Psychological Medicine

cambridge.org/psm

Polygenic liability, stressful life events and risk for secondary-treated depression in early life: a nationwide register-based case-cohort study

Katherine L. Musliner[1,2], Klaus K. Andersen[3], Esben Agerbo[1,2,4], Clara Albiñana[1,2], Bjarni J. Vilhjalmsson[1,2,5], Veera M. Rajagopal[1,6,7,8], Jonas Bybjerg-Grauholm[1,9], Marie Bækved-Hansen[1,9], Carsten B. Pedersen[1,2,4], Marianne G. Pedersen[1,2,4], Trine Munk-Olsen[1,2], Michael E. Benros[1,10], Thomas D. Als[1,6], Jakob Grove[1,5,6,8], Thomas Werge[1,11], Anders D. Børglum[1,6,7], David M. Hougaard[1,9], Ole Mors[1,12], Merete Nordentoft[1,10], Preben B. Mortensen[1,2,4], Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium and Nis P. Suppli[1,10]

[1]The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus, Denmark; [2]National Center for Register-based Research, Department of Economics, Aarhus University, Aarhus, Denmark; [3]Unit for Statistics and Pharmacoepidemiology (SPE), Danish Cancer Society Research Center (DCRC), Copenhagen, Denmark; [4]The Center for Integrated Register-based Research at Aarhus University (CIRRAU), Aarhus, Denmark; [5]Bioinformatics Research Centre (BiRC), Aarhus University, Aarhus, Denmark; [6]Department of Biomedicine, Aarhus University, Aarhus, Denmark; [7]Center for Integrative Sequencing, iSEQ, Aarhus University, Aarhus, Denmark; [8]Center for Genome Analysis and Personalized Medicine, Aarhus, Denmark; [9]Department for Congenital Disorders, Statens Serum Institute, Copenhagen, Denmark; [10]Mental Health Center Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark; [11]Institute of Biological Psychiatry, Copenhagen Mental Health Services, Copenhagen, Denmark and [12]Psychosis Research Unit, Aarhus University Hospital-Psychiatry, Aarhus, Denmark

Original Article

Cite this article: Musliner KL *et al* (2023). Polygenic liability, stressful life events and risk for secondary-treated depression in early life: a nationwide register-based case-cohort study. *Psychological Medicine* **53**, 217–226. https://doi.org/10.1017/S0033291721001410

Received: 15 December 2020
Revised: 24 March 2021
Accepted: 31 March 2021
First published online: 5 May 2021

Key words:
Absolute risk; case-cohort study; depression; interaction; polygenic risk scores; stressful life events

Author for correspondence:
Katherine L. Musliner, E-mail: klm@econ.au.dk

Abstract

Background. In this study, we examined the relationship between polygenic liability for depression and number of stressful life events (SLEs) as risk factors for early-onset depression treated in inpatient, outpatient or emergency room settings at psychiatric hospitals in Denmark.

Methods. Data were drawn from the iPSYCH2012 case-cohort sample, a population-based sample of individuals born in Denmark between 1981 and 2005. The sample included 18 532 individuals who were diagnosed with depression by a psychiatrist by age 31 years, and a comparison group of 20 184 individuals. Information on SLEs was obtained from nationwide registers and operationalized as a time-varying count variable. Hazard ratios and cumulative incidence rates were estimated using Cox regressions.

Results. Risk for depression increased by 35% with each standard deviation increase in polygenic liability ($p < 0.0001$), and 36% ($p < 0.0001$) with each additional SLE. There was a small interaction between polygenic liability and SLEs ($\beta = -0.04$, $p = 0.0009$). The probability of being diagnosed with depression in a hospital-based setting between ages 15 and 31 years ranged from 1.5% among males in the lowest quartile of polygenic liability with 0 events by age 15, to 18.8% among females in the highest quartile of polygenic liability with 4+ events by age 15.

Conclusions. These findings suggest that although there is minimal interaction between polygenic liability and SLEs as risk factors for hospital-treated depression, combining information on these two important risk factors could potentially be useful for identifying high-risk individuals.

Introduction

Depression is a common disorder, affecting up to 20.6% of people at some point during their lifetimes (Hasin et al., 2018). Although most individuals with clinical depression are treated in a primary care setting (Musliner et al., 2019; Olfson, Kroenke, Wang, & Blanco, 2014; Wang et al., 2007), in some cases, depression can require secondary treatment by specialists or even inpatient hospitalization (Pedersen et al., 2014). Although the biological mechanisms that give rise to an episode of depression are not clearly understood, a number of risk factors for depression have been consistently identified, including family history (Weissman et al., 2016), female gender (Weissman et al., 1993), and in particular, stressful life events (SLEs) such as the death of a relative, divorce, or serious illness (Hammen, 2005; Kessler, 1997). The existence of a relationship between stress and depression is beyond doubt (Anda et al., 2006; Dahl et al., 2017); however, most individuals experience stress and SLEs at some point in their lives, and relatively few go on to receive a depression diagnosis in a secondary care setting (Dahl et al., 2017).

CAMBRIDGE UNIVERSITY PRESS

The diathesis-stress model posits that an individual's likelihood of developing depression is a combination of his underlying vulnerability (i.e. 'diathesis') related to factors such as genetics, biology or personality, and the external environments he encounters throughout his life (i.e. 'stress') (Monroe & Simons, 1991). Typically, this model conceptualizes the relationship between diathesis and stress as an interactive one, meaning that the greater the diathesis, the larger the depressogenic impact of stress. Recent findings from large, genome-wide association studies suggest that the underlying genetic architecture of depression is polygenic, meaning that large numbers of common genetic variants, each with small effects, contribute additively to depression (Howard et al., 2019; Wray et al., 2018). This genetic liability can be summarized in a single variable called a polygenic risk score (PRS), which is a weighted sum of risk contributions from many genetic variants.

To our knowledge, nine studies have previously examined the interaction between PRSs and stress as risk factors for depression (Arnau-Soler et al., 2019; Coleman et al., 2020; Colodro-Conde et al., 2018; Fang, Scott, Song, Burmeister, & Sen, 2020; Mullins et al., 2016; Musliner et al., 2015; Peterson et al., 2018; Peyrot et al., 2014, 2018). The first study (Peyrot et al., 2014) showed an interaction between PRS and childhood trauma that appeared to follow the traditional 'fan-shape' where the slope of the PRS effect was steeper among individuals who had experienced childhood trauma relative to those who had not. However, subsequent PRS × stress studies have yielded inconsistent results, with some finding evidence for interaction (Arnau-Soler et al., 2019; Coleman et al., 2020; Colodro-Conde et al., 2018; Fang et al., 2020; Mullins et al., 2016) and some failing to do so (Mullins et al., 2016; Musliner et al., 2015; Peterson et al., 2018; Peyrot et al., 2018).

A great challenge facing G × E research involving SLEs is that previous studies have typically as a matter of necessity been conducted retrospectively, meaning that individuals are classified as cases or non-cases and then asked to report on their past history of SLEs. This approach has several limitations – first, it fails to take into account the time-varying nature of SLEs, which can and often do occur at multiple points in the lifespan. Second, it introduces the potential for recall bias, given that individuals with depression are more likely to recall SLEs that occurred in the past (Colman et al., 2016). Third, it precludes the direct estimation of the incidence (i.e. risk) of developing depression, which requires following a population of unaffected individuals forward in time.

To address these issues, we conducted a prospective analysis of the interaction between PRS for depression and SLEs, measured as a time-varying covariate, in a large, population-based sample of individuals born in Denmark and followed for up to 21 years. Our primary aim in this study was to characterize the individual and combined effects of these two risk factors on risk for developing depression in early life. As a secondary aim, we examined potential differences between men and women, as female sex is a consistent risk factor for both depression and certain types of SLEs, and at least one previous study found evidence that the PRS × SLE interaction was stronger in women (Colodro-Conde et al., 2018).

