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Prolonged Childhood and Adolescent Loneliness in First-Episode Psychosis: Synergistic Polygenic Effects and Functional Outcomes

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ABSTRACT

Background. Prolonged childhood and adolescent loneliness (CAL) may mark an early socio-emotional vulnerability relevant to psychosis and interact with genetic liability. We examined whether CAL increases odds of first-episode psychosis (FEP), relates to diagnostic subtype and functioning, and interacts with polygenic risk scores (PGS) for schizophrenia (SCZ), bipolar disorder (BIP), and major depression (MDD).

Methods. We analysed 2,565 participants (1,084 FEP, 1,481 controls) from EU-GEI. CAL was assessed retrospectively before age 12 (LNL12) and at 12–16 years (LNL12–16). Functioning was rated with a modified Global Assessment of Functioning. Genome-wide PGS for SCZ, BIP, and MDD were calculated using PRS-CS. Mixed-effects logistic and linear regression models tested associations of CAL with FEP, subtype, and functioning,

including sex-stratified analyses. Additive gene–environment interaction was examined using dichotomised PGS and the Relative Excess Risk due to Interaction.

Results. Both LNL12 (OR=2.90, 95% CI 2.30–3.66) and LNL12–16 (OR=2.34, 95% CI 1.94–2.84) were associated with FEP, independent of premorbid social isolation. CAL increased FEP odds in both sexes. LNL12–16, but not LNL12, was associated with affective versus non-affective psychosis (OR=1.37, 95% CI 1.02–1.83), more clearly in females (OR=1.79, 95% CI 1.16–2.77). CAL was also associated with poorer functioning, with 3–4-point lower GAF Disability scores. Significant additive interactions were observed between LNL12–16 and SCZ-PGS, and between LNL12 and MDD-PGS, although the latter did not replicate in European-ancestry sensitivity analyses.

Conclusions. Prolonged CAL is linked to higher risk of FEP, preferentially affective psychosis in females, poorer functioning, and developmental potentiation of polygenic liability.

Keywords: childhood and adolescence; loneliness; first-episode psychosis; schizophrenia; affective psychosis; non-affective psychosis; functionality; polygenic risk scores; gene–environment interaction.

Introduction

First-episode psychosis (FEP) is a heterogeneous syndrome characterized by disturbances in thought, perception, and emotions (1). Approximately 30–55% of individuals with FEP progress to Schizophrenia Spectrum Disorders (SSD) (2,3), while only about one in seven achieve long-term full recovery (4). These findings underscore the importance of early detection and intervention, including identifying early dysfunction markers, to improve long-term outcomes(5).

Childhood and adolescence represent a critical developmental window for psychosis risk due to heightened neurobiological development and plasticity, the onset of major social-emotional transitions, and a greater stress sensitivity (6). Loneliness, a subjective emotion of social disconnection, has become a significant contributor to mental health vulnerability during these stages (7). Prevalence estimates during childhood and adolescence vary across studies, with some reporting rates around 40%, while a recent global meta-analysis estimated pooled adolescent loneliness prevalence between 9.2% and 14.4% across world regions. (6,7) Longitudinal research has linked persistent loneliness across development to adverse mental health outcomes, including psychotic-like experiences, mood instability, and difficulties in social cognition, with recent adolescent data further showing that persistent loneliness is associated with subsequent psychotic experiences and broader affective and well-being outcomes(8–10).

Psychosis is increasingly conceptualized within multifactorial frameworks in which genetic liability and social-environmental exposures may jointly contribute to risk (11). Polygenic scores provide a quantitative measure of liability for major psychiatric disorders and offer a useful framework for examining gene–environment interplay. For individuals at risk of psychosis, loneliness can function as a source of subjective adversity, potentially contributing to increased vulnerability to affective and non-affective symptomatology and impairment in functioning (11). In our previous EU-GEI work, prolonged loneliness during childhood and adolescence(CAL) was associated with SSD, symptom dimensions, and patterns consistent with interaction with schizophrenia-related polygenic liability, while also improving risk stratification beyond SCZ polygenic liability alone (12). In FEP, however, the phenotype is more heterogeneous and diagnostically less consolidated than in established SSD, particularly at illness onset. Accordingly, it is important to determine whether CAL is associated not only with case status, but also with diagnostic subtype, functional impairment, and polygenic liability across SCZ, bipolar disorder (BIP), and major depression (MDD).

The present study aims to address previous research gaps by examining the association between prolonged CAL and FEP focusing on three primary objectives: (i) to assess whether prolonged CAL was associated with FEP and diagnostic subtype; (ii) to assess

the effect of CAL on functional and clinical impairment; and (iii) to investigate the interaction between prolonged CAL and genetic liability for three severe mental disorders (SCZ, BIP, and MDD) in relation to FEP risk and functioning using the Relative Excess Risk due to Interaction (RERI) method. Given sex differences in the clinical presentation of psychosis and evidence that the effect of loneliness on psychosis risk varies by sex (10–14), we also conducted sex-stratified analyses to examine these associations, hypothesizing that females may be more susceptible to CAL-mediated pathways to psychosis.

