RESEARCH ARTICLE

REVISED Genetic and environmental determinants of stressful life events and their overlap with depression and neuroticism [version 2; peer review: 1 approved, 2 approved with reservations]

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Abstract

Background: Stressful life events (SLEs) and neuroticism are risk factors for major depressive disorder (MDD). However, SLEs and neuroticism are heritable and genetic risk for SLEs is associated with risk for MDD. We sought to investigate the genetic and environmental contributions to SLEs in a family-based sample, and quantify genetic overlap with MDD and neuroticism.

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Methods: A subset of Generation Scotland: the Scottish Family Health Study (GS), consisting of 9618 individuals with information on MDD, past 6 month SLEs, neuroticism and genome-wide genotype data was used in the present study. We estimated the heritability of SLEs using GCTA software. The environmental contribution to SLEs was assessed by modelling familial, couple and sibling components. Using polygenic risk scores (PRS) and LD score regression (LDSC) we analysed the genetic overlap between MDD, neuroticism and SLEs.
Results: Past 6-month life events were positively associated with lifetime MDD status (β=0.21, r^2=1.1%, p=2.5 x 10^{-25}) and neuroticism (β =0.13, r^2=1.9%, p=1.04 x 10^{-37}) at the phenotypic level. Common SNPs explained 8% of the phenotypic variance in personal life events (those directly affecting the individual) (S.E.=0.03, p= 9 x 10^{-4}). A significant effect of couple environment was detected accounting for 13% (S.E.=0.03, p=0.016) of the phenotypic variation in SLEs. PRS analyses found that reporting more SLEs was associated with a higher polygenic risk for MDD (β =0.05, r^2=0.3%, p=3 x 10^{-5}), but not a higher polygenic risk for neuroticism. LDSC showed a significant genetic correlation between SLEs and both MDD (r_G=0.33, S.E.=0.08) and neuroticism (r_G=0.15, S.E.=0.07).
Conclusions: These findings suggest that SLEs should not be regarded solely as environmental risk factors for MDD as they are partially heritable and this heritability is shared with risk for MDD and neuroticism. Further work is needed to determine the causal direction and source of these associations.

Keywords
Stress, Depression, Genetics, Neuroticism

This article is included in the Generation Scotland gateway.

Invited Reviewers

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REVISED **Amendments from Version 1**

The current version of the article responds to the reviewers concerns and adds an additional analysis which controls for current mood when testing the association between polygenic risk for MDD and stressful life events.

See referee reports

Introduction

The importance of stressful life events (SLEs) in the aetiology of Major Depressive Disorder (MDD) is widely recognised[1–3]. A longitudinal study showed that the odds ratio for the onset of MDD in the month of reporting a SLE is 5.64[1]. Understanding the precise relationship between reporting SLEs and MDD has, however, proven challenging as factors, such as genetics and early environment, influence both traits[4].

Whilst SLEs are sometimes considered to be random environmental effects, several studies have shown that reporting SLEs is heritable with estimates from twin studies ranging from 20 to 50%[5–8]. SLEs are categorized into dependent events and independent events. Dependent SLEs, such as relationship problems or job loss, may be, in part, the result of a person's own behaviour and directly affect the individual. Independent SLEs events, including death or illness of a relative, are more likely to be beyond the control of the individual. The estimated heritability of dependent life events (28–45%) is higher than independent life events (7%), which tend to be more strongly influenced by familial environment[9,10].

Personality can influence the reporting and experience of SLEs. Neuroticism not only increases risk for MDD but can also moderate the relationship between SLEs and MDD. A study of 7500 twins found that the depressive effects of SLEs were more pronounced in individuals with higher neuroticism[11]. A four-year longitudinal study of young adults also found that neuroticism is associated with greater reporting of negative life events[12].

Genetic risk factors for MDD have been associated with increased propensity of reporting SLEs. Twin studies have shown that the risk for SLEs is greater in monozygotic twins with a depressed co-twin compared to dizygotic twins[1]. It has been hypothesized that individuals with greater genetic risk for MDD may select themselves into high risk environments or have a greater vulnerability to the depressive effects of stress[13]. This is supported by the observation that depressed individuals tend to report more dependent SLEs[14–17]. A co-twin control study, on the other hand, found that neuroticism and depression are related to a higher risk of experiencing SLEs, but this didn't appear to be due to shared genetic risk factors[18]. As neuroticism is highly correlated with depression, both phenotypically[19] and genetically[20,21], it is also possible that personality traits associated with MDD increase the sensitivity to and/or the reporting of SLEs amongst depressed individuals.

Recent studies have aimed to find the proportion of SLE heritability attributed to common genetic variation using genome-wide SNP data. One study estimated the SNP heritability of SLEs to be 29% (p=0.03, S.E.=0.16) in a sample of 2578 unrelated individuals enriched for MDD cases[22]. However, another study of 7179 African American women found the SNP heritability of SLEs to be only 8% (p=0.02, S.E.=0.04)[23]. A significant genetic correlation between SLEs and MDD in African American women was observed by Dunn *et al*. (r=0.95, p=0.01) using bivariate GCTA-GREML, suggesting that genetic variants that influence MDD risk are also relevant for SLEs[23]. The difference in heritability estimates for SLEs may be the result of different genetic architectures and familial or environmental effects across the two samples. Previous studies have shown that more accurate estimates of heritability can be obtained when simultaneously modelling SNP genetic effects in the presence of familial environment[24]. If the correlation between SLEs and MDD can be explained by genetic or familial environmental factors, then this may signpost the most effective strategies for future research by highlighting the optimal periods and opportunities for intervention.

