

## Original Article

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# Specific and cumulative lifetime stressors in the aetiology of major depression: A longitudinal community-based population study

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## Abstract

**Aims.** Early-life stressful circumstances (i.e. childhood maltreatment) coupled with stressful events later in life increase the likelihood of subsequent depression. However, very few studies have been conducted to examine the specific and cumulative effects of these stressors in the development of depression. There is also a paucity of research that simultaneously considers the role of biological factors combined with psychosocial stressors in the aetiology of depression. Guided by the biopsychosocial model proposed by Engel, the present study aims to examine to what extent the experience of stressors across the lifespan is associated with depression while taking into account the role of genetic predispositions.

**Methods.** Data analysed were from the Social and Psychiatric Epidemiology Catchment Area of the Southwest of Montreal (ZEPSOM), a large-scale, longitudinal community-based cohort study. A total of 1351 participants with complete information on the lifetime diagnoses of depression over a 10-year follow-up period were included in the study. Stressful events across the lifespan were operationalised as specific, cumulative and latent profiles of stressful experiences. Latent profile analysis (LPA) was used to explore the clustering of studied stressors including childhood maltreatment, poor parent–child relationship, and stressful life events. A polygenic risk score was calculated for each participant to provide information on genetic liability. Multivariate logistic regression was used to examine the association between specific, cumulative and latent profiles of stressors and subsequent depression.

**Results.** We found that different subtypes of childhood maltreatment, child–parent bonding and stressful life events predicted subsequent depression. Furthermore, a significant association between combined effects of cumulative stressful experiences and depression was found [odds ratio (OR) = 1.20, 95% confidence interval (CI): 1.12–1.28]. Three latent profiles of lifetime stressors were identified in the present study and named as ‘low-level of stress’ (75.1%), ‘moderate-level of stress’ (6.8%) and ‘high-level of stress’ (18.1%). Individuals with a ‘high-level of stress’ had a substantially higher risk of depression (OR = 1.80, 95% CI: 1.08–3.00) than the other two profiles after adjusting for genetic predispositions, socio-demographic characteristics, and health-related factors.

**Conclusions.** While controlling for genetic predispositions, the present study provides robust evidence to support the independent and cumulative as well as compositional effects of early- and later-on lifetime psychosocial stressors in the subsequent development of depression. Consequently, mental illness prevention and mental health promotion should target the occurrence of stressful events as well as build resilience in people so they can better cope with stress when it inevitably occurs.

## Introduction

Major depressive disorder (MDD) is a major global public health problem. It is a common mental disorder in the general population, characterised by depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration (World Health Organization, 2018). It is estimated that depression affects more than 300 million individuals, with a point prevalence of about 5% and a lifetime prevalence of 15% worldwide, making it one of the leading causes of disability (Friedrich, 2017). Depression is a complex disorder which occurrence is explained by the interplay between genetic and environmental factors (Lohoff, 2010; Tafet and Nemeroff, 2016), with multiple small-effect genes involved in complex relationships with psychosocial environmental factors (Whalley *et al.*, 2015). While genetic studies suggest that genetic factors can account for

about 30% of the variance in depression (Henn and Vollmayr, 2005), actual genome-wide analyses of multiple candidate genetic polymorphisms - polygenic risk score, only explained 1.9% of the variance in the risk for MDD (Wray *et al.*, 2018). In contrast, psychosocial environmental factors appear to play a much larger role in the development of MDD (Cohen *et al.*, 2007). Psychosocial stressors, especially early traumatic events and stressful life events have been shown to play an important role in the aetiology of MDD (Tennant, 2002; Su *et al.*, 2021). These stressors can interact with a genetic vulnerability to modify brain chemistry and impact mental health (Loman and Gunnar, 2010).

Lifetime stressors refer to a total sum of various types of early and later-on stressors that a person has experienced over the lifespan, with each form having potentially different consequences for health (Slavich, 2016; Shields and Slavich, 2017). Of note, early life stress (ELS) has a powerful impact on the growth and development of an individual (Seng *et al.*, 2013; Su *et al.*, 2021). ELS was defined as the exposure to events that happened in early life, a sensitive and vulnerable period and such stressors may exceed a child's ability to cope (Pechtel and Pizzagalli, 2011). Commonly studied early life stressors include physical, sexual, emotional abuse, neglect, poor child-parent bonding, social deprivation and household dysfunctions, etc. (Brown *et al.*, 2009). The stress sensitisation model hypothesises that early adverse events can enhance later-on stress responsiveness in adulthood and lower the threshold for adverse stress reactions later in life. The relationship of later life adult stressors and adverse health outcomes is, in part, determined by earlier exposure to childhood adversity (Keyes *et al.*, 2011; Keyes *et al.*, 2012). Life events in adulthood, which are commonly distinguished into early life events to which a role of predisposing factors is assigned, also contribute to the likelihood of mental disorders (Heim *et al.*, 2002; Faravelli *et al.*, 2007). Although psychosocial stress is a strong risk factor for disease, not all people with stressful experiences are affected negatively and develop psychiatric disorders. The diathesis-stress model proposed that stressful experiences across the lifespan trigger illnesses with varying degrees of vulnerability in biological and psychosocial characteristics and circumstances (National Research Council, 2009; Smoller, 2016).

Based on the life course perspective and stress process theory, early-life stressful circumstances (i.e. childhood maltreatment, poor child-parent bonding) are seen to lead to non-normative adverse depression trajectories (Wickrama *et al.*, 2008). Additionally, exposure to stressors during later adult life is also significantly associated with increased mental health problems (Romanov *et al.*, 2003). Accumulation of risks across the lifespan can act as a cumulative, aetiological threat to persistent health problems (Kuh *et al.*, 2003). A growing body of research has documented that psychosocial stressors can have a cumulative effect thus increasing the likelihood of mental illnesses (Raviv *et al.*, 2010; Björkenstam *et al.*, 2015). Extension to the cumulative risk model specifies that such effects will depend on sub-population categories and the diverse patterns of risk factors (Roberts *et al.*, 2018). In the chain of risk model, stressful events may co-occur and exposure to multiple stressors may reflect an interrelated pattern as stressors across lifespan tend to occur in clusters, rather than as single events or experiences (Steel *et al.*, 1999; Rees *et al.*, 2011). Unfortunately, most studies are limited in examining the co-occurrence of environmental stressors throughout the life course, this points to the importance of parcelling out different patterns of stress that occur. Investigations taking the timing of stressors or specific differences by sub-

population into account are needed to capture the complexity of the association between lifetime psychosocial stressors and MDD.