Methods

Study design

Data for this study were drawn from the iPSYCH2012 sample (Pedersen et al., 2018), which has a case-cohort design (Prentice, 1986). A case-cohort design is similar to a nested case-control design in that a case group and a comparison group are selected from a larger cohort (i.e. the 'full cohort'). However unlike a case-control design, members of the comparison group are not controls *per se*, as they are not selected on the basis of the absence of case status. Rather, the comparison group consists of a random sample of individuals (i.e. the 'subcohort'), selected from the full cohort *irrespective of case status*. Thus, some of the cases are also members of the subcohort, and some are not. This design is useful because it allows for the unbiased calculation of risk and hazard ratios for multiple potential outcomes of interest, but at a fraction of the cost of a cohort study as only a subset of non-cases need to be genotyped (Prentice, 1986).

Case-cohort data are analyzed using survival analysis as in cohort studies, with the addition of sample weights to account for the under-sampling of non-cases. All members of the subcohort, including cases, contribute person time to the survival analyses. Cases inside the subcohort are included in the risk sets for other cases who develop the outcome before them. In contrast, cases outside the subcohort do not contribute person time to the analyses, and contribute only to the risk set in which they themselves are the case (Barlow, 1994; Barlow, Ichikawa, Rosner, & Izumi, 1999; Petersen, Sorensen, & Andersen, 2003; Prentice, 1986; Self & Prentice, 1988). For a more comprehensive overview of the design and analysis of case-cohort studies, see Musliner et al. (2019), online Supplementary materials or Barlow et al. (1999).

Data source and case ascertainment

The iPSYCH2012 case-cohort sample was drawn from the full cohort of all singletons born in Denmark between May 1981 and 31 December 2005 who were alive and living in Denmark on their first birthday and who had known mothers ($N = 1\,472\,762$) (Pedersen et al., 2018). The sample includes a random subcohort of 30 000 individuals, and all individuals ($N = 57\,377$) who received a mood disorder, schizophrenia, autism, or ADHD diagnosis in a Danish psychiatric hospital between 1994 and 2012. Psychiatric diagnoses were obtained from the Danish Psychiatric Central Research Register (DPCRR) (Mors, Perto, & Mortensen, 2011) which includes all inpatient contacts at Danish psychiatric hospitals since 1969 and all outpatient and emergency contacts since 1995. As the vast majority of psychiatrists in Denmark operate in publically funded psychiatric hospitals, the DPCRR is considered almost complete in terms of records of diagnoses given in secondary care (Mors et al., 2011). Approximately 4% of individuals in the random subcohort are also cases, meaning they received at least one of the psychiatric diagnoses listed above.

Study sample

For this study, we selected all individuals from the subcohort who were alive and residing in Denmark at age 10 years and who reached the age of 10 before the end of follow-up on 31 December 2012 ($N = 26\,062$). In addition, we included all individuals diagnosed with depression [ICD, 10th revision (ICD-10): F32–F33] from among the cases outside the subcohort ($N = 24\,327$). The sample was further restricted to individuals of European ancestry, individuals who were successfully genotyped and passed quality control (QC), and unrelated individuals (pi-hat < 0.20). The final sample included 38 716 persons:

https://doi.org/10.1017/S0033291721001410 Published online by Cambridge University Press

18 153 depression cases outside the subcohort, and 20 563 subcohort members of whom 379 were also depression cases (18 532 depression cases total). The oldest individuals (those born in 1981) were 31 years old at the end of follow-up, thus the maximum follow-up time was 21 years.

Genetic data

Since May 1981, dried blood spot samples from PKU screenings given to all newborn babies in Denmark have been stored in the Danish Newborn Screening Biobank (Norgaard-Pedersen & Hougaard, 2007). DNA was extracted from these blood spots and amplified in triplicate at the Danish State Serum Institute (Hollegaard et al., 2009, 2011; Pedersen et al., 2018). The samples were genotyped at The Broad Institute of Harvard and MIT (Cambridge, MA, USA) using the Infinium PsychChip v1.0 array (Illumina, San Diego, CA, USA) according to the manufacturer's protocols (Pedersen et al., 2018). This array was developed in collaboration with the Psychiatric Genomics Consortium (Sullivan et al., 2018) to tag ~300 000 SNPs spread across the genome and an additional ~200 000 variants associated with common psychiatric disorders. QC and imputation were conducted using the Ricopili pipeline (Lam et al., 2019). Samples were excluded if they had call rates <95%, inbreeding coefficient >0.2, or if the genetically determined sex did not match the sex recorded in the Danish Civil Registration System (DCRS) (Pedersen, 2011). Altogether, 90% of the sample ($N = 77\,639$) passed QC. Variant calls were improved by a filtering process that excluded variants with call frequency <0.98 or a Hardy–Weinberg Equilibrium p value $< 1 \times 10^{-6}$. Genetic variants that passed QC were phased and subsequently imputed using Shape-IT (Delaneau, Coulonges, & Zagury, 2008) and IMPUTE2 (Howie, Donnelly, & Marchini, 2009) with 1000 genomes phase 3 (Genomes Project Consortium et al., 2015) as the reference panel.

Polygenic risk score

The PRS for depression was generated using a Meta-PRS, which combines externally and internally trained PRSs (Albiñana et al., 2020). This approach of combining internal and external data has been found to improve predictive accuracy over methods that use either external or internal data alone (Albiñana et al., 2020).

The externally trained component (PRS_{ext}) was built using the LDpred software (Vilhjalmsson et al., 2015), using the most recent GWAS results for depression (Howard et al., 2019) as the discovery dataset. To build PRS_{ext}, we used the set of 166 906 SNPs from the iPSYCH2012 genotyped set that overlapped with HapMap3 and the discovery GWAS (excluding SNPs with ambiguous nucleotides). The LD reference panel was obtained from a random sample of 10 000 unrelated individuals of European ancestry from the iPSYCH2012 subcohort. We used the infinitesimal model ($p = 1$), which assumes all variants are causal, as this model resulted in the highest predictive accuracy for depression in an internal cross-validation test.

For the internally trained component (PRS_{int}), we selected 539 744 SNPs from the iPSYCH2012 genotyped set where minor allele frequency >1% and missing values <10%. We then used the BOLT-LMM software (Loh et al., 2015; Loh, Kichaev, Gazal, Schoech, & Price, 2018) on the unrelated individuals of European ancestry to obtain per-SNP prediction βs (BLUP) including in the model genotype wave, sex, age, and the first two ancestral principal components (PCs) as covariates. These βs were then used as weights (w_{int}) to generate PRS_{int}.

Finally, the meta-PRS was obtained from the linear combination of the internally and externally trained components, with weights trained using linear regression (lm function in R):

$$\text{MetaPRS} = w_0 + w_{\text{int}}\text{PRS}_{\text{int}} + w_{\text{ext}}\text{PRS}_{\text{ext}}$$

To avoid overfitting, we used 10-fold cross-validation by training the PRS_{int} using 9/10ths of the data and then using two-fold cross-validation in the remaining 10% of the data to fit the p parameter for the PRS_{ext} and the regression weights for the meta-PRS. The resulting meta-PRS was standardized [mean = 0, standard deviation (S.D.) = 1] using the mean and SD from the iPSYCH2012 subcohort.