In the present study, we aim to estimate the SNP and pedigree heritability of SLEs and also the contribution of couple, sibling and nuclear family effects on SLEs in a family-based cohort drawn from the population of Scotland, Generation Scotland: the Scottish Family Heath Study (GS)[25–27]. A subset of GS that were re-contacted as part of a mental health follow-up study, are used here for the current investigation[28]. Participants provided information on past 6 month life events and lifetime MDD status. We will explore the genetic relationship between MDD, neuroticism and SLE using GWAS summary statistics from external datasets: the Psychiatric Genetic Consortium (PGC) (MDD) and the Social Science Genetic Association Consortium (SSGAC) (neuroticism).

Methods

Sample description

The individuals used in this study were a subset of Generation Scotland: the Scottish Family Health Study (GS), which has been described in detail elsewhere[25–27,29]. Briefly, GS comprises 23,690 individuals aged 18 years and over, recruited via general practitioners' throughout Scotland. In 2014, re-contact of GS participants began as part of a data collection initiative designed to re-assess the mental health of participants. In total, 21,526 GS participants were re-contacted by post and asked to return a questionnaire by post or via a URL link to complete online. In total, 9,618 participants volunteered as part of the mental health follow-up (45% response rate), and these are the participants used in this study. A full description of the re-contact procedure and data collected is provided elsewhere[28]. All components of GS, including its protocol and written study materials have received national ethical approval from the NHS Tayside committee on research ethics (reference 05/s1401/89).

SLEs were assessed using the List of Threatening Experiences[30], which is a self-report questionnaire consisting of 12 life events

that have taken place in the past six months. In order to perform heritability analyses of SLE we created a list of personal life events that should be unique to the individual endorsing them. This was to prevent a potential inflation in heritability estimates from family members endorsing the same life events (e.g. death of a family member) (Supplementary Table 1). For the remainder of the analyses presented in this study we analysed total SLE's reported, dependent life events reported and independent life events reported (Supplementary Table 2).

In the GS mental health cohort, lifetime MDD was assessed using the Composite International Diagnostic Interview – Short Form (CIDI-SF)[31]. The CIDI-SF is a self-report measure of psychiatric symptoms and allows for the ascertainment of lifetime MDD status, age of onset and number of episodes. Neuroticism was assessed during the initial contact of the full GS cohort using the Eysenck personality questionnaire[32]. Current psychological distress was assessed using the General Health Questionnaire-28 and additional detail is reported in the cohort paper[28].

Genome-wide genotype data generated using the Illumina Human OmniExpressExome-8-v1.0 array and was available for 8734 of the 9618 individuals from the GS subset. Genotyping is described in greater detail elsewhere[25]. Population outliers were identified and removed from the sample. Quality control of genotypes involved removing SNPs with a call rate < 98%, a missing rate per individual ≥2%, a minor allele frequency (MAF) <1% and Hardy-Weinberg equilibrium (HWE) $p \leq 1\times10^{-6}$. In total, 561,125 autosomal SNPs remained and were used in subsequent analyses. Multidimensional scaling (MDS) components were created according to the ENIGMA 1000 genomes protocol (ENIGMA, 2013) in the software package PLINK v1.9[33].

Heritability analyses

Only personal SLEs (Supplementary Table 1) were used to estimate the heritability of life events. If individuals in a family endorse the same event (e.g. death of a family member) it will not be clear if the similarities between family members are due to endorsement of the same event or shared genetic effects influencing the reporting of SLE. Furthermore, as heritability estimates in family studies can be distorted by shared environments as well as shared genetic material, we estimated heritability whilst modelling components of the environment[24]. Genetic effects were estimated in GCTA by fitting a pedigree kinship matrix (K) and a genetic relationship matrix (G) alongside 3 environmental components: the environmental effect from the nuclear family F, the environmental effect from the couple relationship C and the environmental effect from the full sibling relationship S. The population prevalence used to transfer heritability estimates for MDD from the observed scale to the liability scale was 0.162[34,35]. The variance explained by these effects were estimated using linear mixed models (LMM) and the statistical significance tested using likelihood ratio (LRT) and Wald tests. Details on the construction of the variance-covariance matrices can be found in the Supplementary Methods.

Genomic and environmental relationship components are fitted in a LMM implemented in GCTA:

$$\boldsymbol{Y = Xb + G + K + F + S + C + \varepsilon}$$

Y is a vector of either a binary MDD phenotype or the score for SLEs. b is the effect of X, a vector of fixed effect covariates which include age, sex and 20 principal components derived from the genome-wide GRM. G and K represent the random genetic effects from the SNPs and the pedigree, respectively. F, S, and C and ε represent the random environmental effects shared by nuclear family members, full-siblings, couples and the error term, respectively.

Backward stepwise model selection was used to select the appropriate model to identify major genetic and/or environmental components contributing to the phenotypic variance. The initial model was the full 'GKFSC' model and LRT and Wald tests were conducted to test each variance component. A variance component was removed if it failed to obtain significance (α=5%) in both tests and among the variance components satisfying (1) it has the highest P value in the Wald test. This process was repeated until all the remaining components were significant in either the LRT or Wald test. This method is described in more detail by Xia *et al*[24].

There were 659 couple pairs, 1928 full sibling pairs and 4523 nuclear families (containing at least 2 individuals) in the present sample. The number of non-zero elements of the KFSC matrices for whom genotypic and all phenotypic information are available in the present sample are shown in Supplementary Table 3. The G matrix does not contain any non-zero elements.