Given the increasing recognition of such limitations in stress research, an alternative approach of operationalising lifetime psychosocial stressors clusters them with regard to stressful exposures. This approach may be more informative in examining their associations with depression. Person-centred methods [e.g. latent profile analysis (LPA)] overcome the limitations of the variable-centred approaches. Variable-centred approaches assume that the population to be homogeneous and overlook diversity within studied populations, whereas person-centred approaches provide multifaceted information about stress sorting individuals into mutually exclusive classes that maximise between-group variance and minimise within-group variance (Adams *et al.*, 2013). It thus reveals the heterogeneity in the within-person configuration with multiple forms of stress. It also reveals how adult psychopathology varied across groups with distinctive patterns emerging (Howard and Hoffman, 2018). This person-centred approach adds to the literature by identifying naturally occurring clusters of individuals with similar patterns of stressors.

Even though studies suggest that cumulative lifetime stress is associated with the increased risk of adverse mental health outcomes, there are inconsistent findings in terms of dose-response relationships between stressors and mental health and wellbeing (Seery *et al.*, 2010; Toussaint *et al.*, 2016; Hubbard *et al.*, 2018). For instance, exposure to a moderate level of stress can predict better mental health and well-being than either exposure to a high level of stress or no stress (Seery *et al.*, 2010). This inconsistency may be explained by stressful events across the lifespan that may foster subsequent resilience promoting positive mental health and wellbeing (Seery *et al.*, 2010). The amount and kinds of stressors that pose mental problems have not been clearly established and are currently insufficient to inform specific public health policy. To the best of our knowledge, no study has been published to explore a life course perspective of different patterns and cumulative effects of life stressors in the development of MDD based on a comprehensive model of biological and psychological attributes. The biopsychosocial model proposed by Engel acts as a guiding theoretical framework identifying the importance of biological and psychosocial attributes in the development of depression (Schotte *et al.*, 2006). However, there is a paucity of research that estimates the associations between lifetime psychosocial stressors and MDD while taking biological (genetic) factors into account. A comprehensive examination of biopsychosocial factors can contribute substantially to our understanding of the pathogenesis of MDD.

A life-course perspective of stressors in the context of a biopsychosocial model could help illustrate stressors as chains of risks in which the early life origins of cumulative stress patterns have an aggregated impact on health outcomes. Building on these frameworks and expanding this literature by studying various profiles of lifetime stressors, the aims of our present study are to (1) examine the individual roles of specific stressors (i.e. childhood maltreatment, parent-child relationship and stressful life events) in the development of subsequent MDD; (2) test the cumulative effects of different trajectories of the lifetime stressors across the lifespan in the development of MDD; (3) explore whether latent profiles of psychosocial stressors are associated with subsequent MDD. In testing these stress hypotheses, we take into account genetic predispositions, sociodemographic

characteristics (age, sex, marital status, ethnicity, education and income) and health-related characteristics (type of drinkers, self-perceived mental health and family history of mental disorders) in the analysis. A schematic diagram of a biopsychosocial model of the stress-depression process used in the study is shown in Fig. 1.

## Methods

### Study sample

The current study used data from the Social and Psychiatric Epidemiology Catchment Area Study of Southwest Montreal (ZEPSOM). The ZEPSOM cohort is a longitudinal, community-based cohort. The cohort is a random sample of area residents between 15 and 65 years of age representing a total of 269 720 inhabitants across five neighbourhoods in southwest Montreal in 2007. At baseline data collection (Wave 1), the sample consisted of 2433 randomly selected participants. More details about the study can be found in the previous research (Caron *et al.*, 2012). The present study sample ( $N = 1351$ ) is restricted to those respondents who completed their interviews at Wave 3, Wave 4 and Wave 5 of the study and had information on depression status at Wave 4, stressful events at Wave 3, early life experiences at Wave 5 and genetic sequencing data at Wave 5. Online Supplementary Fig. S1 illustrates the selection process of the present study.

### Measurements

#### Lifetime stress measurements

**Childhood maltreatment.** Childhood maltreatment was assessed using the Childhood Trauma Questionnaire-short form (Bernstein and Fink, 1998). It has 28 self-reported items assessing childhood abuse and neglect and can be administered to anyone 12 years or older. The Cronbach's alpha value for this study was 0.98.

**Parental bonding.** Parental bonding was assessed using the Parental Bonding Instrument (PBI), which is a 50-item questionnaire designed to measure perceptions of parental behaviours before the age of 16 (Parker *et al.*, 1979). The questionnaire has two subscales including 12 items assessing the dimension of care and 13 items assessing control and overprotection for maternal and paternal bonding, respectively. To be consistent for both the care and control/overprotection subscales of the PBI, we reversed the scores of scale items in the care dimension, thus, a high score on the care subscale indicates more perceived parental neglect and rejection. Similarly, a high score on the overprotection subscale indicates perceived excessive control and intrusive parenting. The Cronbach's alpha value was 0.89 for the maternal care scale and 0.93 for the paternal care scale and 0.84 for both maternal and paternal protection subscale.

**Stressful life events.** The Life's Events Questionnaire was used to measure the stressful life events (Laurin, 1998). The instrument includes a total of 22 life events that can be grouped into five major themes, including work and financial issues, romantic relationships, family and friend relationships, housing and experiences of aggression. Responses were measured on a 4-point Likert scale (1 = 'not stressful', 2 = 'a little stressful', 3 = 'quite stressful', 4 = 'very stressful'). The Cronbach's alpha for the scale was 0.58.

