IMPORTANCE Both adulthood stressful life events (SLEs) and liability for schizophrenia have been associated with poor mental and physical health in the general population, but their interaction remains to be elucidated to improve population-based health outcomes.

OBJECTIVE To test whether recent SLEs interact with genetic and environmental liability for schizophrenia in models of mental and physical health.

DESIGN, SETTING, AND PARTICIPANTS The Netherlands Mental Health Survey and Incidence Study-2 is a population-based prospective cohort study designed to investigate the prevalence, incidence, course, and consequences of mental disorders in the Dutch general population. Participants were enrolled from November 5, 2007, to July 31, 2009, and followed up with 3 assessments during 9 years. Follow-up was completed on June 19, 2018, and data were analyzed from September 1 to November 1, 2019.

EXPOSURES Recent SLEs assessed at each wave and aggregate scores of genetic and environmental liability for schizophrenia: polygenic risk score for schizophrenia (PRS-SCZ) trained using the Psychiatric Genomics Consortium analysis results and exposome score for schizophrenia (ES-SCZ) trained using an independent data set.

MAIN OUTCOMES AND MEASURES Independent and interacting associations of SLEs with ES-SCZ and PRS-SCZ on mental and physical health assessed at each wave using regression coefficients.

RESULTS Of the 6646 participants included at baseline, the mean (SD) age was 44.26 (12.54) years, and 3672 (55.25%) were female. The SLEs were associated with poorer physical health ($B = -3.22$ [95% CI, $-3.66$ to $-2.79$]) and mental health ($B = -3.68$ [95% CI, $-4.05$ to $-3.32$]). Genetic and environmental liability for schizophrenia was associated with poorer mental health (ES-SCZ: $B = -3.07$ [95% CI, $-3.35$ to $-2.79$]; PRS-SCZ: $B = -0.93$ [95% CI, $-1.31$ to $-0.54$]). Environmental liability was also associated with poorer physical health ($B = -3.19$ [95% CI, $-3.56$ to $-2.82$]). The interaction model showed that ES-SCZ moderated the association of SLEs with mental ($B = -1.08$ [95% CI, $-1.47$ to $-0.69$]) and physical health ($B = -0.64$ [95% CI, $-1.11$ to $-0.17$]), whereas PRS-SCZ did not. Several sensitivity analyses confirmed these results.

CONCLUSIONS AND RELEVANCE In this study, schizophrenia liability was associated with broad mental health outcomes at the population level. Consistent with the diathesis-stress model, exposure to SLEs, particularly in individuals with high environmental liability for schizophrenia, was associated with poorer health. These findings underline the importance of modifiable environmental factors during the life span for population-based mental health outcomes.
Accumulating evidence indicates that adulthood stressful life events (SLEs) contribute to the onset and outcome of a broad range of mental disorders. Furthermore, SLEs are key determinants of poor mental and physical health in the general population. Although SLEs are highly relevant for mental and physical well-being, they are seldom screened for in routine clinical practice. A recent Viewpoint has therefore called for integration of the SLE dimension to maximize the clinical utility of electronic health records.

Stressful life events are ubiquitous, with 30% to 40% of the general population experiencing at least 1 major SLE (e.g., death of a relative) each year. However, most people do not develop mental disorders after experiencing an SLE. According to the diathesis-stress model, a possible explanation is that early life events increase the vulnerability to SLEs later in life. Converging evidence for the diathesis-stress model stems from epidemiological studies focusing on the influence of the environment on psychopathology during the life span. Early adverse events, such as childhood adversity, moderate the association between adulthood SLEs and a broad range of multidimensional psychopathology outcomes across the severity spectrum from depression to psychosis. Furthermore, the influences of exposures on psychopathology appear to accumulate in a dose-response fashion: the more severe the exposure, the more severe the outcome.

Similar to the antecedent environmental liability to SLEs, genetic background may emerge as a predisposing factor for the detrimental effect of SLEs on health. The liability-threshold model posits that phenotypic outcomes can be quantified by the combination of cumulative genetic and environmental liability, wherein individuals passing the critical threshold develop expression of the disease phenotype. Recent insight from genome-wide association studies, enabling polygenic risk estimation of phenotypes (polygenic risk score [PRS]: a weighted sum of trait-associated alleles), has galvanized research into polygenic theory of psychopathology and provided a single metric of molecular genetic liability for gene-environment interaction research. Guloksuz et al have shown that the PRS for schizophrenia (PRS-SCZ) interacts with childhood adversities and cannabis use, increasing the likelihood of schizophrenia. Other studies pairing PRS-SCZ with an aggregate environmental score provided further evidence for gene-environment interaction in a sample with first-episode psychosis.