Polygenic risk score (PRS) analyses

Polygenic risk scores (PRS) were created in PRSice v1.25 software using the raw genotype data from a target sample (GS) and summary statistics from an independent discovery sample[36]. This method calculates the sum of associated alleles an individual in the target sample carries across the genome, weighted by their effect size in an independent discovery GWAS. SNPs were linkage disequilibrium pruned using clump-based pruning (r^2=0.1, 250 kb window) prior to creating PRS. Scores were created for a range of p-value thresholds ranging from $p \leq 0.01$ to $p = 1$ in 0.01 increments. Only one PRS was used to test for association and this was based on which p-value threshold score explained most variance in the trait of interest. The p-value thresholds used are shown in Supplementary Table 4.

PRS were created for MDD (MDD-PRS) and neuroticism (N-PRS). The GWAS summary statistics used for MDD were those from the unpublished Psychiatric Genetics Consortium (PGC MDD29) GWAS of MDD (130,664 cases vs 330,470 controls). For neuroticism PRS, the summary statistics from the Social Science Genetic Association Consortium (SSGAC) GWAS of 170,911 individuals were used[37]. Eighteen association tests were carried out between the MDD-PRS/N-PRS and traits of interest, which gave the Bonferroni corrected p-value

of 0.0028 as the threshold for statistical significance (tests presented in Table 3 and Table 4).

All variables were log transformed towards normality where necessary. Continuous variables were scaled to have a mean of 0 and a standard deviation of 1, such that the reported regression coefficients (betas) are standardized. Mixed linear models implemented in the ASReml-R v3.0 software package were used to test the association between MDD-PRS and traits of interest. When associations between binary traits and PRS are reported Taylor series transformation was used to convert beta and standard error values from the linear scale to the liability scale. Age, sex and four MDS components were fitted as fixed effect covariates. To control for family structure pedigree information was used to create an inverse relationship matrix which was fitted as a random effect. Wald's conditional F-test was used to calculate the significance of fixed effects. This method was also used to test the phenotypic association between MDD, SLEs and neuroticism. Relative risk ratios were determined using the R v 3.2.3 package epitools v 0.5-9.

LD score regression

To quantify the degree of genetic overlap in common variants between SLEs and PGC-MDD/SSGAC-neuroticism we used LD score regression (LDSC)[38]. This method analyses the correlational structure of LD between SNPs and the patterns of association between SNPs and traits of interest to calculate genetic correlations. We performed GWAS of independent and dependent life events in the present GS sample to generate summary statistics for LDSC. GWAS was performed using mixed linear model association analyses in GCTA using imputed genotype data, implementing a leave-one-chromosome-out approach, which creates a genetic relationship matrix (GRM) excluding the chromosome on which the candidate SNP tested for association is located[39]. Fitting a GRM controlled for family structure within the GS sample. Sex, age and 20 MDS components were fitted as fixed effect covariates. Genotypes were imputed using the Haplotype Reference Consortium (HRC) reference panel. Individuals with missingness ≥3% were excluded along with SNPs with a call rate ≤98%, HWE p-value ≤ 1×10^{-6} and a MAF ≤ 1%. Genotype SNP data were phased using SHAPEIT2 and imputation performed using PBWT software[40]. Post-imputation SNPs with more than two alleles, monomorphic SNPs and SNPs with an INFO score < 0.8 were removed. QQ plots for the GWAS of independent and dependent life events are shown in Supplementary Figure 2 and Supplementary Figure 3.

Results

The prevalence of lifetime MDD in the present study was 16.4% (1506 cases vs 7667 controls). Individuals with a lifetime diagnosis of MDD had significantly higher neuroticism scores, were significantly younger and were more likely to be female (Table 1). A significant positive association between the number of past 6 month stressful life events (SLEs) and MDD was found (β =0.21, r^2=1.1%, p=2.5 × 10^{-25}) with individuals with MDD reporting, on average, 1.14 SLEs compared to controls who reported an average of 0.83 life events (Table 1). The association between MDD and SLE was significant for dependent (β =0.25, r^2=1.0%, p=1.8 × 10^{-21}) and independent life events (β =0.14, r^2=0.28%, p=5.3 × 10^{-07}). The relative risk (RR) for MDD in individuals experiencing any SLE was 1.44 (95% C.I.-1.31-1.58). The RR risk for MDD peaked in individuals reporting 4 SLEs compared to individuals reporting no life events (RR=1.91, 95% C.I.=1.50-2.44) (Supplementary Figure 1). Neuroticism was significantly and positively associated with SLE (β =0.11, r^2=1.3%, p=4.60 × 10^{-26}) with associations observed for dependent (β=0.10, r^2=1.0%, p=2.4 × 10^{-21}) and independent (β=0.08, r^2=0.71%, p=5.1 × 10^{-15}) life events.

Table 1. Summary of individuals from GS follow up cohort with phenotypic information available. All differences between cases and control significant at ≤ 5.13 × 10^{-12} after controlling for family structure using a pedigree matrix in ASReml.

