How psychosocial stress profile influences the subsequent occurrence of neuropsychiatric comorbidities: A longitudinal population-based cohort study

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Running title: Psychosocial stressors in subsequent neuropsychiatric comorbidities

Highlight:

1. This study was first examined the cumulative effect of multiple stressors in subsequent neuropsychiatric comorbidities.
2. This study used both variable-centered and person-centered approaches to analyze multiple stressors.
3. Higher cumulative stress increased the risk of neuropsychiatric comorbidities.
4. Social support could modify the negative impact of multiple stressors on neuropsychiatric comorbidities.

Abstract

Background

The role of psychosocial stressors in psychiatric disorders and executive dysfunction has been reported, separately. The literature has suggested the involvement of social support and coping strategies in these relationships. However, there is a lack of research conducted to examine the relationships among multiple stressors and neuropsychiatric comorbidities while considering the presence of social support and coping strategies. This study aims to articulate the roles of multiple psychosocial stressors, social support, and coping strategies in the subsequent occurrence of neuropsychiatric comorbidities.

Methods

Data analyzed were from the 6th data collection of a large-scale, longitudinal population-based cohort from Southwest Montreal in Canada. The cumulative effects of multiple stressors were separately examined by a composite score and latent profile analysis (LPA). Multinomial logistic regression models were used to test the relationship between cumulative stressors and neuropsychiatric comorbidities.

Results

A total of 210 participants were included in the analyses. The LPA identified a 2-class model for psychosocial stressors (low and high) and executive function (executive dysfunction and no executive dysfunction), respectively. There were 11.8% of participants with neuropsychiatric comorbidities. Both the composite stress score (RR=1.08, 95%CI=1.01-1.15) and latent stress groups (RR=3.65, 95%CI=1.15-11.57) were associated with neuropsychiatric comorbidities after adjusting for social support and coping strategies. The risk of developing neuropsychiatric comorbidities decreased when the level of social support was high (P<0.05).

Conclusions

Exposures to multiple stressors increased the risk of subsequent neuropsychiatric comorbidities, but the risk can be modified by a higher level of social support.

Keyword: Neuropsychiatric comorbidities; cumulative stress; social support; coping strategies

1. Introduction

Psychiatric disorders contribute significantly to the global burden of disease, including 7% of global disability-adjusted life years (DALYs) and 2.3% of global years lost to disability (YLDs) (Rehm and Shield, 2019). According to the most recent Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), 12.01% of men and 12.83% of women reported common psychiatric disorders (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Psychiatric disorders are often associated with a variety of adverse consequences, such as medical comorbidities (Zolezzi et al., 2017), premature death (Walker et al., 2015), poor well-being (Lu et al., 2018), functional impairment (Hammer-Helmich et al., 2018) and heavy economic burden (Trautmann et al., 2016).

The literature has shown that neurological disorders and psychiatric disorders often co-occur (Lyketsos et al., 2007). For instance, compared to those with cognitive impairment only or depression alone, those suffering from both cognitive impairment and depression reported substantial functional limitations, increased health services utilization and medical costs (Makizako et al., 2016; Xiang and An, 2015). Executive dysfunction has been frequently reported to be associated with several psychiatric disorders (Kamal et al., 2016; Knight and Baune, 2018; Wu et al., 2021). For instance, stroke patients with depression–dysexecutive syndrome (DES) had significantly more brain infarcts affecting their frontal-subcortical circuit structures than patients without DES, or patients with depression but without executive dysfunction (Vataja et al., 2005). Acute ischemic stroke patients who suffered from both depression and executive dysfunction had significantly shorter median survival than patients with depression or executive dysfunction only (Melkas et al., 2010). Executive dysfunction was also reported to have shared polygenic risk factors with five psychiatric disorders, including attention deficit hyperactivity disorder, major depressive disorder, schizophrenia, bipolar disorder, and autism (Chang et al., 2020). An in-depth understanding of attributes associated with the comorbidity between executive dysfunction and psychiatric disorders may assist the etiological explorations of the underlying mechanisms.

The stress transactional theory argued that stress was a product of a transaction between an individual (including multiple systems, such as cognitive, physiological, affective, psychological, and neurological) and a complex environment (Lazarus, 1966; Lazarus, 1984). Stressful life events, especially early life adversities, have been taken as key risk factors for psychiatric disorders, cognitive impairment/executive dysfunction, and their comorbidities (Evans-Polce et al., 2020). For instance, a population-based cohort study found that stressful life events were associated with poorer physical health and mental health (Pries et al., 2020). Childhood maltreatment was negatively associated with working memory strategy, which indicated impaired executive functioning among those with a history of maltreatment(Augusti and Melinder, 2013). Furthermore, a dose-response relationship between the number of adverse childhood experiences and the risk of having psychiatric disorders had been reported (Bright et al., 2016).