Methods

Study Population

Data were collected between 2010 and 2015 across 17 sites in 6 countries (UK, the Netherlands, France, Spain, Italy, and Brazil) as part of WP2 of the EU-GEI project Study Population. The initial recruited sample included 2,627 participants (1,130 FEP and 1,497 HC). The main phenotypic analytic sample comprised 2,565 participants (1,084 FEP and 1,481 HC) with complete data on both developmental loneliness measures. Genome-wide data passing genetic quality control were available for 2,147 participants (903 FEP and 1,244 HC), and the final polygenic score analytic sample comprised 2,000 participants (809 FEP and 1,191 HC) with complete genetic, CAL, and covariate data. The sample was recruited from defined catchment areas, with cases and controls ascertained within the participating geographical areas according to the study protocol. Participants with FEP were included if they were aged 18–64, resided in the catchment area, and had a clinical diagnosis of FEP with minimal prior treatment. Individuals were excluded if they had a previous psychotic disorder, organic psychosis (ICD-10: F09), or psychotic symptoms due to intoxication (ICD-10: F1X.5). Clinically trained psychiatrists identified patients to ensure comprehensive case identification. Further details can be found elsewhere (13) and in **Supplementary Information (SI)**.

Clinical assessment

Recruitment and assessment procedures were conducted by research teams comprising trained nurses and clinical psychologists, supervised by psychiatrists with experience in epidemiological research. Additional details about recruitment strategies, sample representativeness, and assessment methodologies are provided elsewhere (13). Diagnosis of FEP was validated using the Operational Criteria Checklist for Psychotic and Affective Illness (OPCRIT). Clinical diagnoses at baseline were classified into 2 broad categories—schizophrenia-spectrum disorder and affective psychosis—using DSM-IV diagnoses derived from OPCRIT, in line with previous work in this sample (14). We assessed prolonged CAL by asking participants, "Have you ever felt lonely for a significant period (i.e., 6 months or longer)?" at two time points: before the age of 12 (LNL12) and between ages 12 and 16 (LNL12-16). This measure was selected to capture prolonged loneliness during two developmental periods of interest. Recent work has shown that single-item loneliness measures can provide valid screening information in population-based settings, although their use remains more limited than that of multi-item instruments (15,16). We used "peer relationships" and "sociability and withdrawal" scores separately for ages under 12 and ages 12-16 from the Premorbid Adjustment Scale (PAS) as a proxy for social isolation in childhood and adolescence for sensitivity analyses. PAS-based sensitivity analyses were included to examine whether the observed associations remained when accounting for premorbid social isolation and interpersonal functioning. Trained professionals conducted PAS assessments and were based on participants' retrospective reports, which may also be subject to recall bias. To further characterise the overlap between the one-item prolonged loneliness measures and PAS-derived interpersonal domains, Spearman rank correlations were calculated between LNL12, LNL12–16, PAS peer relationships, and PAS sociability/withdrawal scores across the corresponding developmental periods. The Global Assessment of Functioning (GAF) scale was employed to assess both symptom severity (GAF Symptoms) and functional impairment/disability (GAF Disability). Higher scores indicate better functioning (i.e., lower symptom severity and less impairment). For the EUGEI study, a modified version of the GAF was applied, separating the original scale into two distinct components (Symptoms and Disability) to allow for a more specific evaluation. Previous research has shown acceptable reliability of the GAF in both clinical and research settings (17,18).(see **SI**).

Calculation of Severe Mental Disorders polygenic risk scores

Samples were genotyped at Cardiff University using custom Illumina HumanCoreExome-24 BeadChip genotyping arrays (570,038 genetic variants, Illumina, SanDiego,CA). Quality control and variant imputation have been previously described (See(19) or **SI** for detailed description). We used the polygenic risk score–continuous shrinkage (PRS-CS) method(20) to estimate genome-wide polygenic scores of SCZ, BIP, and MDD (SCZ-PGS(21), BIP-PGS(22), MDD-PGS(23)) using European-only leave-one-out summary statistics from the latest schizophrenia PGC3-GWAS (excluding overlapping EUGEI samples), PGC-BIP, and PGC-MDD GWAS. See **Supp Data 8** for further detailed information on GWAS summary statistics. The association of PGS with case-control status was examined through logistic regression, adjusting for age, sex, and the 10 first PCA-derived ancestry components (see **SI**).

Statistical Analyses

Mixed-effects regression models with a random intercept for country were used to assess associations between CAL and both FEP–control status and GAF scores. Separate models examined the effects of LNL12 and LNL12–16 on FEP. Multilevel logistic regression was applied to test associations of LNL12/LNL12–16 with case–control status and with affective versus non-affective psychosis, with age, sex, and loneliness as fixed effects and country as a random effect. Sensitivity analyses included adjustments for peer relationships or sociability/withdrawal during childhood and adolescence. Mixed linear regression models evaluated the association between LNL12/LNL12-16 and log-transformed GAF scores (GAD-symptoms, GAF-Disability), including clinical group (case/control) as an additional fixed effect. This set of analyses was further stratified by case-control status.