The recent series of studies testing the diathesis-stress model of depression in independent samples shows evidence of a positive interaction between the PRS for major depressive disorder (MDD) and SLEs, increasing depression risk. The interaction between the PRS-MDD and SLEs appears to be pleiotropic, extending not only to mental health phenotypes (e.g., schizotypal personality) but also to physical health phenotypes, such as cardiovascular disease and chronic obstructive pulmonary disease. The shared stress vulnerability across disease phenotypes is an anticipated outcome, given the pleiotropic associations of the PRS and SLEs.

The PRS-SCZ clearly outperforms the rest of the PRSs for mental disorder phenotypes that have been estimated so far and appears to be the forerunner for developing PRS-based clinical applications. Genetic liability for schizophrenia shows significant overlap with genetic liability across mental health phenotypes. The PRS-SCZ is associated with a variety of disorders (MDD, quality of life), and subclinical multidimensional phenotypes. Furthermore, the investigation of the electronic health records from the United States revealed that the PRS-SCZ was associated with not only a diagnosis of schizophrenia but also diagnoses of related psychiatric and other medical conditions.

Taken together, these findings indicate that an effect of SLEs is to a degree contingent on an individual’s environmental and genetic liability. The findings of a recent study by Pries et al provide further support to the pleiotropic effect of stress-vulnerability: the PRS-SCZ interacted with stressful life events, moderating the daily variations of negative affect, positive affect, and psychosis expression in the general population. To date, the diathesis-stress theory for SLEs by using the PRS for genetic liability estimation has only been tested cross-sectionally, whereas environmental liability remains to be estimated as a single metric (analogous to the PRS) to embrace the dense network of exposures in general population cohorts.

Herein, we aimed to embrace the complexity of many-to-many nonspecific associations in psychiatry by investigating to what degree all-encompassing health outcomes at the population level were influenced as a function of the interaction between SLEs (precipitating events) and liability for arguably the most severe and chronic form of mental disorders (predisposition), schizophrenia. This analysis takes into consideration the fact that the genetic and environmental liability for schizophrenia, as the selection on the extreme end of the mental disorder severity spectrum, should plausibly have a greater effect on mental health at the population level. By making use of a population-based prospective cohort that includes detailed information on early-life environmental exposures, genome-wide association study data, and repeated assessments of adulthood SLEs and health outcomes, we investigated whether the association of SLEs with mental and physical health was moderated by the PRS-SCZ and the exposome score for schizophrenia (ES-SCZ), a composite score of environmental liability for schizophrenia.

Key Points

Question Is the association of adulthood life stress with mental and physical health moderated by polygenic risk and exposome scores for schizophrenia?

Findings This population-based cohort study of 6646 participants provides novel evidence of the associations of genetic and environmental liability for schizophrenia with mental health in the general population. Both genetic and environmental liability were associated with poor outcomes, particularly mental health, and the association between stressful life events and health outcomes was moderated by exposome score but not polygenic risk score for schizophrenia.

Meaning These findings showing an interaction between adulthood stressful life events and lifetime exposomic liability lend further support to the diathesis-stress model.
Methods

Study Population
The Netherlands Mental Health Survey and Incidence Study–2 was conducted to study the prevalence, incidence, course, and consequences of mental disorders in the Dutch general population. The study was approved by the Medical Ethics Review Committee for Institutions on Mental Health Care, and written informed consent was collected from participants at each wave. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

To ensure representativeness of the sample in terms of age (range at baseline, 18–65 years), region, and population density, a multistage random sampling procedure was applied. Dutch illiteracy was an exclusion criterion. Nonclini- cian, trained interviewers applied the Composite International Diagnostic Interview, version 3.0, to additional questionnaires during home visits. Details of the Netherlands Mental Health Survey and Incidence Study–2 were provided elsewhere. From November 5, 2007, to July 31, 2009, the first baseline wave (T0) enrolled 6646 participants (response rate, 65.1%; mean [SD] interview duration, 95 [33] minutes), who were followed up at 3 visits within 9 years. Response rate at year 3 (T1) was 80.4% (5303 participants, excluding those who died; mean [SD] interview duration, 84 [26] minutes); at year 6 (T2), 87.8% (4618 participants, excluding those who died; mean [SD] interview duration, 83 [26] minutes); and at year 9 (T3), 86.8% (4007; mean [SD] interview duration, 102 [28] minutes), respectively. Follow-up was completed on June 19, 2018. Data from all 4 waves were used. Rates at baseline reflect lifetime occurrence; rates at T1 to T3 reflect the 3-year interval (T0 to T1, T2 to T3, and T2 to T3) occurrence. Attrition from T0 to T3 was not significantly associated with any of the individual 12-month mental disorders at T0 after controlling for sociodemographic characteristics. Genetic data were available in a subsample of 3104 individuals.