Stressful life events

The following SLEs were included in the analyses: family disruption, parental unemployment due to disability, childhood maltreatment, severe somatic illness, and death of a close relative. A prior register-based study from Denmark showed that these events are all individually associated with depression, and that the number of SLEs has a dose–response relationship with depression risk (Dahl et al., 2017). Data on family disruption were obtained from the DCRS, which includes information on peoples' full address and dates of moving (Pedersen, 2011). Family disruption in childhood was broadly defined as all instances in which a child's parents or parental figures ceased to live together, including divorce/separation of biological parents, and divorce/separation between a child's biological parent and a cohabitating step-parent. Family disruption in adulthood was defined as the individual him or herself ceasing to cohabitate with a spouse, or a partner with whom he or she shared a child. Parental unemployment due to disability was measured using employment records from the Danish Register on Personal Labor Market Affiliation (Petersson, Baadsgaard, & Thygesen, 2011). Parental disability was defined as November 1 on the first year a child's mother or father was recorded as receiving a disability pension. Maternal and paternal disability were handled as separate events. Childhood maltreatment was defined as the date on which the child received a diagnosis of neglect or abandonment (ICD-10 codes T74.0), sexual abuse (T74.2, Z61.4, Z61.5), physical abuse (T74.1), psychological abuse (T74.3) or other or unspecified maltreatment syndromes (T74.8, T74.9) in the Danish National Patient Register (DNPR) (Lynge, Sandegaard, & Rebolj, 2011). Severe somatic illness in the individual or the individual's's first-degree relatives (parents, siblings, children) was also determined using diagnoses from the DNPR. Individuals were coded as 0, 1 or 2+ based on their score of the Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987; Thygesen, Christiansen, Christensen, Lash, & Sorensen, 2011). Finally, death of a first-degree relative was assessed using vital statistics from the DCRS. Deaths of a parent, sibling, or child were handled as separate events.

Statistical analyses

Hazard ratios were estimated from Cox regressions with the addition of sample weights to account for the case-cohort design. We assigned weights based on the method proposed by Prentice (1986) in which members of the subcohort, including cases, receive a weight of 1, and cases outside the subcohort receive

https://doi.org/10.1017/S0033291721001410 Published online by Cambridge University Press

weight 0. SLEs were defined as a time-varying count variable representing the number (0–4+) of events experienced by each individual at a given point in time starting at age 10 and ending on the date of first depression diagnosis, death, emigration or 31 December 2012, whichever came first. Individuals entered the analyses with however many SLEs they had experienced prior to age 10, and contributed person time to that strata until they experienced a new SLE, or were censored. Analyses were conducted in R and SAS 9.4.

We first fit main effects models including PRS, SLEs, sex, birth year, and the first five PCs. We evaluated the linearity of the associations by first modeling SLEs as a categorical variable, and modeling the PRS using restricted cubic splines (Gray, 1992; Perperoglou, Sauerbrei, Abrahamowicz, & Schmid, 2019). As the effects of both the PRS and SLE variables were linear, we modeled both SLEs and PRS as continuous linear variables in all subsequent models. Next, we fit an interaction model including all terms from the main effects model as well as an interaction term for PRS and SLEs. We also fit a saturated version of the interaction model including all PRS-by-covariate interaction terms and all SLE-by-covariate interaction terms to account for potential confounding (Keller, 2014). As the results from the saturated model differed only slightly from those of the non-saturated interaction model, we proceeded with the more parsimonious unsaturated model. We examined potential sex interactions by fitting a second interaction model that included two-way interactions for PRS and SLEs, PRS and sex, and SLEs and sex, and a three-way interaction term for PRS × SLEs × sex.

Assessing interaction on the additive scale

Interaction can occur on either the multiplicative or the additive scale. Interaction on the multiplicative scale is present when the combined effects of two risk factors is larger (positive interaction) or smaller (negative interaction) than the *product* of the individual effects. Interaction on the additive scale is present when the combined effects of two risk factors are larger or smaller than the *sum* of the individual effects (Knol, van der Tweel, Grobbee, Numans, & Geerlings, 2007). The absence of interaction on one scale does not preclude the presence of interaction on the other, and it is possible for an interaction to be negative on the multiplicative scale and positive on the additive scale (Knol et al., 2007). Cox regressions assess interaction on the multiplicative scale, therefore to also assess interaction on the additive scale, we calculated the excess risk due to interaction (RERI) (Knol et al., 2007), which has been shown to be the optimal measure for additive interaction in proportional hazards models (Li & Chambless, 2007). The 95% confidence intervals for the RERI were obtained by bootstrapping ($n = 1000$).

Gene-by-environment correlation

Previous research has suggested that genetic liability may be associated with the likelihood of experiencing SLEs – a phenomenon known as gene–environment correlation (Kendler & Karkowski-Shuman, 1997; Middeldorp, Cath, Beem, Willemsen, & Boomsma, 2008). We tested for potential gene–environment correlation by estimating the hazard of experiencing one or more SLEs during the follow-up period associated with each S.D. increase in PRS. Because SLEs are associated with depression and the case-cohort sample includes a disproportionate number of depression cases relative to the true underlying population, we examined the PRS-by-SLE association in the subcohort only ($n = 20\,563$).

Absolute risk

To estimate the absolute risk of depression, we fit Cox regression models with the number of SLEs and PRS quartile as fixed covariates. We used age 15 years as the cut-off for experiencing SLEs and estimated the absolute risk of depression after age 15 years stratified by the number of SLEs prior to age 15 years. Therefore, for these analyses, we used the subsample of individuals who were not diagnosed with depression or censored due to death, emigration, or end of follow-up prior to age 15 (16 520 depression cases, 15 292 subcohort members, total $N = 31\,812$). We then estimated risk by deriving the Nelson–Aalen estimator of the cumulative incidence $C(t)$ as $P(t) = 1 - \exp(-C(t)\exp(PRS \times \beta))$ where β was estimated in the Cox regression model.

Results

Sample characteristics including sex, calendar year at birth, age at depression diagnosis, and number of SLEs at the start of follow-up (age 10) for depression cases and subcohort members are shown in online Supplementary Fig. S1. Compared to subcohort members, depression cases were more likely to be female, to have been born in an earlier calendar year, and to have experienced one or more SLEs before age 10 years. Among cases, median age at first depression diagnosis was 19 years (interquartile range = 17–23 years).

Figure 1 shows the distributions of the number and types of SLEs experienced by the members of the iPSYCH2012 subcohort from birth to age 31 years. Because the subcohort is a random sample of the Danish population, these distributions represent the patterns of SLEs experienced from birth through age 31 in the entire Danish population born during that time period. The number of SLEs increased steadily with age; by their early 30s, over half of the individuals in the subcohort had experienced at least one SLE (Fig. 1a). Predictably, the most common event was family disruption (Fig. 1b). The associations between individual SLE and depression were fairly consistent in our sample (see online Supplementary Fig. S2).

Main effects of PRS and SLEs on depression

Figure 2 illustrates the main effects of both PRS and SLEs on depression. As in prior research (Dahl et al., 2017), there was a dose–response relationship between the number of SLEs and depression risk. Individuals with 4+ SLEs were 3.8 times more likely to develop depression than individuals with no SLEs (HR = 3.8, 95% CI 3.6–4.0). The hazard of depression increased by 36% with each additional SLE (HR = 1.36, 95% CI 1.33–1.39; $p < 0.0001$) (Table 1). Each standard deviation increase in PRS was associated with a 35% increase in risk for depression (HR = 1.35, 95% CI 1.31–1.38; $p < 0.0001$) (Table 1). There was also a smaller, but still significant, association between PRS and risk for SLEs in the subcohort, such that each S.D. increase in PRS was associated with a 9% increase in the hazard of experiencing at least one SLE after age 10 (HR = 1.09, 95% CI 1.07–1.11).