We tested for an interaction (CAL x sex) in each model to formally assess effect modification by sex. In addition, we conducted sex-stratified analyses across all models to examine potential sex-specific effects of CAL. Finally, we assessed the interaction

between LNL12/LNL12-16 and PGS on FEP. We first checked for a correlation between the three severe mental disorders' PGS (SCZ-PGS, BIP-PGS, MDD-PGS) and CAL in controls. Following previous studies with this cohort (24), we used dichotomized PGS using the highest quartile (>75%) of the control population as a cut-off. The interaction between CAL and dichotomized PGS on case-control status was assessed using multilevel logistic models, adjusting for age, sex, and the first 10 PCA ancestry components as fixed effects and country as a random effect. Gene-environment interaction on the additive scale was assessed using the Relative Excess Risk due to Interaction (RERI), which estimates whether the combined effect of CAL and polygenic liability is greater than the sum of their individual effects. 95% confidence intervals (95%CI) were calculated with bootstrap percentile method (1,000 permutations), accounting for the mixed model architecture using *BootMer* R package. In those cases where $RERI > 1$, GxE significance was evaluated by empirical p-values (Boot-p) estimated as the percentage of predictions $RERI < 0$ after bootstrapping. We further assessed the interaction between CAL (LNL12/LNL12-16) and PGS (SCZ-PGS, BIP-PGS, MDD-PGS) on GAF scores (symptoms and disability) using mixed linear regression models adjusting for age, sex, clinical group, and the first 10 PCA ancestry components as fixed effects and country as a random effect.

To account for ancestry heterogeneity within the EU-GEI cohort, sensitivity GxE analyses were conducted, restricting the sample to individuals with >80% estimated European ancestry, as determined by ADMIXTURE analysis using the 1000 Genomes Project as a reference panel (see Supplementary Methods SM4 and Supplementary Figure SF2 for details). These sensitivity models were applied to all GxE combinations, yielding $RERI > 1$ in the main analysis.

We applied a Benjamini-Hochberg false discovery rate (FDR) method for multiple testing correction. All analyses were conducted in R.

Results

Association Between CAL and FEP

Table 1 shows demographic and clinical data for participants with complete childhood/adolescent loneliness data, comprising 2,565 participants, including 1,084 individuals with FEP and 1,481 healthy controls. Overall, the FEP sample was younger and included a higher percentage of males. As expected, FEP patients reported CAL more frequently and showed lower GAF disability and symptom scores than healthy controls, indicating greater functional impairment in the clinical group. Within the FEP group, non-affective psychoses (n = 760) were more frequent than affective psychoses (n = 301) and were associated with slightly lower GAF scores and less frequent CAL; further details on these subtypes are provided in **SI** (ST3, SF1). The top of **Figure 1** summarizes the logistic regression results examining the association between prolonged childhood (LNL12) and adolescent (LNL12–16) loneliness and first-episode psychosis (FEP). In the main models, both LNL12 (OR [95% CI] = 2.90 [2.3; 3.66], FDR p = 7.73×10^{-19}) and LNL12–16 (OR [95% CI] = 2.34 [1.94; 2.84], FDR-p = 1.71×10^{-18}) were significantly associated with higher odds of FEP. When controlling for social isolation through sensitivity analyses using the PAS Peer Relationships or Sociability and Withdrawal subscales at the corresponding time periods, the results remained robust in both effect size and significance, with only a slight reduction in the OR for adolescence. Additional analyses showed moderate temporal continuity of CAL across developmental periods ($\phi = 0.60$; Cohen’s kappa = 0.57), and small correlations with PAS-derived interpersonal domains across developmental periods (Spearman’s rho = 0.17–0.22; all p < 0.001; **see ST1 and ST2**). Sex-stratified analyses indicated that LNL12 and LNL12–16 conferred elevated odds of FEP in both males (OR [95% CI] = 2.86 [2.02; 4.06] and 2.07 [1.58; 2.71]) and females (OR [95% CI] = 2.88 [2.11; 3.95] and 2.52 [1.94; 3.28], respectively), with comparable effects for LNL12 and a trend toward stronger effects in females for LNL12–16; **ST3**).

Association Between CAL and FEP Diagnostic Subtypes
 LNL12-16, but not LNL12, was significantly associated with higher odds of affective relative to non-affective psychosis (OR [95% CI]= 1.37 [1.02-1.83], FDR p = 0.045). Although the interaction between CAL and sex was not significant, sex-stratified analyses indicated that only females reporting LNL12-16 had significantly higher odds of affective relative to non-affective psychosis (OR [95% CI]=1.79[1.16-2.77] FDR p =

0.024), whereas the association was not observed in males (OR=1.08, 95% CI=0.71–1.63; FDR p=0.724; **Figure 1**, Supp Data 3).

Association Between CAL and Functionality

CAL was significantly associated with lower GAF disability scores ($\beta = -3.4$, FDR $p < 0.001$), suggesting poorer functionality among participants reporting prolonged loneliness. These results were consistent with GAF symptom scores (Supp Data 4). The interaction terms with sex were not significant, and sex-stratified analyses yielded similar effect sizes in males (e.g., LNL12 $\beta = -3.53$; FDR $p = 2.22 \times 10^{-3}$; LNL12–16 $\beta = -3.44$; FDR $p = 2.00 \times 10^{-4}$) and females (LNL12 $\beta = -3.41$; FDR $p = 6.65 \times 10^{-4}$; LNL12–16 $\beta = -3.83$; FDR $p = 4.36 \times 10^{-6}$). When analyses were restricted to cases, the pattern remained for GAF disability, with comparable effect sizes for LNL12 ($\beta = -2.69$; FDR $p = 0.042$) and LNL12–16 ($\beta = -2.54$; FDR $p = 0.032$), whereas no clear associations were observed for GAF symptom scores (**Figure 2** and **Supp Data 4**)

Interaction between severe mental disorder PGS and CAL on FEP risk.