#### Lifetime major depression

Major depression was assessed based on the modified version of the World Mental Health (WMH) 2000 project, an international initiative responsible for the development of a newer version of the Composite International Diagnostic Interview (CIDI). The WMH-CIDI is a fully structured diagnostic interview assessing major depression using the definitions and criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) and the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (World Health Organization, 1992; American Psychiatric Association, 2000). This modified WMH-CIDI was previously used in the Canadian Community Health Survey (CCHS cycle 1.2) (Gravel and Béland, 2005). These modifications of the WMH-CIDI were applied to reduce response burden and to clarify concepts (Kessler *et al.*, 1998). Respondents were assessed for their lifetime depressive episodes prior to the diagnostic interview that occurred at Wave 4.

### Covariates

#### Genetic predisposition-polygenic risk score

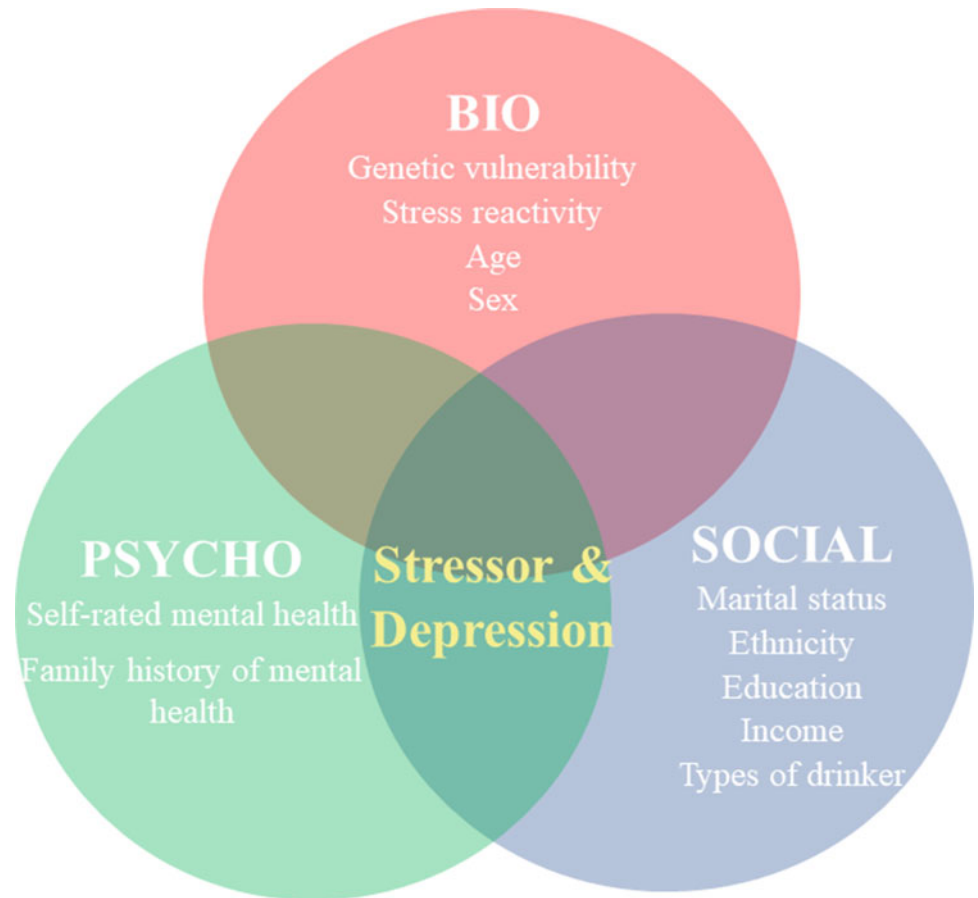
Genetic data were collected for each survey respondent at Wave 5. Polygenic risk score (PRS) is a method of aggregation conceptualised as an indicator of the diathesis used to test the predictive power of multiple genetic variants simultaneously (The International Schizophrenia Consortium, 2009). Genetic liability is captured and characterised in a GWAS or meta-analysis by creating a summary score of weighted effect sizes across all single-nucleotide polymorphisms (SNPs) associated with psychiatric disorders at a pre-specified significance threshold (The International Schizophrenia Consortium, 2009). For the present study, the polygenic risk score for major depression was produced using the GWAS summary statistics of per SNPs from the Psychiatric Genomics Consortium (PGC) with the  $p$ -value threshold of 0.001.  $PRS_{DEP}$  was calculated for each participant.

#### Sociodemographic characteristics

Data on socio-demographic attributes were collected using standard Statistics Canada question items. Information on participants' sex (Male *v.* Female), marital status (Single, Married/Common-law and Separated/Divorced/Widowed), ethnicity (White *v.* Non-White), level of education (Less than secondary, Secondary education and Post-secondary education), and income which was treated as a continuous variable, was collected at Wave 3. Age was categorised into four groups: 18–30 years, 30–45 years, 45–60 years and 60 years and above.

#### Health-related characteristics

Health-related characteristics were also collected at Wave 3, including the type of drinker (Regular drinker, Occasional drinker, Former drinker and Abstainer), self-perceived mental health (Excellent, Very Good, Good, Fair and Poor) and family history of mental disorders (Yes *v.* No). A family history of mental disorders was asked if a biological parent, or both, had been diagnosed by a psychiatrist, or hospitalised for mental health problems, or experienced any of the following problems, including depression, delirium or hallucination, anxiety disorders, substance abuse or suicide (Sobel, 1985).