Interactions between PRS and SLEs as risk factors for depression

Figure 3 shows the interactions between SLEs and PRS. The interaction term for PRS and SLEs was small but statistically significant ($\beta = -0.04$, $p = 0.001$) (Table 1). The interaction effect on

https://doi.org/10.1017/S0033291721001410 Published online by Cambridge University Press

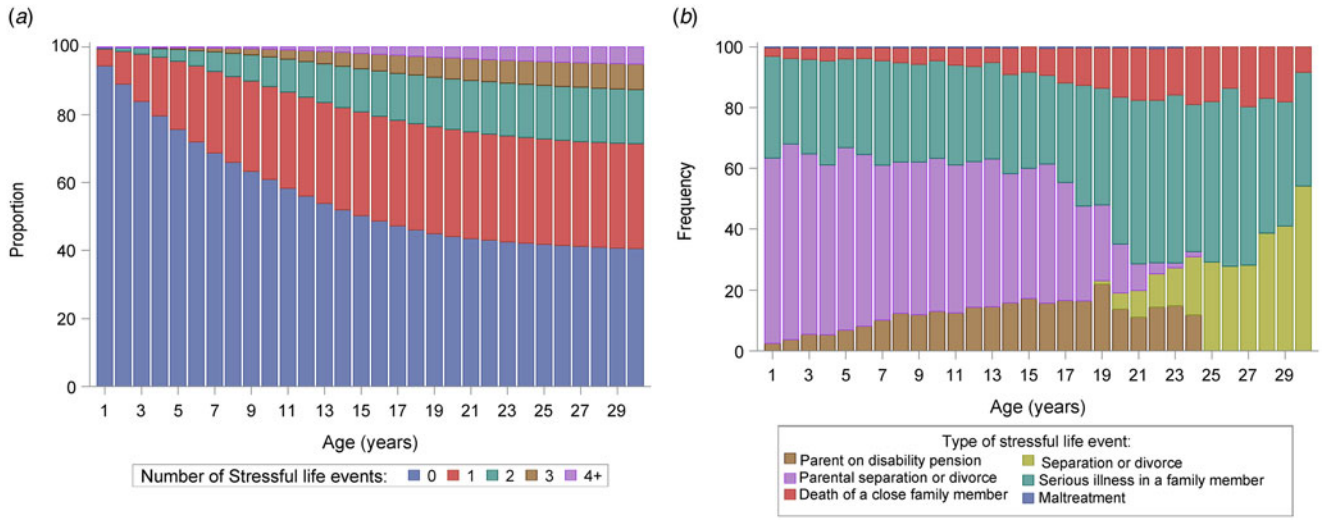

Fig. 1. Distribution of the number and type of stressful life events from birth to age 31 in a random sample of individuals born in Demark between 1981 and 2005. (a) Number of stressful life events. (b) Type of stressful life events.

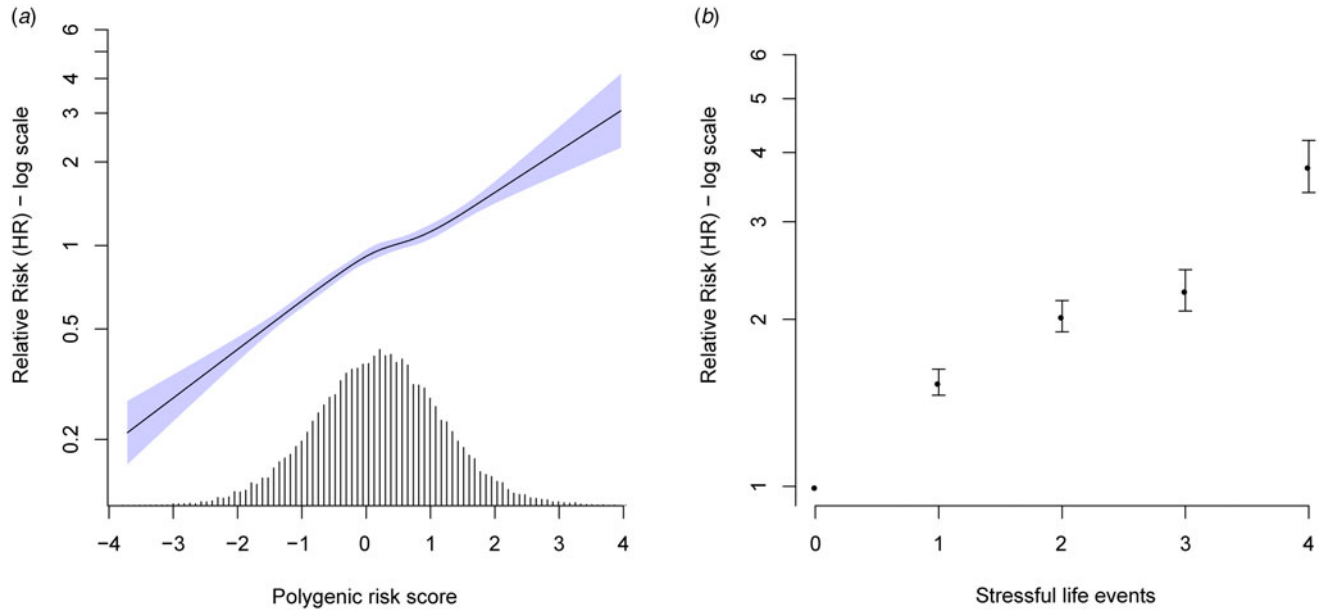

Fig. 2. Main effects of PRS and SLEs on risk for receiving a depression diagnosis in secondary-care settings by age 31. (a) Main effect of PRS on depression. (b) Main effect of SLEs on depression.

Note. Predicted values obtained from a Cox proportional hazards model including the following covariates: SLEs as a categorical variable, PRS as a continuous variable with restricted cubic splines, sex, birth year, and the first five ancestral principal components. Panel A shows the predicted log hazard ratios for PRS with covariates adjusted to the following levels: SLEs = 0, sex = female, birth year = 1989, PC01 = 0.0003836, PC02 = −0.000254, PC03 = 0.00001914, PC05 = 0.00001004. Panel B shows the predicted log hazard ratios for different SLE levels with PRS adjusted to 0, and all other covariates adjusted to the same levels as in Panel A.

the additive scale was again small, and in this instance positive (RERI = 0.09, 95% CI 0.06–0.12). Results from the model including the three-way interaction with gender showed that the effect of PRS was slightly stronger in females (HR_{int} = 1.08, 95% CI 1.01–1.16; p = 0.02), however there was no difference in the interaction between PRS × SLEs by gender (Table 1). The cumulative incidence of secondary-treated depression from age 15 to age 31 stratified by PRS quartile and number of SLEs is shown in Fig. 4. Estimates of the probability of depression ranged from 1.5% among males in the bottom PRS quartile with 0 SLEs at age 15 to 18.8% among females in the top PRS quartile with 4+ SLEs by age 15.

Discussion

Our aims in this study were to characterize the relationship between SLEs and polygenic liability as risk factors for early-onset depression treated in hospital-based care, and determine if this

https://doi.org/10.1017/S0033291721001410 Published online by Cambridge University Press

Table 1. Results from Cox proportional hazards models estimating the main effects and interactions for PRS, SLEs and sex on risk for early-onset depression diagnosed in secondary-care settings

	Main effects model		Interaction model 1: PRS × SLE		Interaction model 2: PRS × SLE × SEX	
Covariate	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
PRS	1.35 (1.31–1.38)	<0.0001	1.42 (1.37–1.47)	<0.0001	1.35 (1.28–1.42)	<0.0001
SLE	1.36 (1.33–1.39)	<0.0001	1.38 (1.357–1.41)	<0.0001	1.39 (1.35–1.44)	<0.0001
Sex	2.27 (2.16–2.39)	<0.0001	2.28 (2.17–2.39)	<0.0001	2.32 (2.17–2.47)	<0.0001
Birth year	1.09 (1.08–1.09)	<0.0001	1.09 (1.08–1.09)	<0.0001	1.09 (1.08–1.09)	<0.0001
PRS × SLE	–	–	0.96 (0.94–0.99)	0.0009	0.99 (0.96–1.02)	0.50
PRS × SEX	–	–	–	–	1.08 (1.01–1.16)	0.02
SLE × SEX	–	–	–	–	0.98 (0.94–1.03)	0.46
PRS × SLE × SEX	–	–	–	–	0.96 (0.92–1.00)	0.08

Note. All models also adjusted for the first five ancestral principal components. PRS and SLEs both modeled as continuous variables.