There were no significant differences in age, sex, or LNL12/LNL12-16 between the complete dataset and the subset with genetic information available (74.24% of the whole dataset) across subjects with FEP or controls (**Supp Data 5**).

We found evidence of additive interaction between SCZ-PGS and LNL12–16 (RERI [95%CI] = 2.04 [-0.18; 5.13]; Boot-p = 0.036) on FEP status (**Figure 3**, **Table 2**). A significant interaction was also observed between MDD-PGS and LNL12 (RERI [95%CI] = 2.14 [-0.16; 5.43]; Boot-p = 0.032). Although bootstrap p-values were below the conventional threshold, both 95% percentile confidence intervals include zero, reflecting the right-skewed distribution of RERI under additive decomposition of multiplicative models rather than a formal inconsistency; accordingly, both findings should be interpreted as exploratory. In sensitivity analyses restricted to individuals with >80% estimated European ancestry (n = 499 cases, 825 controls), the SCZ-PGS $\times$ LNL12–16 interaction was directionally preserved (RERI [95%CI] = 1.42 [-0.78; 4.96]; Boot-p = 0.091), consistent with attenuation due to reduced statistical power. The MDD-PGS $\times$

LNL12 interaction, however, attenuated substantially in this restricted sample (RERI [95%CI] = 0.10 [-2.49; 3.40]; Boot-p = 0.514), and should therefore be interpreted with particular caution (**Supp Data 7, SM4**). No significant G×E interactions were found between BIP-PGS and LNL12 (RERI[95%CI] = 1.95[-0.50;5.47]; Boot-p = 0.061).

These interaction effects observed were not attributable to correlation, as there was no significant association between PGS and CAL within the control group (**Supp Data 6**). Moreover, no significant G×E interactions were detected between SCZ-PGS, BIP-PGS, or MDD-PGS and CAL (LNL12 or LNL12–16) by sex. Likewise, no significant G×E interactions were observed between these PGS and CAL for GAF-Disability or GAF-Symptoms (**Supp Data 7**).

Discussion

To our knowledge, this is the first study to link prolonged CAL with FEP, and the first to report G×E interactions between CAL and genetic liability for different severe mental disorders linked with a FEP. CAL was associated with increased odds of FEP and poorer functional outcomes, indicating worse functioning among those reporting prolonged loneliness. We detected no significant interaction with sex, but found larger effect sizes in females for adolescent loneliness. Regarding G×E, we observed preliminary evidence of an additive interaction between adolescent loneliness and SCZ-PGS for FEP risk, which was directionally preserved in sensitivity analyses restricted to individuals of European ancestry. A significant interaction was also observed between childhood loneliness and MDD-PGS, though this did not replicate in the European-ancestry restricted sample and should therefore be considered with particular caution. Given the marginal bootstrap p-values and confidence intervals spanning zero across all G×E estimates, these findings are best considered hypothesis-generating. Finally, CAL was associated with higher odds of affective psychosis, with this association reaching significance only among females in stratified analyses.

Previous research has linked loneliness to an increased risk of psychosis and poorer outcomes in SSD (9,25). Early-psychosis research has predominantly assessed loneliness

at presentation or in early years; by contrast, our study evaluates prolonged loneliness within defined developmental windows before onset. In the full sample, CAL is associated with higher odds of FEP and with lower global functioning. These findings align with prior work demonstrating that loneliness in youth is associated with impaired cognition and greater symptom severity in individuals at high risk for psychosis (26,27). The observed effect of CAL on FEP risk was smaller than that reported in our previous study focusing on long-term schizophrenia spectrum disorder patients(12). This pattern is broadly consistent with differences in clinical stage, as FEP samples are likely to be less clinically consolidated and less functionally impaired than chronic SSD samples, who report higher rates of childhood adversity and show stronger adversity–symptom associations than FEP samples, resulting in a greater contrast with healthy controls(28,29).

Adolescent CAL was more closely associated with affective than non-affective psychosis, suggesting that prolonged loneliness during this developmental period may be particularly relevant to the affective expression of FEP. This is consistent with broader evidence linking persistent loneliness across adolescence not only to psychotic experiences, but also to depression, anxiety, and diminished well-being(10,30,31), reinforcing the view that loneliness may index a developmental vulnerability with both psychotic and affective disorders. In our sample, this pattern was more apparent in females in stratified analyses, which is in line with our previous EU-GEI findings (12) and with evidence suggesting a potentially greater genomic overlap between loneliness and schizophrenia risk variants in females (32). However, as formal interaction tests with sex were not significant, these findings are best considered exploratory. Nonetheless, they support the clinical relevance of assessing loneliness at the onset of affective symptoms and affective psychosis within FEP.