**Fig. 1.** Biopsychosocial model of stress and depression.

### Statistical analysis

#### Operationalisation of lifetime stressors

Three approaches were used to measure lifetime stressors: (1) treating stressors as separate events, (2) aggregating stressful exposures by a composite score and (3) delineating different profiles of stressful experiences. To test and compare the strengths of associations between three different approaches of lifetime stressors and subsequent depression, we conducted separate analyses for all three approaches. First, each specific stressor (including childhood maltreatment, parent–child bonding and stressful life events) was considered individually. Second, a composite score of cumulative stress index was created by combining three stress domain measures. Childhood maltreatment, parent–child bonding and stressful life events were standardised to a z-score. A continuous cumulative stress score was then calculated by adding the standardised scores of these three domains. Higher scores of the cumulative stress index indicate more cumulative stressors experienced. Third, LPA was used to create a more comprehensive measurement of the lifetime stressors by combining individual stressors into mutually exclusive latent profiles. LPA is a robust statistical technique, commonly employed to identify subtypes of homogeneous latent classes or subgroups based on data from continuous indicator variables (Garrett and Zeger, 2000). LPA is analogous to latent class analysis (LCA) but can be used for continuous and ordinal predictors with several values. Additionally, LPA is a superior mixture-model technique compared to the traditional methods of cluster analysis (DiStefano and Kamphaus, 2006). Maximum likelihood estimation procedure was used with 95% CI, calculated via 1000 non-

parametric bootstrap. The analysis started with the most parsimonious 1-profile model, additional profiles were added. A different number of profiles were tested subsequently to identify the optimal profile solution. The optimal number of profiles was determined by Bayesian information criterion (BIC), Akaike information criterion (AIC) and the sample size adjusted BIC (ssaBIC) (Schwarz, 1978; Akaike, 1987; Sclove, 1987). Lower values indicate a better model fit. The entropy criterion was also examined, which indicates how accurate participants are classified into respective profiles, with higher values indicating a better fit (Aldridge and Roesch, 2008). The bootstrap likelihood-ratio (BLR) test was performed to compare a K class model with a K-1 class model, a significant BLR test indicates that the model with K class is optimal (Arminger *et al.*, 1999). Hence, the best class solution should have lower BIC, AIC, ssaBIC values, but a higher entropy value and a significant BLR *p*-value. In addition, the complete case analysis was conducted as a sensitivity analysis to assess to what extent the missing values would influence the result findings. We conducted the LPA analysis for those participants who completed information on stress measurements.

#### Associations between psychosocial stressors and depression

Firstly, to test hypotheses assessing basic relationships between studied variables, we conducted Pearson correlation analyses between predictor and outcome variables. Then, multivariate logistic regression was conducted to determine whether there were significant associations between the three methods of assessing lifetime stressors and subsequent depression. Two sets of models were fitted for each stress approach: (a) a crude or

**Table 1.** Description of the study sample

Characteristics	All participants	Male participants	Female participants
<i>Sociodemographic characteristic</i>			
Age, <i>M</i> (s.d.)	50.5 (14.0)	51.0 (14.2)	50.8 (13.8)
Age, <i>n</i> (%)			
18–30 years	135 (10.0%)	60 (12.1%)	75 (8.8%)
30–45 years	364 (26.9%)	121 (24.3%)	243 (28.5%)
45–60 years	470 (34.8%)	182 (36.3%)	288 (33.7%)
60 years and above	382 (28.3%)	134 (27.0%)	248 (29.0%)
Marital status, <i>n</i> (%)			
Single	597 (44.2%)	220 (44.3%)	377 (44.1%)
Married/Common-law	498 (36.9%)	212 (42.7%)	286 (33.5%)
Separated/Divorced/Widowed	256 (18.9%)	65 (13.1%)	191 (22.4%)
Ethnicity, <i>n</i> (%)			
White	1179 (87.3%)	432 (86.9%)	747 (87.5%)
Non-white	172 (12.7%)	65 (13.1%)	107 (12.5%)
Highest level of education, <i>n</i> (%)			
Less than secondary education	92 (6.8%)	32 (6.4%)	60 (7.0%)
Secondary education	375 (27.8%)	147 (29.6%)	228 (26.7%)
Post-secondary education	884 (65.4%)	318 (64.0%)	566 (66.3%)
Income, <i>M</i> (s.d.)	62 523 (60 852)	63 490 (60 487)	61 956 (61 095)
<i>Health characteristics</i>			
Type of drinker, <i>n</i> (%)			
Regular	885 (65.5%)	357 (71.8%)	528 (61.8%)
Occasional	249 (18.4%)	56 (11.3%)	193 (22.6%)
Former	157 (11.6%)	65 (13.1%)	92 (10.8%)
Abstainer	60 (4.4%)	19 (3.8%)	41 (4.8%)
Self-perceived mental health, <i>n</i> (%)			
Excellent	217 (16.1%)	105 (21.1%)	112 (13.1%)
Very good	495 (36.7%)	187 (37.6%)	308 (36.1%)
Good	424 (31.4%)	125 (25.2%)	299 (35.0%)
Fair	187 (13.9%)	66 (13.3%)	121 (14.2%)
Poor	28 (2.1%)	14 (2.8%)	14 (1.6%)
Family history of mental disorders, <i>n</i> (%)			
Yes	562 (41.6%)	234 (47.1%)	328 (38.4%)
No	789 (58.4%)	263 (52.9%)	526 (61.6%)

unadjusted model and (b) adjusted for genetic factors ( $PRS_{DEP}$ ), sociodemographic covariates (age, sex, marital status, ethnicity, education and income) and health-related characteristics (type of drinker, self-perceived mental health and family history of mental disorders). These variables were controlled to exclude their potential confounding effects in the associations between lifetime stressors and MDD.

Overall, the missing rate for each variable was less than 15%. We conducted multiple imputations by chained equations using the fully conditional specification method under the

missing-at-random assumption (Royston, 2009). Ten imputed datasets were generated from multivariate linear and logistic regression models using age and sex as potential predictors. Then one single pooled parameter estimate for each analysis was obtained based on Rubin's (1987) rule which took into consideration the variance within and between imputations. Statistical significance for all analyses was set at  $p < 0.05$  (by two-tailed test). In addition, we used maximisation likelihood estimation in the LPA to deal with the missing values. Descriptive statistics, Cronbach's alphas, Pearson's correlation coefficients

**Table 2.** Correlations among individual psychosocial stressor, cumulative stressor, patterns of stressors, polygenetic risk factors and lifetime depression