	Cases (N=1506)	Controls (N=7667)
% Female	76%	59.8%
Age (s.d.)	54.2 (12.4)	56.8 (13.5)
SLE Total (s.d.)	1.14 (1.45)	0.83 (1.25)
Neuroticism	5.35 (3.46)	3.15 (2.87)

To test the heritability of SLE only personal life events were included. These are events that should be unique to an individual. In a family based sample the sum of the G and K effects are equivalent to the narrow sense heritability of a trait, when controlling for shared environment[24]. For personal SLEs, the narrow sense heritability estimate was 0.13 (G=0.07(S.E.=0.04 + K=0.06(S.E.=0.12) but only the SNP genetic effects were statistically significant (p=0.007 and p=0.5 respectively) (Table 2). Using backward stepwise model selection 8% of the variance in personal SLEs were explained by common genetic effects (S.E.=0.03, p=9 × 10^{-4}). A significant couple effect was also detected C=0.13 (S.E.=0.05, p=0.016) (Table 2). A previous study by Zeng *et al.* on the full GS sample (N=19,896) found shared genetics and couple-associated environment explain 61% of the variance in MDD in the total GS sample (K= 0.35(S.E.=0.06), G= 0.12(S.E.=0.05), C=0.14(S.E.=0.07))[41]. In this sub-sample we were not able to detect significant genetic effects on MDD as both the G and the K estimates were not significant. Our study uses a subset of individuals from the Zeng *et al.* study[41], and in the present sample only a significant effect of family was detected, but this may be due to reduced power in a sample of only 1506 MDD cases. Using the GCTA power calculator we estimated that we had only 34% power to detect a SNP genetic effect of 0.12 in the GS mental health follow-up cohort. Also, the mean number of SLE experienced by both cases and controls was low and therefore may have contributed to the reduced power to detect the heritability of these traits. The narrow sense heritability estimates for neuroticism was estimated at 0.32,

Table 2. Partitioning phenotypic variance into environmental and genetic components using the full GKFSC model. Backward stepwise selection was used to select the most parsimonious model for each trait. *Model non-convergence, unconstrained REML performed. Bold values are have significant LRT at $p < 0.05$.

Model	G (S.E.)	K (S.E.)	F (S.E.)	C (S.E.)	S (S.E.)
Personal SLEs					
GKFCS	**0.07 (0.04)**	0.06 (0.12)	0.00 (0.06)	0.14 (0.08)	0.00 (0.03)
GC	**0.08 (0.03)**			**0.13 (0.05)**	
Neuroticism					
GKFCS	**0.11 (0.05)**	0.10 (0.12)	0.03 (0.06)	0.00 (0.07)	0.01 (0.03)
GK	**0.12 (0.05)**	**0.20 (0.06)**			
MDD					
GKFCS*	0.16 (0.10)	-0.23 (0.28)	0.18 (0.14)	0.08 (0.18)	0.05 (0.08)
F			**0.18 (0.04)**		

Table 3. MDD PRS association analyses. Basic model has age, sex and 4 MDS components to control for population stratification and PRS as fixed effects. Family structure was controlled for using a pedigree matrix in AS-Reml. Depression was added as fixed effects in subsequent models. Best threshold PRS for each trait used, for MDD $p \leq 0.5$, SLEs $p \leq 0.35$ and Neuroticism $p \leq 0.23$.

	MDD	SLEs	Dependent SLEs	Indep SLEs	Neuroticism
Basic Model	β=0.113 (0.028), r^2=0.17%, p=3.7 × 10^{-4}	β=0.053 (0.011), r^2=0.28%, p=3.0 × 10^{-6}	β=0.058 (0.011), r^2=0.33%, p=13.5 × 10^{-7}	β=0.037 (0.011), r^2=0.14%, p=1.2 × 10^{-3}	β=0.080 (0.012), r^2=0.61%, p=1.4 × 10^{-11}
Control for Dep	-	β=0.044 (0.011), r^2=0.19%, p=1.3 × 10^{-4}	β=0.046 (0.011), r^2=0.21%, p=4.9 × 10^{-5}	β=0.031 (0.011), r^2=0.09%, p=8.2 × 10^{-3}	β= 0.065 (0.012), r^2=0.41%, p=2.9 × 10^{-8}
Control for GHQ	-	β=0.035 (0.011), r^2=0.12%, p=1.9 x 10^{-3}	β=0.041 (0.011), r^2=0.17%, p=1.6 x 10^{-4}	β=0.022 (0.011), r^2=0.05%, p=5.2 x 10^{-2}	β=0.056 (0.011), r^2=0.30%, p=8.3 x10^{-7}

Table 4. Neuroticism PRS association analyses. Basic model has age, sex and 4 MDS components to control for population stratification and PRS as fixed effects. Family structure was controlled for using a pedigree matrix in AS-Reml. Neuroticism was added as a fixed effect in subsequent model. Best threshold PRS for each trait used, for MDD $p \leq 0.10$ and SLEs/ Neuroticism $p \leq 0.60$.

	MDD	SLEs	Dependent SLEs	Indep SLEs	Neuroticism
Basic Model	β=0.120 (0.028), r^2=0.20%, p=5.4 × 10^{-5}	β=0.022 (0.011), r^2=0.05%, p=0.04	β=0.016 (0.011), r^2=0.03%, p=0.14	β=0.016 (0.011), r^2=0.03%, p=0.14	β=0.12 (0.011), r^2=1.4%, p=8.2 × 10^{-27}
Control for Neurot	β=0.051 (0.029), r^2=0.03%, p=0.11	β=0.01 (0.011), r^2=0.01%, p=0.32	β=0.004 (0.011), r^2=0.00%, p=0.72	β=0.009 (0.011), r^2=0.00%, p=0.45	-

with 12% (S.E.=0.05) of the variance explained by common SNPs (G). The environmental components did not contribute to any of the phenotypic variance in neuroticism and this is in accordance with the findings for neuroticism on the full GS sample reported by Hill *et al.* who reported the narrow sense heritability of neuroticism to be 30% with 11% of the variance explained by common SNPs (S.E.=0.02)[42] (Table 2).

