OR = 1.21 [95% CI: 1.12–1.26], autism spectrum disorder: OR = 1.13 [95% CI: 1.06–1.19], and attention deficit hyperactivity disorder: OR = 1.08 [95% CI: 1.01–1.15]) were associated with the *high loneliness* trajectory, while low PGS for the 'big five' personality traits agreeableness (OR = 0.94 [95% CI: 0.89–0.98]) and conscientiousness (OR = 0.94 [95% CI: 0.89–0.98]), and high PGS for religious participation (OR = 1.06 [95% CI: 1.01–1.11]) were associated with the trajectory *pandemic loneliness*.

In the entire study sample, loneliness and symptoms of depression were moderately correlated, with a correlation coefficient of 0.40. This relationship was stable in December 2020 (r = 0.37) and August 2021 (r = 0.37) but increased to 0.46 by May 2022, coinciding with the removal of most pandemic restrictions in Denmark. Each

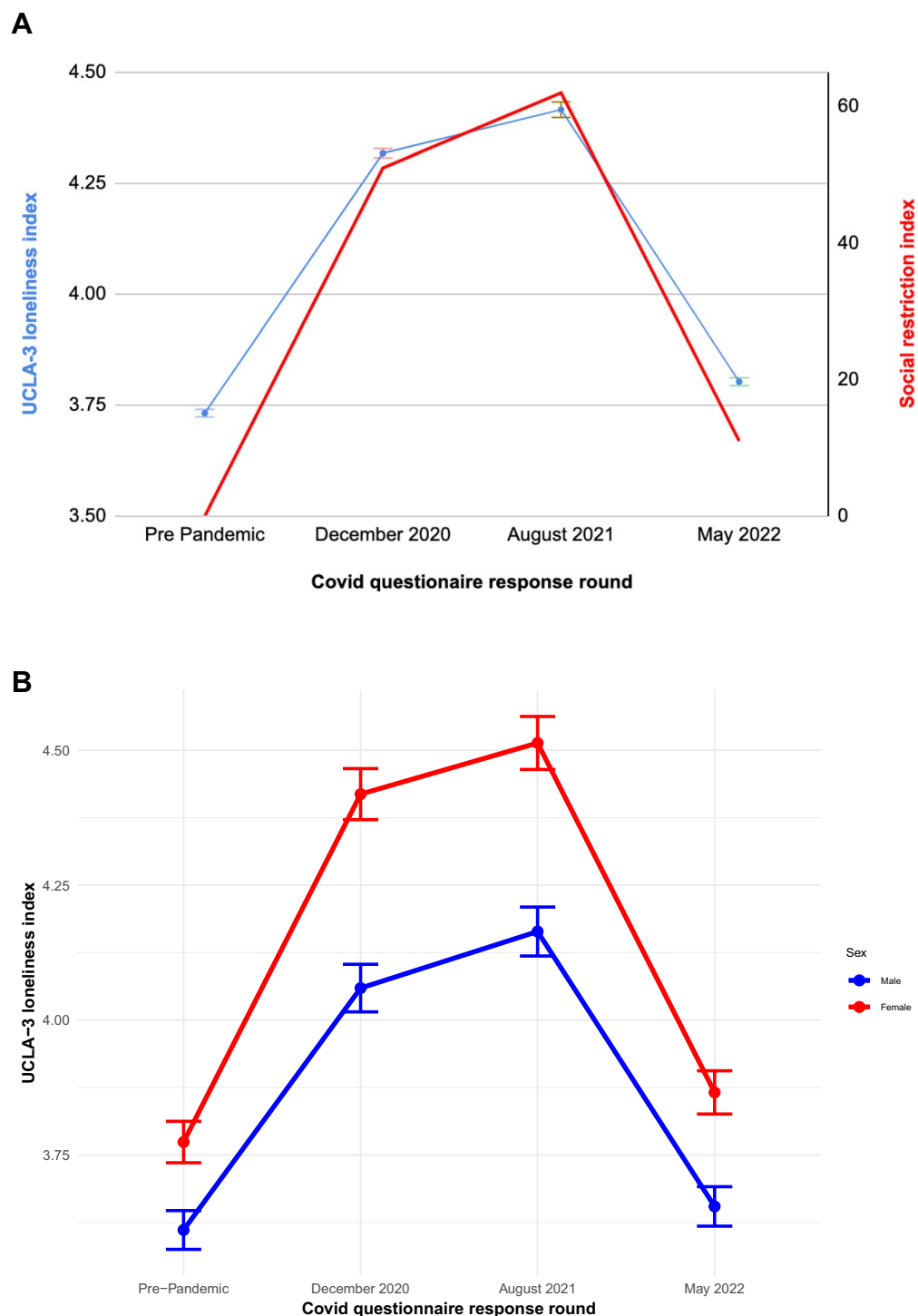


Fig. 2. (A) levels of loneliness and social restriction during different stages of the COVID-19 pandemic, and (B) experienced loneliness stratified on sex. Error bars represent the standard error of the means for both plots.

of the three loneliness trajectories had stable levels of depression symptoms with no marked changes observed throughout the study period. (see Appendix Supplementary Fig. 4).

Attrition

Individuals with less than three questionnaire responses had statistically significantly higher PGS for schizophrenia (mean, less than three responses: 0.01 [95%CI: 0.00–0.01] vs mean, more than three responses: -0.04 [95%CI: -0.06;-0.01]) and ADHD (mean, less than three responses: 0.01 [95%CI: 0.00;0.02] vs mean, more than three responses: -0.05 [95%CI:-0.08;-0.03]), while all other PGSs were not statistically different between these groups (see Appendix Supplementary Fig. 3).