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	13	14	15	16	17	18	
1-Emotional abuse																									
2-Physical abuse	<b>0.64</b>																								
3-Sexual abuse	<b>0.41</b>	<b>0.44</b>																							
4-Emotional neglect	<b>0.66</b>	<b>0.49</b>	<b>0.34</b>																						
5-Physical neglect	<b>0.51</b>	<b>0.48</b>	<b>0.38</b>	<b>0.61</b>																					
6-Less maternal care	<b>0.59</b>	<b>0.40</b>	<b>0.32</b>	<b>0.66</b>	<b>0.48</b>																				
7-Maternal overprotection	<b>0.41</b>	<b>0.31</b>	<b>0.17</b>	<b>0.36</b>	<b>0.29</b>	<b>0.55</b>																			
8-Less paternal care	<b>0.52</b>	<b>0.38</b>	<b>0.26</b>	<b>0.59</b>	<b>0.37</b>	<b>0.43</b>	0.24																		
9-Paternal overprotection	<b>0.36</b>	<b>0.31</b>	<b>0.21</b>	<b>0.35</b>	<b>0.21</b>	<b>0.33</b>	<b>0.52</b>	<b>0.47</b>																	
10-Work and financial issue	<b>0.16</b>	<b>0.15</b>	<b>0.11</b>	<b>0.15</b>	<b>0.12</b>	<b>0.13</b>	<b>0.15</b>	<b>0.10</b>	<b>0.14</b>																
11-Romantic relationship	<b>0.11</b>	0.05	<b>0.07</b>	<b>0.09</b>	<b>0.09</b>	<b>0.11</b>	<b>0.09</b>	<b>0.10</b>	<b>0.09</b>	<b>0.14</b>															
12-Family/friend relationship	<b>0.13</b>	<b>0.12</b>	<b>0.08</b>	<b>0.07</b>	<b>0.11</b>	<b>0.08</b>	<b>0.12</b>	0.05	<b>0.10</b>	<b>0.21</b>	<b>0.19</b>														
13-Housing	<b>0.14</b>	<b>0.06</b>	<b>0.08</b>	<b>0.12</b>	<b>0.08</b>	<b>0.11</b>	<b>0.10</b>	<b>0.10</b>	<b>0.09</b>	<b>0.20</b>	<b>0.15</b>	<b>0.13</b>													
14-Experience of aggression	<b>0.08</b>	<b>0.05</b>	<b>0.06</b>	<b>0.06</b>	<b>0.08</b>	<b>0.07</b>	<b>0.07</b>	0.03	<b>0.06</b>	<b>0.14</b>	<b>1.18</b>	<b>0.15</b>	0.09												
15-Cumulative stress	<b>0.73</b>	<b>0.59</b>	<b>0.48</b>	<b>0.71</b>	<b>0.60</b>	<b>0.68</b>	<b>0.56</b>	<b>0.62</b>	<b>0.56</b>	<b>0.45</b>	<b>0.30</b>	<b>0.43</b>	<b>0.32</b>	<b>0.23</b>											
16-LPA	<b>0.70</b>	<b>0.58</b>	<b>0.41</b>	<b>0.65</b>	<b>0.55</b>	<b>0.58</b>	<b>0.38</b>	<b>0.49</b>	<b>0.37</b>	<b>0.22</b>	<b>0.13</b>	<b>0.16</b>	<b>0.16</b>	<b>0.19</b>	<b>0.69</b>										
17-PRS <sub>DEP</sub>	<b>0.08</b>	<b>0.07</b>	<b>0.10</b>	0.04	<b>0.08</b>	0.04	0.03	0.05	0.04	0.02	-0.01	0.04	0.04	0.03	<b>0.08</b>	<b>0.08</b>									
18-Depression	<b>0.17</b>	<b>0.12</b>	<b>0.11</b>	<b>0.15</b>	<b>0.12</b>	<b>0.16</b>	<b>0.13</b>	<b>0.11</b>	<b>0.11</b>	<b>0.13</b>	<b>0.13</b>	<b>0.15</b>	<b>0.06</b>	<b>0.09</b>	<b>0.25</b>	<b>0.16</b>	0.01	-							

LPA, latent profile analysis; PRS<sub>DEP</sub>, polygenic risk score for depression.  
 Bold font indicates statistical significance,  $p < 0.05$  (2-tailed).

**Table 3.** LPA fit indices for a one-class, two-class, three-class and four-class solution for the childhood maltreatment, child–parent bonding and stressful life events dimensions

Number of profiles	1	2	3	4
AIC	96 580	92 974	91 645	90 535
BIC	96 725	93 198	91 947	90 915
ssaBIC	96 636	93 061	91 763	90 683
Entropy	–	0.934	0.955	0.903
Log-likelihood	–	– 48 262	– 46 444	– 45 765
Difference in log-likelihood	–	0.001*	<b>0.000*</b>	0.000*

AIC, Akaike's information criteria; BIC, Bayesian information criteria; ssaBIC, the sample size adjusted Bayesian information criteria.

\*indicates statistical significance,  $p < 0.05$  (2-tailed).

between all variables, and regression analyses were conducted in Stata, version 15, and the LPA was conducted using Mplus, version 8.

## Results

### A summary of the study cohort

Table 1 shows a detailed description of the study cohort. The present study included a total of 1351 subjects who completed five data collections. The study sample included 36.8% males, 44.2% single, 87.3% White and 65.4% participants having a post-secondary education. The mean age of the sample was 50.5 years (s.d. 14.0). The mean annual family income was \$ 62 523, and male participants earned more on average than female participants. About two-thirds of the study sample reported being a regular drinker with more males than females reporting regular drinking (71.8% *v.* 61.8%). Approximately one-third (36.7%) reported their self-perceived mental health as good. Male participants were slightly more likely to report having good self-perceived mental health than female participants (37.6% *v.* 36.1%). In addition, 47.1% of males and 38.4% of females reported a family history of mental disorders.

We conducted correlation analyses for different stress exposures. Table 2 shows that strong zero-order correlations were observed within different subtypes of childhood maltreatment and correlations were more heterogeneous in magnitude between the other two assessed stressors (parental bonding and stressful events). All different approaches of stress assessments (including specific stressors, cumulative stressors and different patterns of stressors) were associated with the increased risk of subsequent depression.