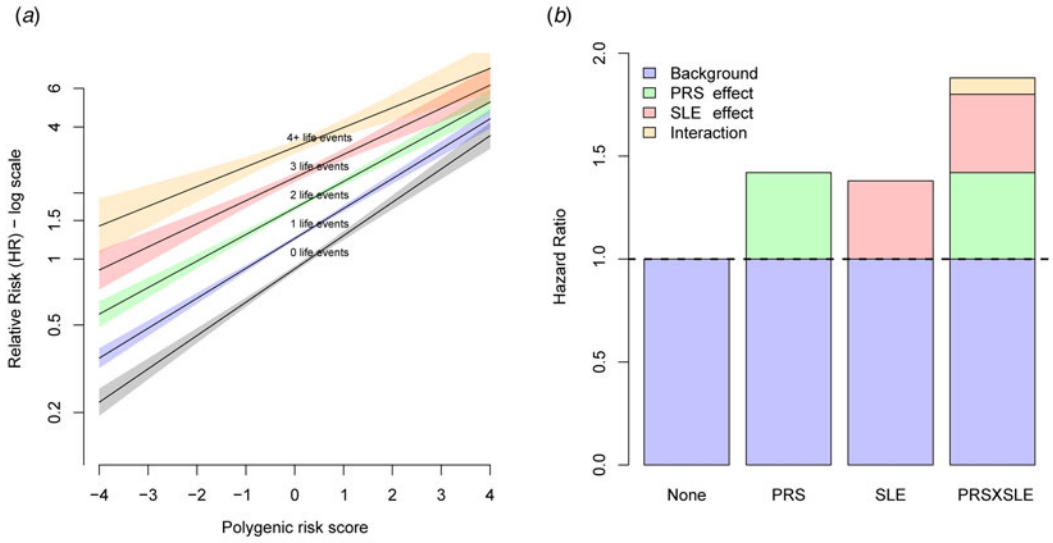

Fig. 3. Multiplicative and additive interactions between PRS and SLEs as risk factors for receiving a depression diagnosis in secondary-care settings by age 31. (a) Effect of PRS on depression by number of SLEs. (b) Hazard ratio by PRS and SLE.
Note. Panel A shows results obtained from a Cox regression model including PRS and SLEs (modeled as continuous variables), sex, birth year and the first five ancestral principal components. Panel B shows results for the interaction on the additive scale. RERI estimates were obtained from the multiplicative Cox model using the following formula described in Knol et al.: $(e^{\beta 1+\beta 2+\beta 3})-e^{\beta 1}-e^{\beta 2}+1$, where β_1 is the coefficient for the effect of SLEs, β_2 is the coefficient for the effect of PRS, and β_3 is the coefficient for the interaction effect between PRS and SLEs. The effect of SLEs represents the increase in depression risk associated with a 1 unit increase in SLEs (i.e. going from 0 to 1 SLE, or going from 1 to 2 SLEs) where PRS = 0. The effect of PRS represents the increase in depression risk associated with each 1 s.d. increase in PRS where SLEs = 0.

relationship differs by sex. We found statistically significant interactions between SLEs and the PRS on the multiplicative and additive scales, however the effect sizes were small and in opposite directions. As a result, we believe these findings do not support the idea that SLEs and PRS interact with one another as risk factors for depression. Although our results suggested that the effect of PRS itself might be slightly stronger in women, the interaction between SLEs and PRS did not differ by gender.

The absence of interaction between PRS and SLEs does not mean there is no value in examining both variables together. Like many prior studies, we found significant main effects for both PRS and SLEs that operated in a more or less additive fashion. The large differences in risk for depression among individuals with high PRS and SLEs *v.* low indicate that combining information on PRS and SLEs could potentially help identify groups of individuals at particularly high risk for developing depression in early life. These individuals might benefit from targeted interventions such as increased monitoring by their primary care physicians, teachers, and counselors; education to improve awareness of depression signs and symptoms; or triage into specialized care upon recognition of early signs or symptoms.

Methodological considerations

This study has numerous strengths, including large sample size, prospective design, and representative sampling. Most notably, the detailed, longitudinal nature of the registers allowed us to

https://doi.org/10.1017/S0033291721001410 Published online by Cambridge University Press

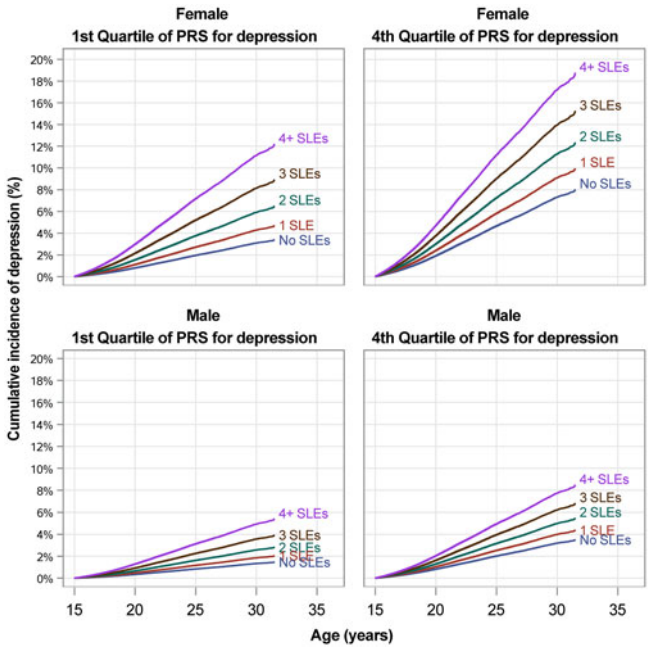

Fig. 4. Probability of receiving a depression diagnosis in a secondary-care setting by age 31, stratified by sex, number of stressful life events experienced prior to age 15, and polygenic risk score quartile.

construct an SLE measure that varied over time, providing a more fine-grained image of how stress is distributed in the Danish population from birth through age 30. To our knowledge, no prior G × E study has been able to incorporate this level of detail on SLEs without relying on retrospective self-report.

A number of methodological considerations need to be kept in mind when interpreting the results, however. First, the iPSYCH2012 sample does not include as cases individuals who experienced depression but were not treated, or treated outside of hospital settings. Prior research has shown that only around 25% of individuals who receive medical treatment for depression in Denmark are seen for depression in secondary-care settings within 5 years of onset (Musliner et al., 2019). Therefore, these results may not generalize to individuals with depression treated outside of secondary care settings, or they may be biased toward the null due to the presence of untreated or primary-care treated cases in the comparison group. In addition, experiencing SLEs and other systematic factors may be directly or indirectly associated with receiving treatment for depression. However, the focus on hospital-treated depression patients also makes these results potentially more useful for psychiatrists operating in these settings, as they pertain precisely to those patients that psychiatrists generally see in their practice.

Second, the register-based nature of the SLE measures has both benefits and drawbacks. Because information on SLEs comes from population-based registers, certain events, such as death of a relative, are nearly 100% accurate and reliable. Others, such as childhood maltreatment, capture only a small proportion of the true cases in the population and still others, such as family disruption, capture the event but not its context. For example, while the death of a family member can be assumed to be highly stressful in virtually all cases, a family separation might be highly stressful, or it might be amicable, or it might even mark the end of a stressful period depending on the context. We were also unable to measure events not included in the registers, such as bullying.

Third, there is likely an association between an individual's genetic makeup and his or her likelihood of experiencing SLEs. Indeed, having a parent with a serious mental illness is *itself* a source of stress in childhood, making it even more difficult to disentangle the relationships between genes, stress, and subsequent psychopathology. In this study, the PRS for depression was associated with SLEs, which suggests that some degree of gene–environment correlation was likely present.

Fourth, the iPSYCH2012 sample is young, with age at first depression diagnosis ranging from 10 to 31 years and a median age at onset of 19. As a result, these findings may not generalize to depression with onset in middle or late life. Furthermore, because of their youth, some of the cases are almost certainly experiencing depression that is in fact part of an as-yet undiagnosed bipolar or schizophrenia illness (Musliner & Ostergaard, 2018; Musliner, Munk-Olsen, Mors, & Østergaard, 2017). Our prior work showed that PRSs for schizophrenia and bipolar disorder were associated with progression to psychotic disorders and bipolar disorder, respectively, among individuals with depression, however PRS for major depression was not (Musliner et al., 2020).