GAF analyses indicate that prolonged CAL was associated with poorer functional outcomes, particularly on the disability dimension. In the full sample, CAL was associated with lower adjusted GAF scores by approximately 3–4 points, and the association with GAF disability remained when analyses were restricted to clinical cases. Although these adjusted effects were modest, they may still reflect an early functional disadvantage(33). In FEP, this may be informative because global functioning at illness

onset has been associated with subsequent functional outcome, suggesting that even modest differences may be relevant to later course(34,35). This pattern highlights the relevance of early loneliness for social and interpersonal functioning and, given the more robust association with GAF disability than with GAF symptom scores, suggests that the functional correlates of developmental loneliness may extend beyond symptom severity alone. (36,37).

While adverse childhood experiences, such as trauma and neglect, are well-established risk factors for psychosis and schizophrenia (38–40), prior research using this same cohort found no evidence of interaction between genetic risk and childhood trauma in FEP (24). This contrasts with findings from related studies, which have reported significant interactions between schizophrenia polygenic scores and broader exposome measures (41). Supporting the importance of developmental timing, we propose that prolonged loneliness represents a distinct psychosocial stressor, positioned at the intersection between biological and subjective experience, qualitatively different from commonly studied forms of adversity (42,43).

We identified a preliminary interaction between adolescent loneliness and SCZ-PGS on FEP risk, supported by bootstrap-based p-values and directionally consistent across the main and European-ancestry restricted analyses. A significant interaction was also observed for childhood loneliness and MDD-PGS in the main analysis; however, given its attenuation in the ancestry-restricted sensitivity analysis, this finding raises the possibility of differential modulation of depression-related polygenic liability by early loneliness, but requires independent replication before substantive interpretation. Together, these patterns are broadly consistent with stage-specific gene–environment × time interactions reported in the literature, including the adolescent stress and 5-HTTLPR interaction in depression and the childhood Epstein–Barr virus × HLA-DRB1-15 interaction implicated in pediatric-onset multiple sclerosis (29,30). However, both studies relied on a single allele and had limited power. Despite earlier evidence of gene–environment interactions influencing early psychosis adjustment (44), no interaction effects were observed for GAF outcomes. Additional research is necessary to validate these gene–environment interactions and investigate their underlying mechanisms.

Given that loneliness can be systematically identified through brief self-report screening in early intervention settings(15) and is amenable to psychosocial treatment (e.g., CBT-based approaches and social skills interventions)(45,46), our findings support further investigation of loneliness-focused approaches within preventive and clinical pathways in youth mental health services, particularly as an early marker of socio-emotional vulnerability (47).

Limitations

Several limitations should be acknowledged. First, CAL was assessed retrospectively using a single-item measure and may therefore be influenced by recall bias. At the same time, recent evidence supports the utility of brief single-item loneliness measures in large-scale assessments, including acceptable construct validity in population-based samples (15). Recent preprint work has also reported strong convergence between a direct one-item loneliness measure and short multi-item loneliness scales, although this evidence remains preliminary (16). No contemporaneous measure of loneliness was available in this sample; therefore, we could not directly examine the relationship between retrospective CAL and current loneliness. Although this limits direct validation in the present sample, recent longitudinal evidence supports the developmental and clinical relevance of repeated brief loneliness assessments across adolescence, including subsequent psychotic experiences and broader adverse mental health outcomes (10). Sensitivity analyses using PAS scores remained significant, although PAS was also assessed retrospectively in adulthood and is therefore not exempt from recall bias. Additional supplementary analyses further characterised temporal continuity and cross-period CAL–PAS associations; nevertheless, further validation of retrospective CAL measures using objective childhood indicators or contemporaneous functioning measures would be valuable. In addition, EU-GEI WP2 is not an epidemiological population sample, and findings may therefore be influenced by factors related to case ascertainment and service-based recruitment. Second, while our study benefits from a large sample size, stratification by genetic risk and CAL, particularly childhood loneliness, may have resulted in reduced statistical power. Third, medication status and substance use were not included as covariates in the present analyses. Both may influence functioning at assessment and, potentially, retrospective reporting, and should

therefore be considered in future work. Fourth, our sample predominantly comprises individuals of European ancestry, limiting generalizability to other populations. Moreover, the use of a dichotomized genetic risk measure may limit the precision of our interaction analyses. We acknowledge that this approach may reduce statistical power and precision relative to continuous PGS models, particularly in stratified analyses with smaller cell sizes. However, this dichotomization strategy was adopted to maintain consistency with prior work in this cohort and to enable the estimation of additive G×E interaction via RERI, which requires binary exposure classifications. In particular, the G×E interaction results using RERI should be considered exploratory given the marginal bootstrap p-values and the inclusion of zero in the 95% percentile confidence intervals, the latter being an expected consequence of the right-skewed bootstrap distributions rather than an indication of formal inconsistency. Furthermore, whereas the SCZ-PGS × adolescent loneliness interaction was directionally preserved in sensitivity analyses restricted to individuals of >80% estimated European ancestry, the MDD-PGS × childhood loneliness interaction attenuated substantially in this restricted sample, precluding firm conclusions about this specific finding and underscoring the need for replication in larger, ancestry-diverse cohorts. Future studies should employ continuous PGS specifications and larger samples to improve power and precision. In addition, heterogeneity within FEP subtypes and the relatively smaller size of some subgroups (e.g., female participants and specific diagnostic categories) may have limited power to detect more subtle interaction effects. Future studies should incorporate more granular genetic and environmental data to refine predictive models. Finally, given the number of statistical tests conducted, our findings should be interpreted with caution and considered most robust where results converged across FDR-corrected and bootstrap-based estimates.