Genetic overlap between SLEs and MDD/neuroticism was tested using PRS. For these analyses we tested the association with total, and also independent and dependent life events. Dependent life events have shown greater association at the phenotypic level with MDD[15,16]. MDD-PRS were significantly associated with MDD (β=0.11, r^2=0.17%, p=3.7 × 10^{-4}) (Table 3) and neuroticism (β=0.08, r^2=0.61%, p=1.4 × 10^{-11}) (Table 4). MDD-PRS were also associated with total SLEs (β=0.053 r^2=0.28%, p=3.0 × 10^{-6}). Individuals reporting more SLE had a higher polygenic risk for MDD. The effect was similar for dependent life events (β=0.058, r^2=0.33%, p=3.5 × 10^{-7}) compared to independent life events (β=0.037, r^2=0.14%, p=1.2 × 10^{-3}) (Table 3). After controlling for MDD status, the association between polygenic risk for MDD and SLEs was still significant although the effect was attenuated (β=0.053 vs β=0.044). After controlling for current psychological distress (GHQ score) the association with total life events was attenuated further (β=0.041) but remained significant. The association between polygenic risk for MDD and independent life events was no longer significant after controlling for current psychological distress. This suggests that the association is not driven solely by the increased presence of lifetime MDD or current mood in individuals with higher total or dependent SLE scores. These findings were supported by the results of the LDSC analyses. There was a significant genetic overlap between total SLEs and MDD (r_G=0.33, S.E.=0.08); however the genetic correlation was not significantly stronger (Z=1.76, p=0.08) for dependent SLEs (r_G=0.60, S.E.=0.19) compared to independent SLEs (r_G=0.21, S.E.=0.07) (Table 5).

Genetic overlap between SLEs and neuroticism was tested using neuroticism PRS (N-PRS). N-PRS were associated with neuroticism (β=0.12, r^2=1.4%, p=8.2 × 10^{-27}) and MDD (β=0.12, r^2=0.2%, p=5.4 × 10^{-5}). N-PRS were nominally associated with total SLEs (β=0.022, r^2=0.05%, p=0.04); however, the association was weaker compared to MDD-PRS (β=0.053, r^2=0.38%, p=2.6 × 10^{-6}) and not significant after correction for multiple testing. The association between independent or dependent SLEs and N-PRS were not significant and after controlling for neuroticism the association with SLEs became weaker (Table 4). A significant genetic overlap between neuroticism and total reported SLEs was detected (r_G=0.15, S.E.=0.07) using LD score regression (Table 5). The genetic correlation between neuroticism and dependent SLEs was 0.25 (S.E.=0.10), but this was not significantly greater (Z=1.56, p=0.06) than the genetic correlation with independent SLEs. The genetic correlation between neuroticism and independent SLEs was not significant.

Table 5. Genetic correlation (rG) between SLEs and MDD using LD score regression (Bulik-Sullivan *et al*, 2015). All estimates in bold are statistically significant p ≤ 0.05. PGC-MDD GWAS summary statistics taken from PGC GWAS of MDD (unpublished).

	PGC-MDD (S.E.)	Neuroticism (S.E.)
Total SLEs	**0.33 (0.08)**	**0.15 (0.07)**
Independent SLEs	**0.20 (0.07)**	0.06 (0.07)
Dependent SLEs	**0.60 (0.19)**	**0.25 (0.10)**

Discussion

Using a polygenic risk score (PRS) approach MDD and SLEs were found to have shared polygenic architecture. MDD polygenic risk was found to be higher in individuals reporting more SLEs. LD score regression showed a genetic correlation between MDD and SLEs using summary statistics from an independent MDD cohort. We also report a positive genetic correlation between neuroticism and SLEs. The variance in reporting of personal SLEs can be partly explained by common SNP effects and the environment shared by couples. 8% of the variance in personal SLEs was attributable to common genetic variants and an additional 13% of was explained by couple shared environment. This left 79% of the variance in personal SLEs unexplained by genetic or familial environmental effects.

The narrow sense heritability point estimate for personal SLEs in the current sample was 13%, which is lower than the 20–50% range of estimates derived from twin studies[5–7]. Furthermore, the pedigree contribution to this effect was not statistically significant. When personal SLEs were analysed modelling both genetic and environmental components, the SNP heritability estimate was significant and accounted for 8% of the variance in SLEs. This is the same as the estimate derived from the population-based study of African American women that found the SNP heritability of SLEs to be 8%[23]. However, another study found SNP effects account for roughly a third of variance in SLEs[22]. This is in contrast to our own findings and those of Dunn *et al*. and may be due to the high proportion of clinically ascertained MDD cases in the Power *et al*. sample. As MDD and SLEs are genetically correlated this may inflate heritability estimates if samples have a high proportion of MDD cases. In the present study we model genetic and environmental influences using different types of relationships and find that the heritability of SLEs are much lower than is often reported in twin studies.

We also detected a significant effect of the environment shared by couples on personal SLEs. The effect of couple shared environment on variance in MDD has previously been reported on the full GS cohort[41] to be 15–22%. We find that 13% of the variance in self-reported SLEs in this sample is attributable to shared couple environment. A study of 354 male Vietnam era veterans found that spousal correlations in depression were due to common stressors and that there were crossover effects so that depression in one spouse was influenced by stressors reported by the other[43]. Our data support this finding

and reinforces the importance of recent shared environment on MDD and SLEs. We find little evidence for the effect of nuclear family or sibling environment on reporting SLEs. A recent study of anthropometric and cardiometabolic traits in GS found that ~11% of variation across traits could be explained by the environment common to couples suggesting that recent shared environment is important when modelling the heritability of complex diseases[24]. However, it should be noted that there might be assortative mating between spouses in which case modelling the couple correlation entirely as an environmental effect may inflate heritability estimates[44].