Fifth, the sample was restricted to individuals of European ancestry, which limits the potential for confounding due to population stratification, but also limits the generalizability of the results to non-European populations. The almost exclusive focus on samples of European ancestry is a disturbing trend in the field which could exacerbate health disparities if/when PRSs are incorporated into clinical care (Martin et al., 2019).

Finally, the PRS used in this study was calculated using summary statistics from GWAS studies of depression that did not incorporate information on stress – thus, any SNPs that only have an association with depression among individuals exposed to stress, or SNPs with strong plasticity effects, would not have been included.

Conclusions

In this large, population-based sample of individuals born in Denmark between 1981 and 2002, we did not find convincing evidence to support the existence of a clinically meaningful interaction between PRS and SLEs as risk factors for secondary-treated depression in early life. However, differences in risk based on PRS and number of SLEs suggest that combining individual-level information on PRS and SLEs could help identify groups of individuals at increased risk for developing depression before age 31.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721001410

Acknowledgements. The iPSYCH project is funded by the Lundbeck Foundation (grant numbers R102-A9118 and R155-2014-1724) and the universities and university hospitals of Aarhus and Copenhagen. The first author is funded through a postdoctoral fellowship grant from The Lundbeck Foundation (grant number R303-2018-3551). Genotyping of the iPSYCH2012 sample was supported by grants from the Lundbeck Foundation, the Stanley Foundation, the Simons Foundation (SFARI 311789), and the National Institutes of Mental Health (NIMH 5U01MH094432-02). The Danish National Biobank resource is supported by the Novo Nordisk Foundation. Development of the methodology for the meta-PRS was supported by The Danish National Research Foundation (Niels Bohr Professorship to Professor John J. McGrath). The authors gratefully acknowledge the Psychiatric Genomics Consortium (PGC) and the research participants and employees of 23andMe Inc. for making available

the summary statistics that were used to generate the depression polygenic risk score, and the Broad Institute for genotyping. Finally, the authors extend special thanks to Dr Matthew W. Loftis for his help calculating bootstrap confidence intervals for the RERI analysis. The Major Depressive Disorder Working of the Psychiatric Genomics Consortium is a collaborative co-author for this article. The individual authors are (affiliations listed in the Supplement): Naomi R Wray, Stephan Ripke, Manuel Mattheisen, Maciej Trzaskowski, Enda M Byrne, Abdel Abdellaoui, Mark J Adams, Esben Agerbo, Tracy M Air, Till F M Andlauer, Silviu-Alin Bacanu, Marie Bækvad-Hansen, Aartjan T F Beekman, Tim B Bigdeli, Elisabeth B Binder, Julien Bryois, Henriette N Buttenschøn, Jonas Bybjerg-Grauholm, Na Cai, Enrique Castelao, Jane Hvarregaard Christensen, Toni-Kim Clarke, Jonathan R I Coleman, Lucía Colodro-Conde, Baptiste Couvy-Duchesne, Nick Craddock, Gregory E Crawford, Gail Davies, Franziska Degenhardt, Eske M Derks, Nese Direk, Conor V Dolan, Erin C Dunn, Thalia C Eley, Valentina Escott-Price, Farnush Farhadi Hassan Kiadeh, Hilary K Finucane, Jerome C Foo, Andreas J Forstner, Josef Frank, Héléna A Gaspar, Michael Gill, Fernando S Goes, Scott D Gordon, Jakob Grove, Lynsey S Hall, Christine Søholm Hansen, Thomas F Hansen, Stefan Herms, Ian B Hickie, Per Hoffmann, Georg Homuth, Carsten Horn, Jouke-Jan Hottenga, David M Hougaard, David M Howard, Marcus Ising, Rick Jansen, Ian Jones, Lisa A Jones, Eric Jorgenson, James A Knowles, Isaac S Kohane, Julia Kraft, Warren W. Kretzschmar, Zoltán Kutalik, Yihan Li, Penelope A Lind, Donald J MacIntyre, Dean F MacKinnon, Robert M Maier, Wolfgang Maier, Jonathan Marchini, Hamdi Mbarek, Patrick McGrath, Peter McGuffin, Sarah E Medland, Divya Mehta, Christel M Middeldorp, Evelin Mihailov, Yuri Milaneschi, Lili Milani, Francis M Mondimore, Grant W Montgomery, Sara Mostafavi, Niamh Mullins, Matthias Nauck, Bernard Ng, Michel G Nivard, Dale R Nyholt, Paul F O'Reilly, Hogni Oskarsson, Michael J Owen, Jodie N Painter, Carsten Bøcker Pedersen, Marianne Giørtz Pedersen, Roseann E Peterson, Wouter J Peyrot, Giorgio Pistis, Danielle Posthuma, Jorge A Quiroz, Per Qvist, John P Rice, Brien P. Riley, Margarita Rivera, Saira Saeed Mirza, Robert Schoevers, Eva C Schulte, Ling Shen, Jianxin Shi, Stanley I Shyn, Engilbert Sigurdsson, Grant C B Sinnamon, Johannes H Smit, Daniel J Smith, Hreinn Stefansson, Stacy Steinberg, Fabian Streit, Jana Strohmaier, Katherine E Tansey, Henning Teismann, Alexander Teumer, Wesley Thompson, Pippa A Thomson, Thorgeir E Thorgeirsson, Matthew Traylor, Jens Treutlein, Vassily Trubetskoy, André G Uitterlinden, Daniel Umbricht, Sandra Van der Auwera, Albert M van Hemert, Alexander Viktorin, Peter M Visscher, Yunpeng Wang, Bradley T. Webb, Shantel Marie Weinsheimer, Jürgen Wellmann, Gonneke Willemsen, Stephanie H Witt, Yang Wu, Hualin S Xi, Jian Yang, Futao Zhang, Volker Arolt, Bernhard T Baune, Klaus Berger, Dorret I Boomsma, Sven Cichon, Udo Dannlowski, EJC de Geus, J Raymond DePaulo, Enrico Domenici, Katharina Domschke, Tõnu Esko, Hans J Grabe, Steven P Hamilton, Caroline Hayward, Andrew C Heath, Kenneth S Kendler, Stefan Kloiber, Glyn Lewis, Qingqin S Li, Susanne Lucae, Pamela AF Madden, Patrik K Magnusson, Nicholas G Martin, Andrew M McIntosh, Andres Metspalu, Ole Mors, Preben Bo Mortensen, Bertram Müller-Myhsok, Merete Nordentoft, Markus M Nöthen, Michael C O'Donovan, Sara A Paciga, Nancy L Pedersen, Brenda WJH Penninx, Roy H Perlis, David J Porteous, James B Potash, Martin Preisig, Marcella Rietschel, Catherine Schaefer, Thomas G Schulze, Jordan W Smoller, Kari Stefansson, Henning Tiemeier, Rudolf Uher, Henry Völzke, Myrna M Weissman, Thomas Werge, Cathryn M Lewis, Douglas F Levinson, Gerome Breen, Anders D Børglum, Patrick F Sullivan.

Financial support. This work was funded by grants from The Lundbeck Foundation (grant# R102-A9118 and R155-2014-1724).

Conflict of interest. Thomas Werge has served as a scientific advisor to H. Lundbeck A/S. Cathryn Lewis is a member of the Scientific Advisory Board for Myriad Neuroscience. Hans J. Grabe has received travel grants and speakers honoraria from Fresenius Medical Care, Neuraxpharm, Servier and Janssen Cilag as well as research funding from Fresenius Medical Care. Gerome Breen has received consultancy and speaker fees from Eli Lilly, Otsuka, and Illumina. Aartjan T. F. Beekman is on speaker's bureaus for Lundbeck and GlaxoSmithKline. Gregory E. Crawford is a cofounder of Element Genomics. Enrico Domenici was an employee of Roche (2010–2015) and has received research support from Roche in the period 2016–2018. Qingpin Li is an employee of Janssen Research & Development, LLC and owns equity in the company. Sarah Paciga is an employee of Pfizer, Inc. and owns stock in the company. Jorge A. Quiroz is a former employee of Hoffmann–La Roche. Stacy Stenberg, Hreinn Stefansson, Kari Stefansson, and Thorgeir E. Thorgeirsson are employees of deCODE Genetics/Amgen. Patrick F. Sullivan is a member of advisory committees/boards at Lundbeck and Pfizer, and has received speaker or consultancy fees from Element Genomics and Roche. All other authors report no biomedical financial interests or potential conflicts of interest.