Conclusion

Our findings highlight the association between prolonged CAL and increased risk for FEP, as well as functional impairment. The preferential association of CAL with affective psychosis suggests a potential role of mood dysregulation, especially in females. Additionally, the interaction between adolescent loneliness and schizophrenia genetic liability suggests a degree of time-genetic specificity in psychosis risk, with preliminary

evidence for a parallel pattern with depression-related liability that warrants replication. Given the necessity of prodromal markers that capture clinical trajectories, these findings support the importance of early identification strategies for modifiable psychosocial factors, such as prolonged loneliness, to mitigate their long-term impact. Future research should further elucidate the biological and psychosocial mechanisms underlying these associations and refine predictive models by incorporating loneliness alongside additional environmental and genetic factors. In parallel, youth-focused loneliness interventions should be tested in high-risk and early psychosis services to determine whether targeting loneliness can modify illness trajectories.

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	<i>ALL</i>	<i>FEP</i>	<i>HC</i>
<i>N</i>	2565	1084	1481
<i>Age (mean, SD)</i>	34.00 (12.2)	31.21 (10.61)	36.05 (12.9)
<i>Females (N, %)</i>	1198 (46.7%)	415 (38.3%)	783 (52.9%)
<i>Males (N, %)</i>	1367 (53.3%)	669 (61.7%)	698 (47.1%)
<i>Country: UK</i>	564 (22.0%)	230 (21.2%)	334 (22.6%)
<i>Country: Holland</i>	401 (15.6%)	193 (17.8%)	208 (14.0%)
<i>Country: Spain</i>	419 (16.3%)	198 (18.3%)	221 (14.9%)
<i>Country: France</i>	240 (9.4%)	95 (8.8%)	145 (9.8%)
<i>Country: Italy</i>	448 (17.5%)	177 (16.3%)	271 (18.3%)
<i>Country: Brazil</i>	493 (19.2%)	191 (17.6%)	302 (20.4%)
<i>Loneliness < 12 (N,%)</i>	382 (14.9%)	239 (22.0%)	143 (9.7%)
<i>Loneliness 12–16 (N,%)</i>	640 (25.0%)	365 (33.7%)	275 (18.6%)
<i>GAF Disability (mean, SD)</i>	70.29 (21.62)	50.93 (16.78)	84.36 (11.33)
<i>GAF Symptom (mean,SD)</i>	67.78 (22.95)	46.94 (17.54)	82.89 (11.83)

Table 1. Demographic and clinical characteristics of participants with complete CAL data. Age, sex, country, childhood and adolescence loneliness (CAL), and Global Assessment of Functioning (GAF) disability and GAF symptom scores (mean, SD) are presented for participants with complete CAL data, including patients with first-episode psychosis (FEP), and healthy controls (HC). GAF = Global Assessment of Functioning. LNL12 = prolonged (i.e., 6 months or more) loneliness experienced before age 12. LNL12–16 = prolonged (i.e., 6 months or more) loneliness experienced between ages 12 and 16.

Panel A — SCZ-PGS × Adolescent loneliness (LNL12–16)						
PGS	Loneliness	FEP (n)	Controls (n)	Total (n)	% FEP	OR
Low	No	263	743	1,006	26.1%	Ref.
Low	Yes	130	149	279	46.6%	2.47
High	No	285	238	523	54.5%	3.38
High	Yes	131	61	192	68.2%	6.07
<i>RERI = 2.04 [95% CI: -0.18; 5.13], Bootstrap p = 0.036</i>						
Panel B — MDD-PGS × Childhood loneliness (LNL12)						
PGS	Loneliness	FEP (n)	Controls (n)	Total (n)	% FEP	OR
Low	No	390	816	1,206	32.3%	Ref.
Low	Yes	99	75	174	56.9%	2.76
High	No	249	268	517	48.2%	1.94
High	Yes	71	32	103	68.9%	4.64
<i>RERI = 2.14 [95% CI: -0.16; 5.43], Bootstrap p = 0.032</i>						
Panel C — BIP-PGS × Childhood loneliness (LNL12)						
PGS	Loneliness	FEP (n)	Controls (n)	Total (n)	% FEP	OR
Low	No	369	815	1,184	31.2%	Ref.
Low	Yes	102	77	179	56.9%	2.93
High	No	270	269	539	50.1%	2.22
High	Yes	68	30	98	69.4%	5.01
<i>RERI = 1.95 [95% CI: -0.50; 5.47], Bootstrap p = 0.061</i>						

Table 2. Distribution of FEP cases and controls across strata defined by polygenic score (PGS) level and childhood/adolescent loneliness (CAL). Odds ratios relative to the low-PGS / no LNL reference group. PGS high = top quartile (>75th percentile) of the control distribution. OR = crude odds ratio, unadjusted for covariates. Reference group (Ref.) = low PGS + no loneliness. Highlighted rows indicate co-occurrence of both risk factors with significant GxE in the multilevel logistic regression models including all covariates. RERI = Relative Excess Risk due to Interaction; 95% CI estimated by bootstrap percentile method (1,000 permutations).