Measurements

cScz Score for Schizophrenia
Guided by the approach validated in a large international study, the continuous ES-SCZ was calculated by summing log odds-weighted environmental exposures (cannabis use, winter birth, hearing impairment, and childhood adversities [emotional neglect, psychological abuse, physical abuse, sexual abuse, and peer maltreatment]) at baseline. Details are found in the eMethods in the Supplement.

Adulthood SLEs
On the basis of the list of threatening experiences by Brugha et al., participants were asked whether they experienced 1 of 9 life events within the last 12 months (T0) or since the last interview (T1 to T3) (eTable 2 in the Supplement). Consistent with previous work from this cohort, we used the single binary SLEs variable (present: ≥1 life events; absent: 0 life events).

Mental Health and Physical Health
The 36-Item Short Form Health Survey consists of 9 subscales, with each subscale score ranging from poor (0) to good (100) functioning. Based on the 36-Item Short Form Health Survey manual, mental health, role limitations due to emotional problems, social functioning, and vitality subscales were used to calculate a mean mental health dimension, whereas general health perceptions, physical functioning, role limitation due to physical health problems, and bodily pain subscales were used to calculate a mean physical health dimension. The 36-Item Short Form Health Survey was assessed at each time point and refers to the past 4 weeks.

Polygenic Risk Score for Schizophrenia
The PRS-SCZ was created from best-estimate genotypes at 6 different 2-tailed P value thresholds (.50, .10, .05, 5 × 10−3, 5 × 10−5, and 5 × 10−8) (eMethods, eFigures 1 and 2, and eTable 1 in the Supplement). For our primary analyses, we used the threshold of P < .05, because this threshold optimally captures liability to the disorder in the Psychiatric Genomics Consortium analysis and performed well for the current phenotypes (eTable 3 in the Supplement).

Statistical Analysis
Data were analyzed from September 1 to November 31, 2019. All analyses were performed using Stata, version 15 (StataCorp LLC). Two-tailed P < .05 was considered nominally statistically significant. Baseline correlation between the PRS-SCZ and SLEs was tested using logistic regression models. Using data from all 4 assessment points, we fitted multilevel mixed regression models using the MIXED command in Stata to test the association of recent SLEs, ES-SCZ, and PRS-SCZ with mental and physical health outcomes. Stressful life events and health outcomes were assessed at each point and therefore time varying; the genetic (PRS-SCZ) and environmental (ES-SCZ) liabilities were antecedents and time invariant. Likelihood ratio tests comparing models with different covariance structures (independent and autoregressive) indicated that a first-order autoregressive covariance structure was the most suitable for the present analyses. The continuous independent variables (PRS-SCZ and ES-SCZ) were standardized and centered (minimum, 0; SD, 1) at baseline. Given the hierarchical structure of the data, multilevel mixed-effect models were applied to cluster the multiple assessments per individual. All analyses were additionally a priori adjusted for age, sex, and educational level (primary, lower secondary, higher secondary, and higher professional education). Models including the PRS-SCZ were conducted in a subsample of 3104 individuals with genotype results and additionally adjusted for 3 principal components. To adequately control for confounding, interaction models with PRS-SCZ included the covariates as well as covariate by SLEs and covariate by PRS-SCZ interaction terms. Univariate and multiple logistic regression models were applied to compare the baseline characteristics between individuals who completed all 4 assessments and those who dropped out at any time point. The multivariable model indicated that younger age and lower educational level at baseline were associated with attrition during the study period.
The longitudinal mixed regression models indicated that recent SLEs were associated with poorer mental health ($B = -3.64$ [95% CI, $-3.66$ to $-3.29$]; $P < .001$) and physical health ($B = -3.69$ [95% CI, $-4.12$ to $-3.26$]; $P < .001$). The ES-SCZ was likewise associated with poorer mental health ($B = -3.16$ [95% CI, $-3.44$ to $-2.88$]; $P < .001$) and physical health ($B = -3.09$ [95% CI, $-3.48$ to $-2.71$]; $P < .001$). Increased PRS-SCZ was associated with decreased mental health ($B = -0.90$ [95% CI, $-1.30$ to $-0.51$]; $P < .001$), but no significant association was found between PRS-SCZ and physical health ($B = -0.38$ [95% CI, $-0.92$ to $0.17$]; $P = .17$). The results were similar after adjusting for age, sex, and educational level (Table 2), with SLEs associated with poorer physical health ($B = -3.22$ [95% CI, $-3.66$ to $-2.79$]; $P < .001$) and mental health ($B = -3.68$ [95% CI, $-4.05$ to $-3.32$]; $P < .001$); genetic and environmental liability for schizophrenia associated with poorer mental health (ES-SCZ: $B = -3.07$ [95% CI, $-3.35$ to $-2.79$]; $P < .001$; PRS-SCZ: $B = -0.93$ [95% CI, $-1.31$ to $-0.54$]; $P < .001$); and environmental liability also associated with poorer physical health ($B = -3.19$ [95% CI, $-3.56$ to $-2.82$]; $P < .001$).