References

Albiñana, C., Grove, J., McGrath, J. J., Agerbo, E., Wray, N. R., Werge, T., … Vilhjálmsson, B. J. (2020). Leveraging both individual-level genetic data and GWAS summary statistics increases polygenic prediction. *Biorxiv*, 2020.2011.2027.401141. doi: 10.1101/2020.11.27.401141

Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C., Perry, B. D., … Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *European Archives of Psychiatry and Clinical Neuroscience*, *256*(3), 174–186. doi: 10.1007/s00406-005-0624-4

Arnau-Soler, A., Adams, M. J., Clarke, T. K., MacIntyre, D. J., Milburn, K., Navrady, L., … Thomson, P. A. (2019). A validation of the diathesis-stress model for depression in Generation Scotland. *Translational Psychiatry*, *9*(1), 25. doi: 10.1038/s41398-018-0356-7

Genomes Project Consortium, Auton, A., Brooks, L. D., Durbin, R. M., Garrison, E. P., Kang, H. M., … Abecasis, G. R. (2015). A global reference for human genetic variation. *Nature*, *526*(7571), 68–74. doi: 10.1038/nature15393

Barlow, W. E. (1994). Robust variance estimation for the case-cohort design. *Biometrics*, *50*(4), 1064–1072.

Barlow, W. E., Ichikawa, L., Rosner, D., & Izumi, S. (1999). Analysis of case-cohort designs. *Journal of Clinical Epidemiology*, *52*(12), 1165–1172.

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Disorders*, *40*(5), 373–383.

Coleman, J. R. I., Peyrot, W. J., Purves, K. L., Davis, K. A. S., Rayner, C., Choi, S. W., … Breen, G. (2020). Genome-wide gene-environment analyses of major depressive disorder and reported lifetime traumatic experiences in UK Biobank. *Molecular Psychiatry*, *25*(7), 1430–1446. 10.1038/s41380-019-0546-6.

Colman, I., Kingsbury, M., Garad, Y., Zeng, Y., Naicker, K., Patten, S., … Thompson, A. H. (2016). Consistency in adult reporting of adverse childhood experiences. *Psychological Medicine*, *46*(3), 543–549. doi: 10.1017/S0033291715002032

Colodro-Conde, L., Couvy-Duchesne, B., Zhu, G., Coventry, W. L., Byrne, E. M., Gordon, S., … Martin, N. G. (2018). A direct test of the diathesis-stress model for depression. *Molecular Psychiatry*, *23*(7), 1590–1596. doi: 10.1038/mp.2017.130

Dahl, S. K., Larsen, J. T., Petersen, L., Ubbesen, M. B., Mortensen, P. B., Munk-Olsen, T., & Musliner, K. L. (2017). Early adversity and risk for moderate to severe unipolar depressive disorder in adolescence and adulthood: A register-based study of 978647 individuals. *Journal of Affective Disorders*, *214*, 122–129. doi: 10.1016/j.jad.2017.03.014

Delaneau, O., Coulonges, C., & Zagury, J. F. (2008). Shape-IT: New rapid and accurate algorithm for haplotype inference. *BMC Bioinformatics*, *9*, 540. doi: 10.1186/1471-2105-9-540

Fang, Y., Scott, L., Song, P., Burmeister, M., & Sen, S. (2020). Genomic prediction of depression risk and resilience under stress. *Nature Human Behavior*, *4*(1), 111–118. doi: 10.1038/s41562-019-0759-3

Gray, R. J. (1992). Flexible methods for analyzing survival data using splines, with applications to breast cancer prognosis. *Journal of the American Statistical Association*, *87*(420), 942–951.

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology*, *1*, 293–319. doi: 10.1146/annurev.clinpsy.1.102803.143938

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*, *75*(4), 336–346. doi: 10.1001/jamapsychiatry.2017.4602

Hollegaard, M. V., Grauholm, J., Borglum, A., Nyegaard, M., Norgaard-Pedersen, B., Orntoft, T., … Hougaard, D. M. (2009). Genome-wide scans using archived neonatal dried blood spot samples. *BMC Genomics*, *10*, 297. doi: 10.1186/1471-2164-10-297

Hollegaard, M. V., Grove, J., Grauholm, J., Kreiner-Moller, E., Bonnelykke, K., Norgaard, M., … Hougaard, D. M. (2011). Robustness of genome-wide scanning using archived dried blood spot samples as a DNA source. *BMC Genetics*, *12*, 58. doi: 10.1186/1471-2156-12-58

Howard, D. M., Adams, M. J., Clarke, T. K., Hafferty, J. D., Gibson, J., Shirali, M., … McIntosh, A. M. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience*, *22*(3), 343–352. 10.1038/s41593-018-0326-7.

Howie, B. N., Donnelly, P., & Marchini, J. (2009). A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genetics*, *5*(6), e1000529. doi: 10.1371/journal.pgen.1000529

Keller, M. C. (2014). Gene x environment interaction studies have not properly controlled for potential confounders: The problem and the (simple) solution. *Biological Psychiatry*, *75*(1), 18–24. doi: 10.1016/j.biopsych.2013.09.006

Kendler, K. S., & Karkowski-Shuman, L. (1997). Stressful life events and genetic liability to major depression: Genetic control of exposure to the environment? *Psychological Medicine*, *27*(3), 539–547.

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual Review of Psychology*, *48*, 191–214. doi: 10.1146/annurev.psych.48.1.191

Knol, M. J., van der Tweel, I., Grobbee, D. E., Numans, M. E., & Geerlings, M. I. (2007). Estimating interaction on an additive scale between continuous determinants in a logistic regression model. *International Journal of Epidemiology*, *36*(5), 1111–1118. doi: 10.1093/ije/dym157

Lam, M., Awasthi, S., Watson, H. J., Goldstein, J., Panagiotaropoulou, G., Trubetskoy, V., … Ripke, S. (2019). RICOPILI: Rapid imputation for COnsortias PIpeLIne. *Bioinformatics*, *36*(3), 930–933. 10.1093/bioinformatics/btz633.

Li, R., & Chambless, L. (2007). Test for additive interaction in proportional hazards models. *Annals of Epidemiology*, *17*(3), 227–236. doi: 10.1016/j.annepidem.2006.10.009

Loh, P. R., Kichaev, G., Gazal, S., Schoech, A. P., & Price, A. L. (2018). Mixed-model association for biobank-scale datasets. *Nature Genetics*, *50*(7), 906–908. doi: 10.1038/s41588-018-0144-6

Loh, P. R., Tucker, G., Bulik-Sullivan, B. K., Vilhjalmsson, B. J., Finucane, H. K., Salem, R. M., … Price, A. L. (2015). Efficient Bayesian mixed-model analysis increases association power in large cohorts. *Nature Genetics*, *47*(3), 284–290. doi: 10.1038/ng.3190

Lynge, E., Sandegaard, J. L., & Rebolj, M. (2011). The Danish national patient register. *Scandinavian Journal of Public Health*, *39*(7 Suppl), 30–33. doi: 10.1177/1403494811401482

Martin, A. R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B. M., & Daly, M. J. (2019). Clinical use of current polygenic risk scores may exacerbate health disparities. *Nature Genetics*, *51*(4), 584–591. doi: 10.1038/s41588-019-0379-x

Middeldorp, C. M., Cath, D. C., Beem, A. L., Willemsen, G., & Boomsma, D. I. (2008). Life events, anxious depression and personality: A prospective and genetic study. *Psychological Medicine*, *38*(11), 1557–1565. doi: 10.1017/S0033291708002985

Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin*, *110*(3), 406–425.