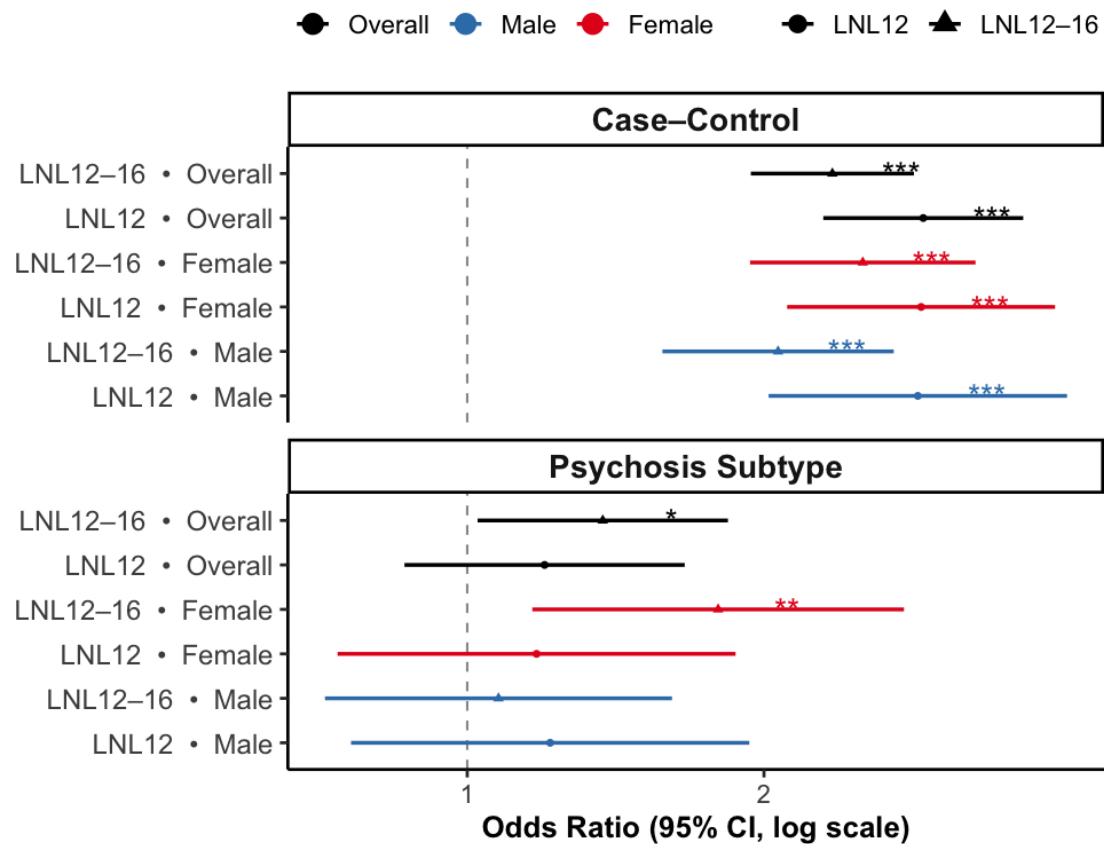


Figure 1. Main and Sex-Stratified Effects of Prolonged Loneliness on Case-Control Status and Psychosis Diagnostic Subtypes. Forest plots displaying odds ratios (95% CIs) from random-intercept multilevel logistic regression models (adjusted for age and country clustering) for the associations between prolonged loneliness (assessed as LNL12 and LNL12-16) and both case-control status (first-episode psychosis vs. controls) and psychosis diagnostic subtype (affective versus non-affective psychosis). Asterisks denote statistical significance: * $p < .05$; ** $p < .01$; *** $p < .001$.