### Latent profile analysis

Table 3 presents the model fit indices for all the latent profile models examined. AIC, BIC and ssaBIC decreased as the number of profiles increased. Because the *p*-value of the log-likelihood test showed no statistical significance between the 3-profile model and the 4-profile model, the model specification did not improve from the 3-profile model to the 4-profile model. The 3-profile model had a higher entropy value than the 4-profile model and was easier to illustrate, therefore we decided to take the 3-profile model as the best fitting parsimonious model.

Figure 2 provides visual illustrations of the mean scores for all of the selected lifetime stressors among the three identified stressor profiles. As shown in Fig. 2, profile 1 was the most prevalent profile ( $N = 1015$ , 75.1%). Participants in this profile reported a low level of stress across their lifespan and were labelled as the 'low stress' group. Individuals in profile 2 ( $N = 92$ , 6.8%) and profile 3 ( $N = 244$ , 18.1%) included those who had scores that fell within the moderate and high levels of childhood maltreatment, adverse child–parent bonding and stressful life events. Profiles 2 & 3 reported above-average stress levels thus were labelled as moderate- and high-stress groups, respectively.

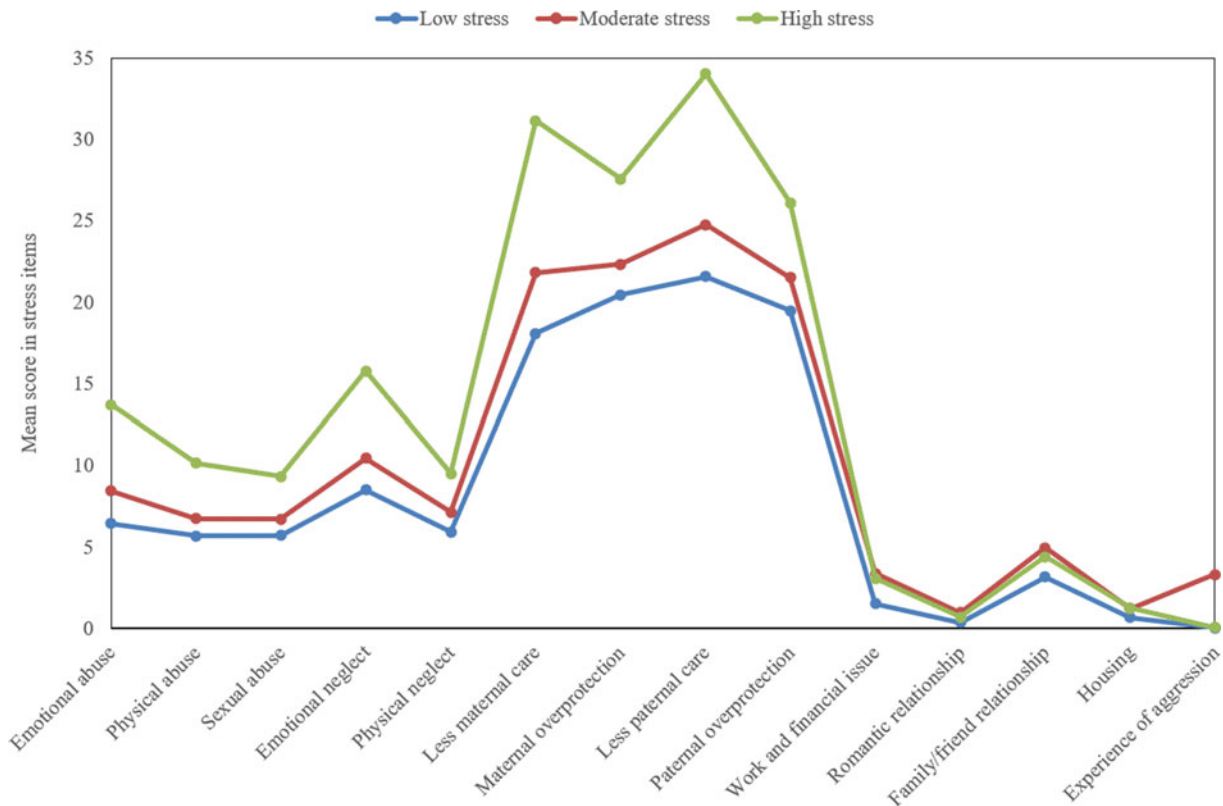
### Exploring specific and cumulative stressors in associations with depression

Table 4 shows unadjusted and adjusted associations between stressors and the risk of depression. For specific stressors, we found that people with emotional abuse/neglect, the experience of lack of parental/maternal care and having the stress related to family/friend relationships, were more likely to report depression. After adjusting for genetic factors (PRS<sub>DEP</sub>), sociodemographic covariates (age, sex, marital status, ethnicity, education and income) and health-related characteristics (type of drinker, self-perceived mental health and family history of mental disorders), for the domain of childhood maltreatment, emotional abuse (OR = 1.25, 95% CI: 1.09–1.43), physical abuse (OR = 1.20, 95% CI: 1.05–1.38), sexual abuse (OR = 1.16, 95% CI: 1.02–1.33), emotional neglect (OR = 1.22, 95% CI: 1.06–1.41) and physical neglect (OR = 1.19, 95% CI: 1.04–1.37) were significantly associated with depression. Concerning child–parent bonding, parental over-control (OR<sub>Maternal</sub> = 1.21, 95% CI: 1.05–1.39; OR<sub>Paternal</sub> = 1.20, 95% CI: 1.04–1.39) and lack of parental care (OR<sub>Maternal</sub> = 1.24, 95% CI: 1.09–1.44; OR<sub>Paternal</sub> = 1.26, 95% CI: 1.10–1.45) were all associated with depression. Similarly, except for housing-related stress, other four constructs including stressful events related to work and financial issues (OR = 1.18, 95% CI: 1.03–1.36), romantic relationship (OR = 1.15, 95% CI: 1.01–1.32), family/friend relationship (OR = 1.30, 95% CI: 1.13–1.50) and experience of aggression (OR = 1.15, 95% CI: 1.00–1.31) were associated with depression.