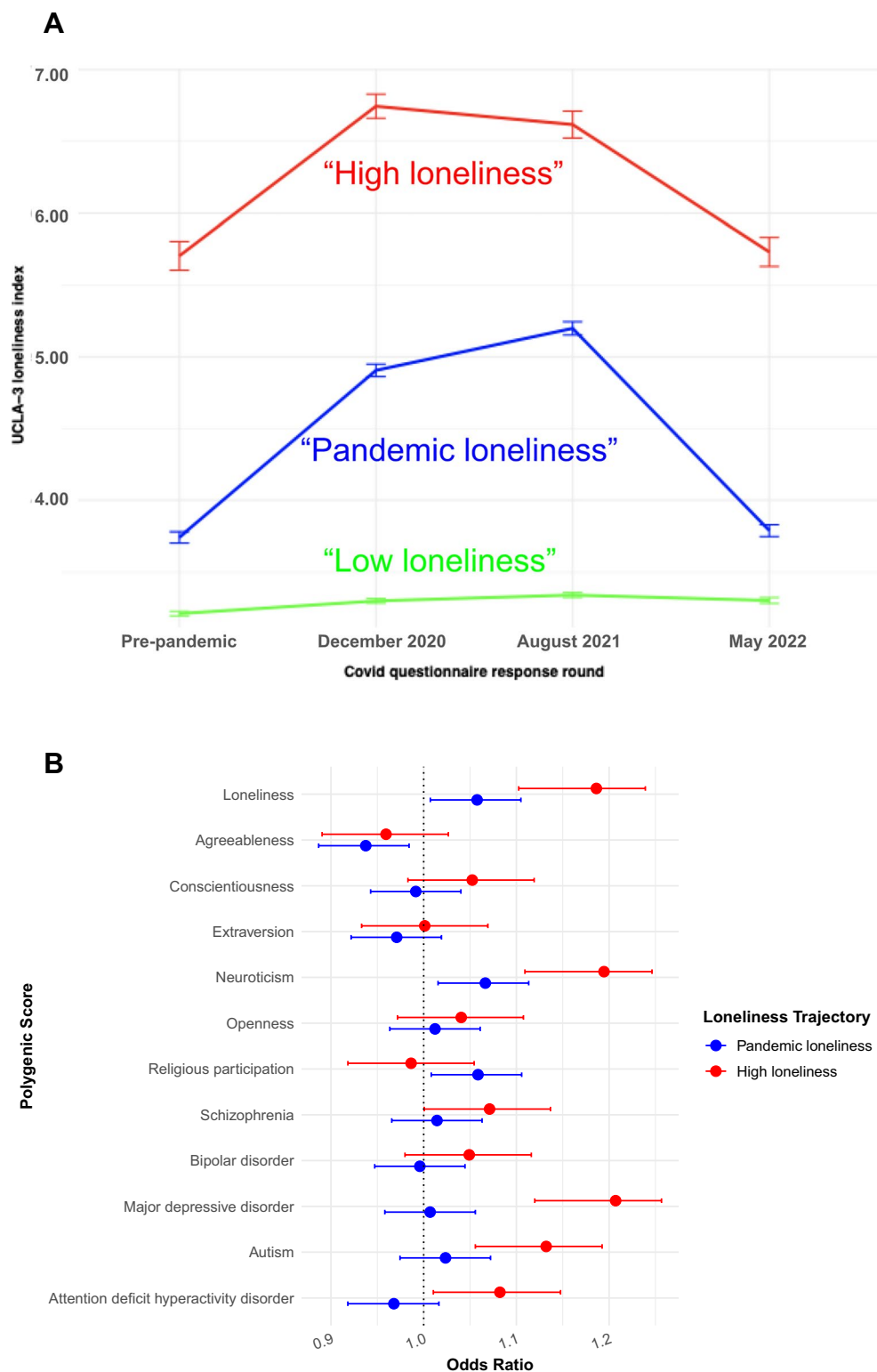


Fig. 3. (A) the three distinct COVID-19 loneliness trajectories: *high loneliness* ($n = 4463$), *pandemic loneliness* ($n = 2555$), and *low loneliness* ($n = 1024$). (B) comparisons of PGS between the loneliness trajectories (*high loneliness* and *pandemic loneliness*) and the trajectory *low loneliness* using a multinomial regression model. Error bars represent the standard error of the means for both plots.

Sensitivity analyses

The polygenetic profiles were generally robust to inclusion of the PGS for loneliness in the model (see Appendix Supplementary Fig. 2).

Discussion

In this large cohort study of 8,042 individuals from the DBDS with multiple follow-ups, we found an overall relationship between loneliness and pandemic restriction stringency index. Additionally, we identified three distinct trajectories of loneliness during the COVID-19 pandemic: *high loneliness*, *pandemic loneliness*, and *low loneliness*. Compared with individuals in the *low loneliness* trajectory, individuals in the *high loneliness* trajectory had higher PGS for loneliness, the 'big five' personality trait neuroticism, and each of the major psychiatric disorders. Moreover the individuals in this trajectory had low PGS for extraversion. Individuals in the *pandemic loneliness* trajectory had high PGS for loneliness, the 'big five' personality trait neuroticism and religious participation in addition to low scores on the 'big five' personality traits agreeableness and conscientiousness.

Analysis of the overall data revealed a significant but modest association between levels of reported loneliness and pandemic restriction stringency index (Fig. 2). Trajectory analysis revealed 55% of study participants reported consistently low levels of loneliness throughout the study period (Fig. 3). However, among the remaining individuals who reported marked increases in loneliness at the height of the pandemic, the relationship between pandemic restriction stringency index and loneliness showed the impact of lockdown measures on loneliness but also that the population returned to pre-pandemic levels of loneliness after the pandemic. This reflects a very situational manifestation of loneliness overall. The observed interaction between sex and restriction stringency index reflects concerns that negative impacts of lockdown measures such as loneliness were felt disproportionately by women⁴².