Evidence suggested a significant interaction between recent SLEs and ES-SCZ on mental health ($B = -1.09$ [95% CI, $-1.48$ to $-0.70$]; $P < .001$) and physical health ($B = -0.63$ [95% CI, $-1.11$ to $-0.16$]; $P = .009$); after adjusting for age, sex, and educational level, the interaction model showed that ES-SCZ moderated the association of SLEs with mental (B = -1.08 [95% CI, -1.47 to -0.69]; $P < .001$) and physical (B = -0.64 [95% CI, -1.11 to -0.17]; $P < .008$) health (Table 2 and Figure). No gene-environment correlation was detected: no large or significant association was found between PRS-SCZ and recent SLEs (odds ratio [OR], 1.03 [95% CI, 0.96-1.10]; $P = .45$). No evidence was found for an interaction between recent SLEs and PRS-SCZ on mental (B = -0.25 [95% CI, -0.73 to 0.23]; $P = .31$) or physical (B = -0.14 [95% CI, -0.72 to 0.45]; $P = .65$) health; the results of the variance in baseline mental and physical health, respectively. The PRS-SCZ at a threshold of $P < .05$ explained 0.5% of the variance in baseline mental health ($P < .001$), but PRS-SCZ was not significantly associated with physical health at baseline (eTable 3 in the Supplement).

To test the robustness of our findings, we conducted several sensitivity analyses. We first tested whether the results of recent SLEs converged to previous SLEs (at $T - 1$), aiming to assess temporal association and proximity. Further, the analyses were conducted by replacing independent variables one at a time with the following sensitivity measures: PRS-SCZ with a threshold of $P < .10$ (PRS-SCZ-.10); PRS-MDD, ES-SCZ without cannabis use history, the sum score of recent SLEs, and recent SLEs split into independent and dependent categories. Finally, we repeated the primary analyses using the narrow dimensions of mental health (mental health and role limitations due to emotional problems scales) and physical health (physical functioning, role limitation due to physical health problems, and bodily pain) as outcomes ($P < .001$) (eMethods in the Supplement).

Results

Of the 6646 participants included at baseline, the mean (SD) age was 44.26 (12.54) years, 3672 (55.25%) were female, and 2974 were male (44.75%). Table 1 reports sample characteristics at the different points and missing values at baseline. Regression analyses of baseline data only revealed that recent SLEs explained 5.0% ($P < .001$) and 3.7% ($P < .001$) of the variance in baseline mental and physical health, respectively, whereas ES-SCZ explained 5.5% ($P < .001$) and 3.2% ($P < .001$) of the variance in baseline mental and physical health, respectively. The PRS-SCZ at a threshold of $P < .05$ explained 0.5% of the variance in baseline mental health ($P < .001$), but PRS-SCZ was not significantly associated with physical health at baseline (eTable 3 in the Supplement).

Abbreviations: NA, not applicable; SLE, stressful life event; T, time.

Indicates mean of mental health, role limitations due to emotional problems, social functioning, and vitality subscales of the 36-Item Short Form Health Survey. Scores range from 0 (poor) to 100 (good).

Indicates mean of general health perceptions, physical functioning, role limitation due to physical health problems, and bodily pain subscales of the 36-Item Short Form Health Survey. Scores range from 0 (poor) to 100 (good).

Indicates mean of physical health, role limitation due to physical health problems, and vitality subscales of the 36-Item Short Form Health Survey. Scores range from 0 (poor) to 100 (good).