Mors, O., Perto, G. P., & Mortensen, P. B. (2011). The Danish psychiatric central research register. *Scandinavian Journal of Public Health*, *39*(7 Suppl), 54–57. doi: 10.1177/1403494810395825

Mullins, N., Power, R. A., Fisher, H. L., Hanscombe, K. B., Euesden, J., Iniesta, R., … Lewis, C. M. (2016). Polygenic interactions with environmental adversity in the aetiology of major depressive disorder. *Psychological Medicine*, *46*(4), 759–770. doi: 10.1017/S0033291715002172

Musliner, K. L., Krebs, M. D., Albinana, C., Vilhjalmsson, B., Agerbo, E., Zandi, P. P., … Ostergaard, S. D. (2020). Polygenic risk and progression to bipolar or psychotic disorders among individuals diagnosed with unipolar depression in early life. *American Journal of Psychiatry*, *177*(10), 936–943. doi: 10.1176/appi.ajp.2020.19111195

Musliner, K. L., Liu, X., Gasse, C., Christensen, K. S., Wimberley, T., & Munk-Olsen, T. (2019). Incidence of medically treated depression in Denmark among individuals 15-44 years old: A comprehensive overview based on population registers. *Acta Psychiatrica Scandinavica*, *139*(6), 548–557. doi: 10.1111/acps.13028

Musliner, K. L., Munk-Olsen, T., Mors, O., & Østergaard, S. D. (2017). Progression from unipolar depression to schizophrenia. *Acta Psychiatrica Scandinavica*, *135*(1), 42–50. doi: 10.1111/acps.12663

Musliner, K. L., & Ostergaard, S. D. (2018). Patterns and predictors of conversion to bipolar disorder in 91 587 individuals diagnosed with unipolar depression. *Acta Psychiatrica Scandinavica*, *137*(5), 422–432. doi: 10.1111/acps.12869

Musliner, K. L., Seifuddin, F., Judy, J. A., Pirooznia, M., Goes, F. S., & Zandi, P. P. (2015). Polygenic risk, stressful life events and depressive symptoms in older adults: A polygenic score analysis. *Psychological Medicine*, *45*(8), 1709–1720. doi: 10.1017/S0033291714002839

Norgaard-Pedersen, B., & Hougaard, D. M. (2007). Storage policies and use of the Danish Newborn Screening Biobank. *Journal of Inherited Metabolic Disorders*, *30*(4), 530–536. doi: 10.1007/s10545-007-0631-x

Olfson, M., Kroenke, K., Wang, S., & Blanco, C. (2014). Trends in office-based mental health care provided by psychiatrists and primary care physicians. *Journal of Clinical Psychiatry*, *75*(3), 247–253. doi: 10.4088/JCP.13m08834

Pedersen, C. B. (2011). The Danish civil registration system. *Scandinavian Journal of Public Health*, *39*(7 Suppl), 22–25. doi: 10.1177/1403494810387965

Pedersen, C. B., Bybjerg-Grauholm, J., Pedersen, M. G., Grove, J., Agerbo, E., Baekvad-Hansen, M., … Mortensen, P. B. (2018). The iPSYCH2012 case-cohort sample: New directions for unravelling genetic and environmental architectures of severe mental disorders. *Molecular Psychiatry*, *23*(1), 6–14. doi: 10.1038/mp.2017.196

Pedersen, C. B., Mors, O., Bertelsen, A., Waltoft, B. L., Agerbo, E., McGrath, J. J., … Eaton, W. W. (2014). A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry*, *71*(5), 573–581. doi: 10.1001/jamapsychiatry.2014.16

Perperoglou, A., Sauerbrei, W., Abrahamowicz, M., & Schmid, M. (2019). A review of spline function procedures in R. *BMC Medical Research Methodology*, *19*(1), 46. doi: 10.1186/s12874-019-0666-3

Petersen, L., Sorensen, T. I., & Andersen, P. K. (2003). Comparison of case-cohort estimators based on data on premature death of adult adoptees. *Statistical Medicine*, *22*(24), 3795–3803. doi: 10.1002/sim.1672

Peterson, R. E., Cai, N., Dahl, A. W., Bigdeli, T. B., Edwards, A. C., Webb, B. T., … Kendler, K. S. (2018). Molecular genetic analysis subdivided by adversity exposure suggests etiologic heterogeneity in major depression. *American Journal of Psychiatry*, *175*(6), 545–554. doi: 10.1176/appi.ajp.2017.17060621

Petersson, F., Baadsgaard, M., & Thygesen, L. C. (2011). Danish registers on personal labour market affiliation. *Scandinavian Journal of Public Health*, *39*(7 Suppl), 95–98. doi: 10.1177/1403494811408483

Peyrot, W. J., Milaneschi, Y., Abdellaoui, A., Sullivan, P. F., Hottenga, J. J., Boomsma, D. I., & Penninx, B. W. (2014). Effect of polygenic risk scores on depression in childhood trauma. *British Journal of Psychiatry*, *205*(2), 113–119. doi: 10.1192/bjp.bp.113.143081

Peyrot, W. J., Van der Auwera, S., Milaneschi, Y., Dolan, C. V., Madden, P. A. F., Sullivan, P. F., … Penninx, B. (2018). Does childhood trauma moderate polygenic risk for depression? A meta-analysis of 5765 subjects from the psychiatric genomics consortium. *Biological Psychiatry*, *84*(2), 138–147. doi: 10.1016/j.biopsych.2017.09.009

Prentice, R. L. (1986). A case-cohort design for epidemiologic cohort studies and disease prevention trials. *Biometrika*, *73*(1), 1–11.

Self, S. G., & Prentice, R. L. (1988). Asymptotic distribution theory and efficiency results for case-cohort studies. *The Annals of Statistics*, *16*(1), 64–81.

Sullivan, P. F., Agrawal, A., Bulik, C. M., Andreassen, O. A., Borglum, A. D., Breen, G., … Consortium, P. G. (2018). Psychiatric genomics: An update

and an agenda. *American Journal of Psychiatry*, *175*(1), 15–27. doi: 10.1176/appi.ajp.2017.17030283

Thygesen, S. K., Christiansen, C. F., Christensen, S., Lash, T. L., & Sorensen, H. T. (2011). The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish national registry of patients. *BMC Medical Research Methodology*, *11*, 83. doi: 10.1186/1471-2288-11-83

Vilhjalmsson, B. J., Yang, J., Finucane, H. K., Gusev, A., Lindstrom, S., Ripke, S., … Price, A. L. (2015). Modeling linkage disequilibrium increases accuracy of polygenic risk scores. *American Journal of Human Genetics*, *97*(4), 576–592. doi: 10.1016/j.ajhg.2015.09.001

Wang, P. S., Aguilar-Gaxiola, S., Alonso, J., Angermeyer, M. C., Borges, G., Bromet, E. J., … Wells, J. E. (2007). Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. *Lancet (London, England)*, *370*(9590), 841–850. doi: 10.1016/S0140-6736(07)61414-7

Weissman, M. M., Bland, R., Joyce, P. R., Newman, S., Wells, J. E., & Wittchen, H. U. (1993). Sex differences in rates of depression: Cross-national perspectives. *Journal of Affective Disorders*, *29*(2–3), 77–84.

Weissman, M. M., Wickramaratne, P., Gameroff, M. J., Warner, V., Pilowsky, D., Kohad, R. G., … Talati, A. (2016). Offspring of depressed parents: 30 years later. *American Journal of Psychiatry*, *173*(10), 1024–1032. doi: 10.1176/appi.ajp.2016.15101327

Wray, N. R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E. M., Abdellaoui, A., … Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics*, *50*(5), 668–681. doi: 10.1038/s41588-018-0090-3