This is also corroborated by the loneliness trajectories where the two loneliness trajectories with elevated levels of loneliness had a higher proportion of females compared with the *low loneliness* trajectory. Concerns about women's mental wellbeing generally during the pandemic have been raised in many studies, with suggested factors including asymmetrical impacts on working life⁴³, childcare burdens⁴⁴ and domestic violence⁴⁵. As a result of these potential additional stressors, women may also have experienced increased levels of social isolation.

The three loneliness trajectories identified in this study, including both a dynamic trajectory characterised by high situational loneliness as well as a stable trajectory largely unaffected by the pandemic, are in line with previous research^{24–27}. This underscores the existence of different patterns of reaction to restrictions and lockdown depending on the liability of the individual and their circumstances. High PGS for loneliness and the 'big five' personality trait neuroticism were associated with the elevated *loneliness* trajectories (*low loneliness* and *pandemic loneliness*). This reflects that individuals with a high genetic liability for loneliness and neuroticism were more vulnerable to experiencing loneliness when macro-levels factors, like governmental enforced lockdowns were implemented. While it is not surprising that genetic liability for loneliness is associated with higher experienced loneliness, the results for neuroticism are also in line with the existing research, reporting that individuals with high PGS for neuroticism were more prone to experience loneliness⁹. It has previously been reported that individuals scoring high for neuroticism are likely to have disengaging coping strategies including denial, withdrawal, and wishful thinking as responses to a stressor⁴⁶. Hence, a disengaging coping strategy can often result in inappropriate responses to stressors and in this light it seems plausible that high genetic liability to neuroticism was associated with being placed in one of the elevated *loneliness* trajectories.

High PGS's for psychiatric disorders were associated with the *high loneliness* trajectory; hence, the increased experience of loneliness in this trajectory could be explained by poor mental health, which is supported by the high prevalence of pre-pandemic psychiatric disorders in this trajectory. Thus, it is not unlikely that poor mental health could result in less energy to establish and maintain a strong and supportive social network, especially in a pandemic setting with imposed lockdowns. This pattern may also be further reinforced by the low PGS for the 'big five' personality trait extraversion associated with this trajectory, as extraversion often is described by facets such as being active, assertive, energetic, enthusiastic, outgoing, and talkative⁴⁷.

Low PGS for the 'big five' personality traits agreeableness and conscientiousness were associated with the *pandemic loneliness* trajectory. Agreeableness characterises an individual's degree of trust in others, straightforwardness, altruism, social compliance, modesty, and tender-mindedness⁴⁸. Hence, this personality trait is highly related to social interaction as it influences both self-image, social attitude, and life philosophy⁴⁸. In this perspective, it seems plausible that individuals with low genetic liability for agreeableness experienced more loneliness during the COVID-19 pandemic, as they may have been less compliant and flexible to shifting social norms including imposed lockdowns. Additionally, it has previously been demonstrated that low scores on conscientiousness combined with high scores on neuroticism were associated with higher exposure to stress and strain, and a lower degree of problem-focused and engaging coping strategies⁴⁹.

Finally, the *pandemic loneliness* trajectory had high PGS for religious participation, potentially reflecting a vulnerability to loneliness when deprived of the social bonds usually maintained through religious practice. Research has shown that individuals who partake in active religious practice are happier than those who are inactive or not affiliated⁵⁰. On this background, it seems likely that individuals with high PGS for religious participation would have had an increase in loneliness when deprived of religious participation and its associated social environment during the pandemic lockdowns.