Indicates mean of physical health, role limitation due to physical health problems, and bodily pain subscales of the 36-Item Short Form Health Survey. Scores range from 0 (poor) to 100 (good).

Indicates mean of physical health, role limitation due to physical health problems, and vitality subscales of the 36-Item Short Form Health Survey. Scores range from 0 (poor) to 100 (good).

Indicates mean of physical function, role limitation due to physical health problems, and vitality subscales of the 36-Item Short Form Health Survey. Scores range from 0 (poor) to 100 (good).

Indicates mean of physical function, role limitation due to physical health problems, and vitality subscales of the 36-Item Short Form Health Survey. Scores range from 0 (poor) to 100 (good).

Indicates mean of physical function, role limitation due to physical health problems, and vitality subscales of the 36-Item Short Form Health Survey. Scores range from 0 (poor) to 100 (good).
did not change after adjusting for age, sex, and educational level. In accordance with the analyses in the total sample, adjusted main effect analyses in the genotyped subsample revealed that recent SLEs were associated with poorer mental health ($B = -3.68$ [95% CI, −4.05 to −3.32]; $P < .001$) and physical health ($B = -3.22$ [95% CI, −3.66 to −2.79]; $P < .001$). Furthermore, ES-SCZ was associated with poorer mental health ($B = -3.07$ [95% CI, −3.35 to −2.79]; $P < .001$) and physical health ($B = -3.19$ [95% CI, −3.56 to −2.82]; $P < .001$). The interaction model showed that ES-SCZ moderated the association of previous SLEs with mental health ($B = -0.50$ [95% CI, −0.97 to −0.03]; $P = .04$). However, the interaction between previous SLEs and ES-SCZ on physical health was not nominally significant. Estimates for previous SLEs were generally lower than those of recent SLEs.

### Table 2. Main Associations and Interactions of Recent SLEs, ES-SCZ, and PRS-SCZ on Health Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mental health $B$ (95% CI)</th>
<th>$P$ value</th>
<th>Physical health $B$ (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main associations</strong></td>
<td></td>
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<tr>
<td>SLE</td>
<td>$-3.68$ (−4.05 to −3.32)</td>
<td>&lt;.001</td>
<td>$-3.22$ (−3.66 to −2.79)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ES-SCZ</td>
<td>$-3.07$ (−3.35 to −2.79)</td>
<td>&lt;.001</td>
<td>$-3.19$ (−3.56 to −2.82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PRS-SCZ$^b$</td>
<td>$-0.93$ (−1.31 to −0.54)</td>
<td>&lt;.001</td>
<td>$-0.49$ (−1.01 to 0.03)</td>
<td>.06</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE × ES-SCZ</td>
<td>$-1.08$ (−1.47 to −0.69)</td>
<td>&lt;.001</td>
<td>$-0.64$ (−1.11 to −0.17)</td>
<td>.008</td>
</tr>
<tr>
<td>SLE × PRS-SCZ$^b$</td>
<td>$-0.25$ (−0.74 to 0.24)</td>
<td>.33</td>
<td>$-0.17$ (−0.76 to 0.42)</td>
<td>.58</td>
</tr>
</tbody>
</table>

Abbreviations: $B$, regression coefficient from the multilevel mixed models; ES-SCZ, exposome score for schizophrenia; PRS-SCZ, polygenic risk score for schizophrenia; SLE, stressful life event.

*All analyses were adjusted for sex, age, and educational level.

$^b$Additionally adjusted for 3 principal components.

### Sensitivity Analyses

The sensitivity analyses provided support for the robustness of the findings. Adjusted analyses with previous SLEs (at $T − 1$) showed similar results to those with recent SLEs (Table 3); previous SLEs were associated with poorer mental health ($B = -0.91$ [95% CI, −1.35 to −0.47]; $P < .001$) and physical health ($B = -1.83$ [95% CI, −2.35 to −1.30]; $P < .001$). The interaction model showed that ES-SCZ moderated the association of previous SLEs with mental health ($B = -0.50$ [95% CI, −0.97 to −0.03]; $P = .04$). However, the interaction between previous SLEs and ES-SCZ on physical health was not nominally significant. Estimates for previous SLEs were generally lower than those of recent SLEs.