For cumulative stress measurement, when controlling for genetic and sociodemographic as well as health-related characteristics, the cumulative lifetime stress index was a significant risk factor for subsequent depression (OR = 1.20, 95% CI: 1.12–1.28). For the stress patterns, while there was evidence of confounding towards the null, the statistical significance of estimates did not change between unadjusted and adjusted models. Compared to those in the low level of stress group, those in the moderate level of stress group were associated with an increased risk of depression (OR = 1.65, 95% CI: 1.17–2.32), and individuals with a high level of stress exposures were 1.80 times (95% CI: 1.08–3.00) more likely to have depression.

### Sensitivity analysis

For the complete case analysis, a 3-profile solution outperformed other models, and the final three-profile solution included 77.0% of the sample with a low level of stress ( $N = 823$ ), 6.6% of the sample with a moderate level of stress ( $N = 71$ ) and 16.4% of the sample with a high level of stress ( $N = 175$ ) (see online Supplementary Table S1). The results of complete case analysis reinforce the findings in the whole sample with the 3-profile model, which shows a



**Fig. 2.** The latent profiles based on childhood maltreatment, child–parent bonding and stressful events.

dose–response relationship between lifetime stressors and the increased risk of subsequent depression.

## Discussion

This study is the first study to use different approaches to articulate how lifetime stressors are associated with subsequent depression using a longitudinal community-based cohort. Our present study used both person-centred and variable-centred approaches to verify the association between lifetime stressors and subsequent depression. Lifetime stressors had a cumulative effect on the risk of subsequent depression after adjusting for genetic predispositions and other sociodemographic characteristics. Those with a high level of lifetime stressors were more likely to develop depression compared to those with a low level of lifetime stressors. The findings of the study provide additional evidence to support the diathesis-stress model in terms of the impact of lifetime stressful experiences in depression. The current study adds to the existing literature by examining both the individual effects and their collective impact. Our findings reinforce the complexity of lifetime stressful experiences in the development of depression and direct the research on individuals' heterogeneity of stress linking with different risks of depression.

There is ample evidence to explain how stress interferes with normal functioning and increases the risk of developing physical and mental health problems. Stress itself is not only caused by a specific experience happening to the individual but is also caused by a lack of resources for effectively dealing with the initial stressor that can have a cascade effect resulting in more stress (Lazarus and Folkman, 1984). Effective stress responses are integral to emotional well-being. Stress reactivity is coordinated by an

interplay of the neuroendocrine system and the sympathetic nervous system. The hypothalamus–pituitary–adrenal (HPA) axis plays a key role in orchestrating bodily responses to stress, and axis activity can be modified by a wide range of experiential events. Exposures like early life adversity and adverse stressful events during life serve as general vulnerability factors that accelerate future HPA axis reactivity in ways that make individuals more sensitive to stress challenges, and therefore feed forward into the exacerbation of ongoing, or greater susceptibility towards, future stress-related disease states (Dannowski *et al.*, 2012; Ludwig *et al.*, 2018). Epidemiological and clinical studies have provided compelling evidence for establishing the association between various early-life stressors and elevated risk of depressive disorders (Heim and Binder, 2012; O'Mahen *et al.*, 2015; Gallo *et al.*, 2017). Adverse parental bonding which captures dimensions of care and overprotection between parent and child bonding predicts the risk of depression in adulthood (Sato *et al.*, 2000). Additionally, based on the stress sensitisation hypothesis, experiences of early adversities make people more susceptible to later-occurring stressors such as stressful life events (Hammen *et al.*, 2000; Estrada-Martinez *et al.*, 2012; Hassanzadeh *et al.*, 2017). Stressful life events include discrete quantifiable circumstances, such as work conflicts, financial issues and intense interpersonal relationships, which can impact psychological well-being thus increase the risk of depression (Hassanzadeh *et al.*, 2017).

In the present study, we found that cumulative effects of lifetime psychosocial stressors are associated with the elevated risk of depression after controlling for genetic predispositions of depression and other psychosocial covariates. Our results are consistent with the existing literature on the relationship between cumulative psychosocial stressors and depression. An ongoing



**Table 4.** Associations between psychosocial stress measures and depression – individual psychosocial stress, cumulative psychosocial stress and LPA-derived psychosocial stress clusters

	Crude model		Adjusted model <sup>a</sup>	
	OR	95% CI	OR	95% CI
<i>Individual psychosocial stress</i>				
Emotional abuse	1.41	1.26, 1.58	1.25	1.09, 1.43
Physical abuse	1.28	1.14, 1.44	1.20	1.05, 1.38
Sexual abuse	1.28	1.14, 1.43	1.16	1.02, 1.33
Emotional neglect	1.40	1.24, 1.58	1.22	1.06, 1.41
Physical neglect	1.28	1.15, 1.44	1.19	1.04, 1.37
Less maternal care	1.44	1.28, 1.62	1.24	1.09, 1.44
Maternal overprotection	1.36	1.20, 1.53	1.21	1.05, 1.39
Less paternal care	1.38	1.22, 1.56	1.26	1.10, 1.45
Paternal overprotection	1.29	1.14, 1.46	1.20	1.04, 1.39
Work and financial issue	1.32	1.18, 1.48	1.18	1.03, 1.36
Romantic relationship	1.30	1.16, 1.46	1.15	1.01, 1.32
Family/friend relationship	1.40	1.24, 1.58	1.30	1.13, 1.50
Housing	1.13	1.00, 1.27	1.10	0.96, 1.27
Experience of aggression	1.21	1.08, 1.32	1.15	1.00, 1.31
<i>Cumulative psychosocial stress</i>				
Cumulative stress index	1.27	1.20, 1.34	1.20	1.12, 1.28
<i>LPA-derived psychosocial stress clusters</i>				
Low-stress level	–	–	–	–
Moderate stress	2.19	1.39, 3.46	1.65	1.17, 2.32
High stress level	2.39	1.76, 3.24	1.80	1.08, 3.00

LPA, latent profile analysis; OR, odds ratio; 95% CI, 95% confidence interval.