The overall moderate correlation between loneliness and depression observed in the present study aligns with previous research highlighting the strong relationship between the phenomena. Interestingly, the correlation remained stable during the pandemic's height (December 2020) and midpoint (August 2021) but increased markedly by May 2022, when most pandemic restrictions were lifted in Denmark. This could reflect that other factors such as social restrictions and lockdowns had a larger impact on levels of loneliness during the pandemic, but once these restrictions were lifted, other personal factors such as symptoms of depression became more

important for the experienced level of loneliness. Hence, individuals who remained lonely post-pandemic may represent a particularly vulnerable subgroup (i.e., members of the *high loneliness* trajectory), contributing to the stronger correlation observed during this period. This explanation is also consistent with the stable levels of depression symptoms observed in each trajectory. While the *high loneliness* trajectory remained high in both loneliness and depression symptoms at the end of the pandemic when the correlation increased, the *pandemic loneliness* trajectory decreased their level of loneliness at this point.

Strengths and limitations

Several strengths of this study deserve mention. Firstly, the large study population provided increased statistical power and reduced random errors. Secondly, our measure of loneliness was sensitive to changes in social restriction index (a macro level factor expected to impact on loneliness), indicating that UCLA-3 is sensitive to shifting norms over time. Thirdly, the multiple follow-up design allowed prospective assessment of the same individuals over time enabling assessment of changes and lowering risk of bias related to cohort effects. Finally, we included a broad range of both genetic, demographic, and socioeconomic factors allowing thorough descriptions of each identified trajectory. However, information on psychiatric diagnoses and psychotropic medication was only available from 1995 and onwards, potentially resulting in misclassification.

For the trajectory analysis it was required that participants had responded to all three questionnaires, this may have resulted in lower functioning individuals to be excluded, although this not is a major concern as the attrition analysis showed very small difference between individuals with three and individuals with less than three responses. In addition, the study was conducted among recurrent blood donors who are known to be healthier than the general population and reflect differing underlying demographic properties⁵¹. The skew towards middle-aged and older adults, with limited representation of younger individuals restricts the scope of conclusions about loneliness trajectories in younger populations and highlights an important direction for future research. Thus, the identified impact of social restrictions might be lower than in the general population and the findings from the study may not be generalisable to other cohorts. Finally, estimation of loneliness prior to the pandemic was based on a retrospective measure obtained during the pandemic, which could result in differential recall. Moreover, differential misclassification could also exist if individuals scoring high on e.g. neuroticism were more likely to report higher levels of loneliness than individuals scoring low on neuroticism.

Conclusions

The present study showed that the nationwide restriction levels related to the COVID-19 pandemic had a clear overall effect on levels of loneliness, with particular vulnerability for females at the height of social restriction measures.

Trajectories of loneliness during the COVID-19 pandemic were characterised by different demographic and polygenic profiles, relevant for interventions against loneliness. Hence, this study consistently showed that the individuals most severely impacted by social restrictions during the pandemic were already vulnerable to mental illness and had a personality composition allowing for tailored focus and intervention. Based on these findings, prevention of loneliness should target individuals with low mental wellbeing, as this was the best indicator of liability to general loneliness and loneliness in a pandemic setting and thus likely applicable in other macro-level scenarios beyond disease pandemics and associated societal restrictions.

Data availability

Person-level data from DBDS needed to reproduce this study cannot be made publicly available due to confidentiality legislation. Meta-data and programs are available from the authors upon reasonable request and with permission of the DBDS steering committee, the Ethical Committee, and the Danish Data Protection Agency. Enquiries about legal possibilities for accessing these data within DBDS, scripts/codes and further information should be addressed to the corresponding author.

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Author contributions

L.Q. and L.C. wrote and prepared the manuscript text. L.Q., L.C., and O.B.P. devised the analyses and hypotheses. L.Q. carried out all analyses and prepared all the figures. All authors reviewed the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

All procedures performed in study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (The Zealand and Central Denmark Regional Committees on Health Research Ethics [SJ-740 and 1-10-72-95-13] and the Data Protection Agency [P-2019-99]). Furthermore, genetic studies in the DBDS cohort were approved by the Danish National Committee on Health Research Ethics (NVK-1700407). Informed consent was obtained from all individuals included in the study.

Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-025-02293-4>.

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