### Marginal Effect Plots

Marginal effect plots based on adjusted multilevel mixed regression of the interaction between exposome score for schizophrenia (ES-SCZ) and recent stressful life events (SLEs) on continuous measures of mental health (A) and physical health (B) and between polygenic risk score for schizophrenia (PRS-SCZ) and SLEs on continuous measures of mental health (C) and physical health (D). Raw data associations are visualized as scatter. Mental health, role limitations due to emotional problems, social functioning, and vitality subscales of the 36-Item Short Form Health Survey were used to calculate a mean mental health dimension, whereas general health perceptions, physical functioning, role limitation due to physical health problems, and bodily pain subscales were used to calculate a mean physical health dimension, with scores ranging from 0 (poor) to 100 (good).
Discussion

In this prospective cohort study, we tested the moderating role of genetic and environmental liability on the association between recent SLEs and health outcomes in the general population. Our results illustrate that recent SLEs along with environmental (ES-SCZ) and genetic (PRS-SCZ) liability to schizophrenia were associated with poor mental health at the population level. The ES-SCZ and SLEs were independently and interactively associated with health outcomes, particularly mental health. Although PRS-SCZ was associated with poorer mental health, the association between PRS-SCZ and physical health was significant for trend after adjusting for age, sex, and educational level. The PRS-SCZ did not moderate the association between SLEs and health outcome. The current findings were confirmed by the converging results obtained from sensitivity analyses.

This study adds valuable knowledge to the literature on the longitudinal association between SLEs and mental health. Our findings show that recent SLEs and environmental liability (ES-SCZ) in the general population were associated with poorer mental and physical health. This aligns with previous findings showing that environmental exposures pleiotropically associate with psychosis spectrum disorder. Supporting the notion of a temporal association between SLEs and health, the analyses with previous SLEs yielded a similar association pattern to those of recent SLEs. However, estimates were higher when investigating the more recent SLEs, indicating that proximity influences the association of SLEs with the outcome. Furthermore, along the lines of the diathesis-stress model, we demonstrated that the exposomic liability moderates susceptibility to SLEs later in life. This is in accordance with accumulating evidence indicating that early environmental exposures moderate the association...
between SLEs later in life and multidimensional psychopathology.35-39 The results show that the network of early and late environmental exposures needs to be elucidated to gain insight into the etiological basis of mental illness.

Our study reports novel findings on the association between PRS-SCZ and mental health in a prospective general population sample. Although the literature shows inconsistent results for the association between PRS-SCZ and multidimensional psychosis spectrum phenotype (eg, psychosis expression and negative symptoms),39,41-44,68-70 the present results suggest that genetic liability to schizophrenia is pleiotropically associated with broad psychopathology.39,41,42,71,72

We did not find a moderating effect of PRS-SCZ on the association between SLEs later in life and health outcomes. This finding is in line with several previous studies investigating the interaction between PRS-MDD and SLEs on depression73,74 and previous findings showing that the association of daily life stressors with positive affect, negative affect, and psychosocial proneness at population level was not moderated by PRS-SCZ.34 However, a recent line of research showed that PRS-MDD moderated the association between SLEs and depression risk.32-34

Given the inconsistencies, further research is needed to understand whether PRS-SCZ moderates stress sensitivity.

Limitations
Some limitations should be acknowledged. Although our ES estimation conforms to the approach validated in a large international study, the ES was limited by the degree to which the exposures that were used in the original model were reliably assessed in the current sample, and thereby lacking other exposures that might be of relevance (eg, obstetric and pregnancy complications).75 Although participants were asked to report past SLEs and current health outcomes, differences in the estimates of independent and dependent SLEs demonstrate that the reporting of SLEs might be influenced by current mental and physical health. Notwithstanding, the analyses using previous SLEs provide some support for temporal association. Furthermore, although our analysis revealed nominally statistically significant associations of PRS-SCZ with mental health, larger samples may be required to detect a gene-environment interaction in the general population, given smaller effect sizes.

Conclusions
In this study, we found that the genetic and environmental liability for schizophrenia were associated with broad mental health outcomes at the population level. Our findings showing that the network of antecedent environmental liability increased the vulnerability to stressful events later in life provide further support to the diathesis-stress theory. From a clinical perspective, our results suggest that the integration of SLEs can increase the clinical utility of electronic health records. From a public health perspective, our findings underline the promise for investment in public health strategies that focus on modifiable environmental factors over the life span to improve population-based mental health outcomes.

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Administrative, technical, or material support: van Os, ten Have, Bak, Lin, Kenis, Richards, Guloksuz.

Supervision: van Os, ten Have, de Graaf, O’Donovan, Rutten, Guloksuz.

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