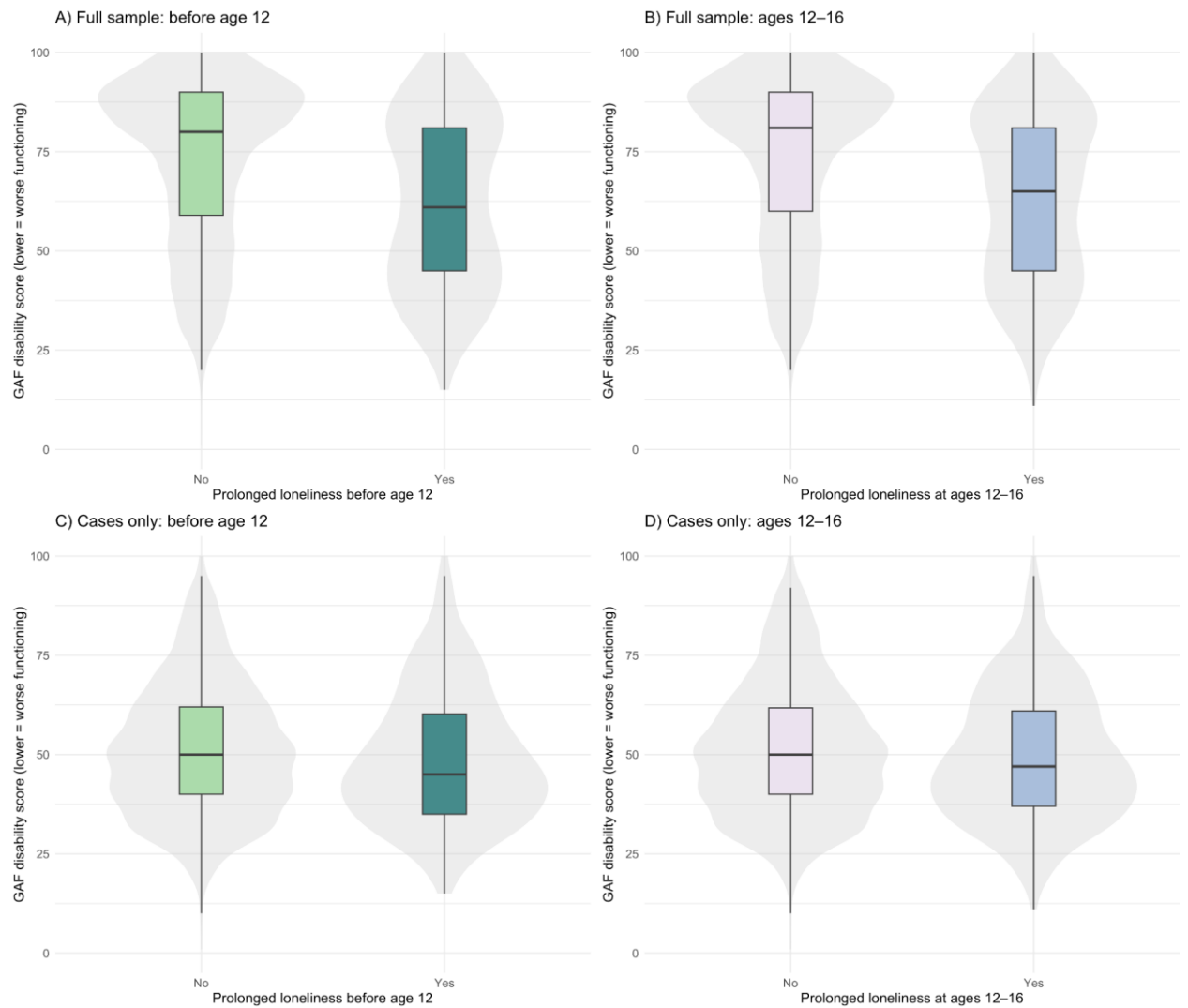


Figure 2. Distribution of GAF disability scores according to prolonged CAL exposure. Panels A and B show the full sample (cases and controls combined) for loneliness before age 12 and at ages 12–16, respectively. Panels C and D show the corresponding case-only analyses. Lower scores indicate poorer functioning.

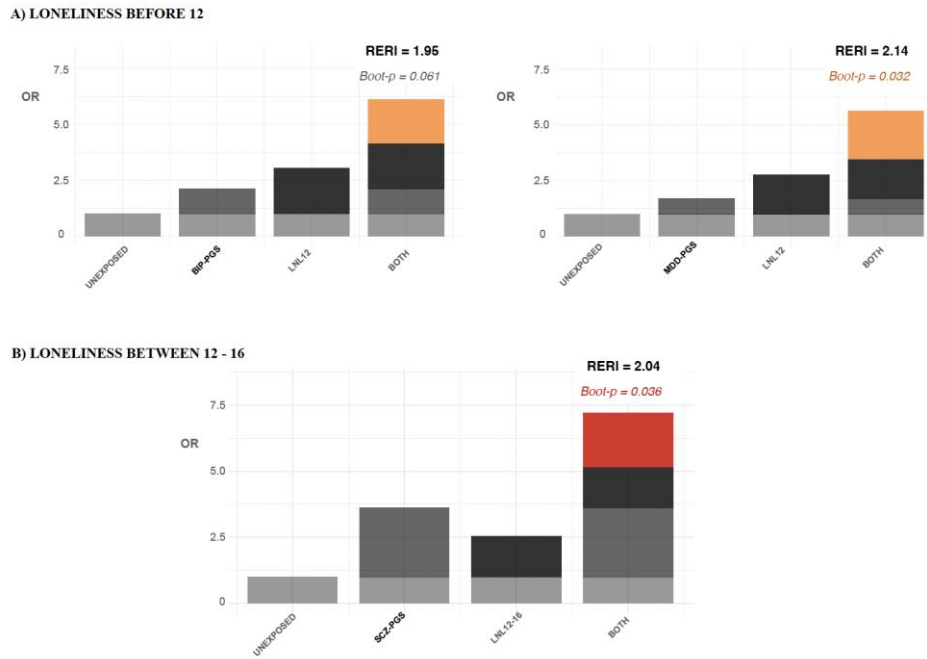


Figure 3. Additive effects of (A) loneliness before age 12 (LNL12) and (B) between ages 12 and 16 years (LNL12-16) on the association between polygenic risk score (PGS; 75% cut-off point) and first episode psychosis (FEP). The relative excess risk due to interaction (RERI) was estimated from multilevel logistic regression models including country as a random effect and age, sex, and ten principal components for ancestry. Dichotomized PGS (**75% cut-off point**) for schizophrenia (SCZ-PGS), bipolar disorder (BIP-PGS) and Major depression (MDD-PGS) were used. Additive GxE interaction was only evaluated when a significant correlation between LNL and PGS was absent.