A significant genetic correlation between SLEs and MDD was identified in this sample. PRS for MDD were associated with both dependent and independent SLEs even after controlling for MDD status. Another family-based study of SLE found a significant interaction between polygenic risk for MDD and SLE, such that the risk for MDD in individuals experiencing SLE was greater in those at high genetic risk for MDD[45]. Using LD score regression, we found that the genetic overlap between dependent life events and MDD (0.60) was nominally higher than for independent life events (0.20). This is in line with the findings by Dunn *et al*. who found a strong genetic correlation between MDD and SLEs in women (r_G=0.95)[23]. The genetic overlap between SLEs and MDD calls for a different interpretation of the effect of SLEs on MDD. Rather than considering SLEs simply as risk factors for MDD, the SNPs which predispose to MDD also increase risk for SLEs. This may arise from individuals selecting themselves into high risk stress environments or via personality traits, such as neuroticism, which prime them to respond negatively to life events[11]. Given that independent SLE may be co-morbid with illnesses and disease which are also co-morbid with MDD, this could explain some of the shared genetic aetiology of these traits. We found a significant genetic correlation between neuroticism and SLEs that was more pronounced for dependent SLEs. This supports previous studies that have shown that neuroticism is associated with increased reporting and sensitivity to SLEs. The discrepancy between the N-PRS and the LDSC analyses is likely due to the small amount of variance that can be explained by PRS.

There are a number of limitations to this study. Firstly, we rely on self-reported measures of MDD and SLEs, which are subject to recall bias. However, a recent study of GS found self-reported and SCID defined MDD to be highly genetically correlated[41]. Secondly, the full GKSFC model has its own limitations as a number of the matrices will be correlated such as the nuclear family matrix and the sibling matrix. This could prevent accurate estimates of familial effects. In order to account for this, we performed backward stepwise selection to select the most influential components to each trait however a superior approach would be to use a much larger sample size with more familial relationships. In our case, we were limited by the number of participants in our follow-up mental health study, and the familial structure within this sub-sample of GS. We did not have power to detect common SNP genetic effects for MDD in this sample. Our study suggests that the SNP heritability of personal SLEs are likely to be low and therefore larger samples are warranted to investigate this further. Determining the familial environmental effects on SLEs is challenging when families will endorse the same events solely because they have occurred within the same social network, such as 'did a close relative of yours die?'. This is also true for couples where major financial crises will be reported by both spouses due to shared assets. We attempted to control for this by creating a personal SLE category and also excluding events that could be inferred by spouses, however people may still endorse an event that happens to a spouse or family member as their own as they find it to be stressful to themselves. It is not possible to ascertain with the data available from this cohort, whether events endorsed by members of a couple reflect the same event, or whether each individual experiences an independent event. Finally, neuroticism was measured several years prior to the reporting of the stressful life events. Although this will not change the interpretation of the genetic correlations between neuroticism and SLE the phenotypic association between these traits should be treated with some caution.

In conclusion, we provide evidence that personal SLEs are heritable but that the effect attributable to common genetic SNPs is likely to be small. The recent environment such as that shared by couples is also likely to contribute to SLEs. There is strong genetic overlap between MDD and SLEs and some genetic overlap between neuroticism and SLEs. These findings underlie the importance of appropriately modelling environmental effects when studying these traits. Furthermore, our results demonstrate that the relationship between SLEs, MDD and personality may not be directionally causal, but a consequence of common genetic effects that influence these traits.

Data availability

Non-identifiable information from GS is available to researchers in the UK and to international collaborators upon request to the GS Access Committee (resources@generationscotland.org). GS operates a managed data access process including an online application form, which will be reviewed by the GS Access Committee. Summary information to help researchers assess the feasibility and statistical power of a proposed project is available on request by contacting resources@generationscotland.org. GWAS summary statistics arising from the analysis of GS in the current study will be made available on request. The GWAS summary statistics for the PGC GWAS of depression are available to download at https://www.med.unc.edu/pgc/results-and-downloads and the SSGAC neuroticism GWAS summary statistics from https://www.thessgac.org/data.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

We are grateful to the families who took part in GS, the GPs and Scottish School of Primary Care for their help in recruiting them, and the whole GS team, which includes academic researchers, clinic staff, laboratory technicians, clerical workers, IT staff, statisticians and research managers. The full list of consortium members in given in Supplementary File 1.

Supplementary material

Supplementary File 1: File containing supplementary methods, tables (S1–S4), and figures (S1–S3) mentioned in this article, and a list of the members of the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium.

Click here to access the data.

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Open Peer Review

Current Peer Review Status: ✔ ? ?

Version 2

Reviewer Report 28 January 2019

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✔ **Margaret Gatz**
Center for Economic and Social Research, University of Southern California, Los Angeles, CA, USA

The additional analyses of the association between independent life events and MDD-PRS and controlling for current psychological distress when looking at the association between stressful life events and MDD make the results more compelling. The paper now makes a useful contribution to sorting out genetic and environmental explanations for the overlap of stressful life events and depression.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 16 August 2018

https://doi.org/10.21956/wellcomeopenres.15103.r32922

? **Sarah Cohen-Woods**
[1] School of Psychology, Faculty of Social and Behavioural Sciences, Flinders University, Adelaide, SA, Australia
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[3] Centre for Neuroscience, Flinders University, Adelaide, SA, Australia

This manuscript is very clearly written, with methods well-articulated and described. The authors need to be commended for such an "easy read".