Adjusted model <sup>a</sup> adjusted for PRS<sub>DEP</sub>, sociodemographic covariates (age, sex, marital status, ethnicity, education, income) and health-related characteristics (type of drinker, self-perceived mental health and family history of mental disorders).

longitudinal study explored the cumulative effects of different stressors across early and middle childhood on internalising behaviours and suggested that the combined effect of multiple stressors could explain variations in internalising behaviours (Appleyard *et al.*, 2005). Likewise, the Rochester Longitudinal Study also found that the experience of multiple stressors potentiated the development of psychopathology (Sameroff, 2000). This research adds to the literature in terms of the dose–response relationship between various levels of stress and the risk of subsequent depression – those having low levels of stress across the lifespan had the lowest risk of depression. While those with moderate to high levels of childhood maltreatment, adverse child–parent bonding and stressful life events reported a higher risk of depression. Our results further support the stress sensitisation theory, which conceptualised stressors become increasingly capable of triggering depressive symptoms (Hammen *et al.*, 2000). Similarly, prior research also showed that stress sensitisation of depressive disorders was found at high levels of adult stressful events (Kendler *et al.*, 2004; Espejo *et al.*, 2007; McLaughlin *et al.*, 2010).

We also examined how specific stressors across lifetime influenced the risk of depression after controlling for genetic

predispositions and other covariates. We found that different early-life stressors including childhood maltreatment and poor parental bonding were associated with an increased risk of depression after controlling for PRS<sub>DEP</sub>. Additionally, except for the major theme on housing, other subtypes of stressful events predicted a higher risk of depression. Although a wide range of stressors has demonstrated stress sensitisation with the risk of depression, stress-related to family, for instance, less parental care and childhood emotional maltreatment had a stronger independent impact on depression. Our study findings are consistent with a UK longitudinal cohort study which found that individuals with early adversity experience were more likely to report psychotic symptoms when controlling for genetic vulnerability to psychosis (Arseneault *et al.*, 2011). Similarly, Musliner *et al.* (2015) found that stressful life events were significantly and independently associated with depressive symptoms when disentangling the effects of polygenic risk.

The learned helplessness paradigms and chronic mild stress are two common depressive animal models used to delineate the pathogenesis of depression considering both genetic and psychosocial environmental factors (Yin *et al.*, 2016). The learned helplessness paradigms, initially developed by Seligman and Overmier (Overmier and Seligman, 1967), derived from a cognitive view of depression in which the behavioural condition is induced through the application of uncontrollable and unpredictable aversive stimuli leading to feelings of anxiety and helplessness. This model also has a genetic component since stress-evoked or genetically induced reductions of brain-derived neurotrophic factor (BDNF) increase learned helplessness (Vollmayr and Gass, 2013). The chronic mild stress model was first proposed by Katz *et al.* (1981) and developed further by Willner (1997) focusing on relatively minor and unanticipated irritations of everyday life has been shown to increase depression-like behaviours and reduce hippocampal volume (Andrus *et al.*, 2012). It is important to note that it induced incoordination in prefrontal cortical GABAergic and glutamatergic neurons, which is dependent on their genetic background and maybe the pathological basis for depressive mood (Xu *et al.*, 2016). In addition to animal stress models, recent human stress studies hypothesise that activations of the sympathetic division of the autonomic nervous system and pathological alterations in the stress-responsive hypothalamic-pituitary-adrenal (HPA) axis relate to the aetiology of depression through the activation of neural and neuroendocrine cascades of molecular events responding to stress (Tafet and Nemeroff, 2016). If such stress response continues in a prolonged and excessive manner it can turn maladaptive and contribute to the development of disease, such as depression, particularly in individuals with heightened genetic vulnerability (Tsigos *et al.*, 2016). The presence of these genetic variations appears to be involved in the development of depression in response to stressful events, including adverse experiences during childhood and environmental stressors during adulthood (Tafet and Nemeroff, 2016).

### Strengths and limitations

The present study has originality in utilising and quantifying different measurements of psychosocial stressors across the lifespan while adjusting for the polygenic risk factors and a wide range of psychosocial covariates. This is the first longitudinal study testing three different operationalisations of lifetime psychosocial

stressors-specific stressors, cumulative stress index and stressors clusters—and their associations with depression.

Nevertheless, several limitations are to be noted. First, stressors were self-reported. Measurements of stressors are subject to information bias. Second, the Cronbach's alpha value of stressful life events was 0.58. This suggests that the items of stressful life events had relatively low internal consistency. Future research with the improved internal consistency of this assessment is needed. Third, stress has multiple aspects, including frequency, duration and severity. These aspects of stress collectively influence the aetiological trajectory of depression (Musliner et al., 2015). However, we did not have information on frequency, duration, or severity. Lastly, this present study focused on the role of lifetime stressors in depression while taking into account genetic predispositions. The dynamic interplay between stressors and genetic predispositions was not analysed in this study.

## Conclusions

Overall, the present study observed significant individual effects of specific stressors as well as the cumulative effects of psychosocial stressors across the lifespan on the subsequent depression. These effects persisted even after controlling genetic predispositions and sociodemographic characteristics. Exposures to these stressors predicted an elevated risk of subsequent depression. The current study adds to the stress theories about different operationalisations of lifetime stressors predicting different risks of subsequent depression. This is true for both specific and cumulative lifetime stressors. Future research articulating the roles of multiple aspects of stressors and depression is warranted. Future research could also further investigate the underlying neurobiological mechanisms linking stressors and depression. From a prevention perspective, our study underscores that early identification of stressors (including specific and cumulative stressors) could better direct effective prevention and intervention strategies focusing on minimising the negative consequences of stressors, reducing the onset of stressors and providing necessary support for those with various kinds of lifetime stressors to better cope with the stressful experiences.

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**Conflicts of interest.** None declared.

**Ethical standards.** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

**Availability of data and materials.** The ZEPSOM data is not currently freely available to researchers in general due to ethical and data management

requirements. Interested researchers can directly contact the Research Team at: [Zepsom.Coordo@douglas.mcgill.ca](mailto:Zepsom.Coordo@douglas.mcgill.ca)

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