The authors highlight limitations themselves, in particular with respect to the need to create a "personal" list of life events which inevitably excludes a number of independent stressors. Further highlighted is the restricted power in the mental health GS cohort.

Minor points:
Abstract: where the author writes "were positively correlated with lifetime MDD status..." in results, they would be better positioned to state associated as the statistics presented relate to association primarily.

Page 6 - reference to Table 4 for MDD-PRS and dependent/independent SLEs - should be Table 3.

Significant points:
Moderation: In the discussion there is a brief mention of one MDD-PRS*life event interaction study. There is more than one publication in the literature looking at this moderation effect (with conflicting findings). Why did the authors not look at moderation in this cohort? (power / issues with correlation)? This should be mentioned / discussed.

Comorbidity and mortality in MDD: the distinction between dependent and independent SLEs is interesting, particularly within the hypothesis that one may be more correlated with MDD-PRS than the other. Findings in this paper do not support this; it is worth considering that factors within the independent SLEs may be markers of elevated illness comorbidity / mortality risk in MDD. This could, to some extent, explain some of the correlation seen in these SLEs and MDD.

Measurement timing: the measurement of neuroticism is prior to the measurement of SLEs; this needs to be discussed if it has any impact on interpretation.

Current mood confounds: Did the authors look at impact of current mood (e.g. BDI?) and influence on i) SLE reporting, ii) MDD reporting? Controlling for current mood may be necessary to further disentangle the genetic correlations.

An interesting addition to the post-GWAS literature.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Jan 2019

Toni-Kim Clarke, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, UK

1. We have changed our abstract to read as the reviewer suggests.
2. The references to table 3 and table 4 have been checked and changed where suggested. There was also incorrect referencing of table 5 which has now been updated.
3. *We did not analyse the interaction between MDD-PRS and life events in this study as we did not wish to duplicate the efforts of a parallel study of ours which has now been published and covers this topic. (Available here on biorxiv https://www.biorxiv.org/content/early/2018/11/28/479691 and currently in press at Translational Psychiatry).*
4. Re comorbidity and mortality in MDD: *This is an interesting point raised by the reviewer and we have added the following sentence to the discussion to acknowledge this 'Given that independent SLE may be co-morbid with illnesses and disease which are also co-morbid with MDD, this could explain some of the shared genetic aetiology of these traits'.*
5. Re measurement timing: *We add the following section to the discussion to acknowledge this 'Finally, neuroticism was measured several years prior to the reporting of the stressful life events. Although this will not change the interpretation of the genetic correlations between neuroticism and SLE the phenotypic association between these traits should be treated with some caution.'*
6. Re current mood confounds: *When analysing the genetic correlation between PRS and SLE we controlled for MDD status and found that the genetic correlations remained although they were slightly attenuated and we have stated this in the results section. We perform an additional analysis controlling for current psychological distress assessed using the General Health Questionnaire-28, which was completed at the same time that the participants reported on SLE. This has been added to Table 3 and shows a further attenuation of the association between MDD-PRS and SLE, but a significant association remains for total and dependent SLE.*

Competing Interests: No competing interests were disclosed.

Reviewer Report 24 July 2018

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The authors are commended for a clearly articulated example of the information available from so-called post-GWAS genomic analyses. While the sample size is limited regarding the heritability of stressful life events (SLEs), major depressive disorder (MDD) and neuroticism, the present manuscript describes intriguing analyses of the association of genetic risk for MDD and neuroticism with SLEs. The authors demonstrate that, as expected, genetic risk for MDD and neuroticism, assessed using polygenic risk score and linkage disequilibrium (LD) score regression, seem more strongly associated with dependent than independent SLEs.

As the authors note, limited statistical power hampers the influence of this manuscript, which reports heritability estimates for SLEs, MDD, and neuroticism below those found in larger samples and meta-analyses. However, Tables 3 and 4 present compelling evidence that genetic risk for MDD is associated with both dependent and independent SLEs even after adjusting for depression. These findings encourage future research to examine the role of SLEs in the development of MDD rather than as solely a consequence of the disorder. That said, greater detail is needed regarding the timing of self-reported major depressive episodes. Whether SLEs occur following a major depressive episode would not gravely undermine the present findings, but this detail would aid readers' interpretation of the present study. Additionally, if the data permits, I recommend that the authors adjust for depression severity rather than the binary diagnosis.

Finally, the authors contrast associations among MDD, neuroticism, and dependent and independent SLEs. Statistical approaches, including bootstrapping procedures, permit estimating confidence intervals on parameters reported in the present manuscript. These should be added to substantiate comparisons, such as the association of the PRS for MDD with dependent and independent SLEs prior to and following adjustment for MDD.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Jan 2019

Toni-Kim Clarke, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, UK

1. Re timing of events and current mood
The MDD case status represents lifetime depression and in most cases would precede the SLE as these are only past 6 month events. In order to try to control for the current mood we have performed an additional analysis controlling for General Health Questionnaire (GHQ) scores. This questionnaire was answered at the same time as participants reported their SLE and represents current psychological distress. The adjustment attenuates the association between MDD-PRS and SLE somewhat but the association remains significant for total and dependent life events. An additional row has been added to table 3 to add these analyses.

2. Re comparing effect sizes for associations after adjustment of MDD
The PRS and SLE scores were scaled to have a mean of 0 and a standard deviation of 1 prior to regression analyses. The reported beta are therefore standardized and should be comparable across the different traits and post/ prior MDD/GHQ adjustment.

Competing Interests: No competing interests were disclosed.

Reviewer Report 02 July 2018

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The authors build a persuasive case why it is important to sort out genetic and environmental explanations for overlaps of stressful life events, depression, and neuroticism. Phenotypically, the authors show that lifetime major depressive disorder (MDD) is associated with neuroticism, stressful life events (SLEs) over the past 6 months are associated with MDD, and neuroticism is associated with SLEs. Following a usual practice in stressful life events research, the authors distinguish between dependent events, which are nominally under the individual's control, and independent events, whose occurrence are beyond the individual's control. The association with MDD holds for both types of events.

The sample under study was from Generation Scotland, including nuclear families, couples, and siblings. Therefore, for the genetic analyses, the authors create a category that they call personal life events. These are events extracted from the longer list of SLEs where the events would not be shared by members of the family. This step was essential to assure that correlations between family members did not simply reflect shared events, but rather, their shared genetic relationship. MDD was assessed using the CIDI-SF interview that ascertains lifetime MDD status, age of first onset, and whether there were subsequent episodes. Neuroticism was assessed at initial contact; MDD and SLEs at re-contact.

In the genetic analyses, using Genome-wide Complex Trait Analysis (GCTA), the authors report heritability = .13 for personal life events, and heritability = .32 for neuroticism, while heritability was not significant for MDD. In polygenic risk score (PRS) association analyses, the authors report that those with higher PRS_{MDD} reported more SLE, both dependent and independent, even controlling for occurrence of MDD. The genetic correlation calculated with LD regression was .60 between MDD and dependent SLE, and .21 between MDD and independent SLE. In turn, higher $PRS_{Neuroticism}$ was not significantly predictive of SLE, once controlling for neuroticism. The genetic correlations between neuroticism and dependent and independent SLE were .25 and .06, respectively.

These heritability figures are somewhat lower than estimated heritability from twin studies, as is typically found. Indeed, MDD is generally considered substantially heritable. Previous Generation Scotland work, not cited in this report, found pedigree-based heritability of MDD to be between .28 and .44. Twin studies similarly place the estimated heritability of MDD at .37 (95% CI, .31 to .42). Although not the main focus of the current report, the discrepancy between twin and family-based estimates and GCTA is puzzling with regard to our understanding of MDD.

The finding of shared heritability between SLE and MDD has the important implication that life events should not be regarded as simply environmental risk factors for depression. The further implication is that common genetic effects may explain why personality plays a role in reporting more life events.

There are two substantial limitations to the study: One stems from the need to use personal life events for the genetic analyses. The personal life events were largely dependent life events, that is, events to whose occurrence the individual likely contributes, e.g., marital separation, being sacked from one's job. Independent life events were largely excluded, because they are predominantly events that happen to close family members and therefore affect the individual,

but are not under the individual's own control, such as death of a spouse or child. These latter are also two of the life events typically deemed most disruptive. Dependent life events are more likely to be correlated with personal characteristics such as neuroticism or depressive tendencies, as was found in the present study. Similarly, heritability of dependent events is expected to be higher than heritability of independent events. Unpacking the association between independent life events and MDD is potentially the question of most interest.

Another issue with the life events questionnaire is its timing. The List of Threatening Life Experiences as developed by Brugha and colleagues (1985; 1990) asked about life events that occurred in the six months preceding onset of a psychiatric problem. In the present study, it is not clear that the interview to assess MDD captured age at onset of most recent episode of depression, including whether it was within the last 6 months and thus after the life events had occurred. It seems probable that most episodes of MDD preceded the life events reported on the questionnaire and used in these analyses, and therefore, the reported life events cannot be considered a risk factor for MDD. It is also unknown whether respondents actually were depressed (or not) when completing the life events instrument, and therefore the extent to which being depressed in itself may inflate the reporting of life events. Finally, the mean number of total SLE was 1.14 for cases and 0.83 for controls, so it is also likely that a large number of cases and controls experienced no life events, personal or otherwise, in the last 6 months, potentially affecting observed variances and covariances.

The authors give some consideration to the former limitation, although not in its fullness, and not to the latter limitation at all.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

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Author Response 09 Jan 2019

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We agree with the reviewer that the association between independent life events and MDD is most interesting; however, as we are estimating heritability using family members, and family members will tend to endorse the same independent life events (e.g. death of a family member), the heritability of independent life event will be inflated and so we had to restrict the life events to those which are personal to the individual. We did look at the genetic correlation between independent life events and MDD using LD score regression and polygenic risk scores and show that there is genetic overlap between the two.
The timing of the life events and the MDD is an issue as the rightly reviewer states. To address this add an additional analysis to control for current mood when testing the association of MDD-PRS with life events. We control for current psychological distress which was assessed using the General Health Questionnaire-28 at the same time as individuals reported their SLE. The associations between MDD-PRS and total and dependent SLE remain significant after controlling for current mood however the association with independent SLE becomes non-significant (p=0.052). We have added the results to table 3 and add the following to the results section:
"Also, the mean number of SLE experienced by both cases and controls was low and therefore may have contributed to the reduced power to detect the heritability of these traits."
"After controlling for current psychological distress (GHQ score) the association with total life events was attenuated further (β=0.041) but remained significant. The association between polygenic risk for MDD and independent life events was no longer significant after controlling for current psychological distress."

Competing Interests: No competing interests were disclosed.