It is not uncommon to experience several stressors across the life span, but few studies have been conducted to examine the cumulating effect of multiple psychosocial stressors in neuropsychiatric comorbidities. Identification of cumulative effects of stressors could help to

evaluate the role of co-occurring risk factors in disease outcomes (Kuh et al., 2003). Individuals with multiple psychosocial stressors reported worse health outcomes compared to those with a single stressor (Raviv et al., 2010). There are different approaches to quantifying the cumulating effects of multiple stressors: 1) adding up the number of stressors; 2) using a composite score to factor in both the number of exposures and the contribution of individual stressors in the overall measure (Slopen and Cuevas, 2021); 3) applying a person-centered approach, e.g., latent profile analysis (LPA), to discover naturally-occurring clusters of individuals with similar patterns of stress exposures and explore the differences across classes (Merians et al., 2019). Studies have shown that person-centered approaches could provide insights into how stressors might be organized and interrelated at an individual level and may help to better conceptualize and measure multiple stressors (Russell et al., 2021).

Social support and coping strategies are the most frequently studied psychological and social factors that may buffer the negative consequences of stressful experiences (Babore et al., 2020; Labrague and De los Santos, 2020). Social support refers to the provision or the exchange of emotional, instrumental, or informational resources by non-professionals, in the context of a response to the perception that others need it (Cohen et al., 2000). Coping strategies refer to an action, a series of actions, or a thought process used in meeting a stressful or unpleasant situation or in modifying one's reaction to such a situation. The literature on social support and positive coping strategies has provided consistent evidence to support the stress-buffering hypothesis (Dardas and Ahmad, 2015; McGuire et al., 2018; Talwar, 2016). Their buffering effects can influence stress-induced mental health outcomes (Ciarleglio et al., 2018; Savitsky et al., 2020), comorbidity of depression and anxiety (Evan, 2021), and trajectories of physical and mental health comorbidities (Pugh et al., 2018). However, there is a lack of research to examine the relationships among stressors, social support, coping strategies, and neuropsychiatric comorbidities. Untangling the complex relationships among stressors, social support, coping strategies, and the comorbidity between executive dysfunction and psychiatric disorders may corroborate evidence of the shared etiological mechanisms.

The present study aims to (1) comprehensively examine the cumulative effects of multiple psychosocial stressors in the subsequent occurrence of neuropsychiatric comorbidities of executive dysfunction and psychiatric disorders using a longitudinal population-based cohort and (2) articulate the roles of social support and coping strategies in these neuropsychiatric comorbidities.

2. Methods

2.1. Data source

Data analyzed were from the Zone d'Épidémiologie Psychiatrique du Sud-Ouest de Montréal (ZEPSOM) cohort. The ZEPSOM cohort is a large-scale, longitudinal, population-based cohort from Southwest Montreal in Canada (Caron et al., 2012). In 2007, a total of 2,433 participants (aged 15~65 years) were randomly selected to assess the prevalence and incidence of psychological distress, psychiatric disorders, and quality of life and to understand the impact of the social, economic, and physical aspects on mental health. This initial cohort was followed through five complete interview cycles (2007 to 2018). A second cohort compensating for attrition of the first

cohort (N= 1,029) was followed through 3 complete cycles (2011-2018). In 2020, ZEPSOM participants and their biological offspring (aged ≥15 years) were invited to participate in the 6th data collection. The detailed data collection process can be found in a previous article (Li et al., 2021). The present study analyzed data collected in the 6th wave of ZEPSOM. The ZEPSOM study was approved by the Institutional Review Board of the Douglas Mental Health University Institute in accordance with the Helsinki Declaration (#IUSMD-18/17).

Among 366 eligible ZEPSOM participants who were invited to participate in the 6th data collection, a total of 286 participants completed the data collection (the response rate was 78.1%). The present study included a total of 210 participants with data on psychosocial stress, diagnosis of psychiatric disorders, and executive function.

2.2. Measurements

2.2.1. Psychosocial stressors

Childhood maltreatment

Childhood maltreatment was measured at Wave 5 by the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1994). The 28-item CTQ has been widely used to assess five different subgroups of childhood maltreatment (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect) (Liebschutz et al., 2018). Good psychometric properties have been demonstrated previously (Fink et al., 1995; Liebschutz et al., 2018). Participants were asked to rate each item on a 5-point Likert scale (1-never true, 5-very often true). The total score ranged from 25 to 125, with higher scores indicating more severe maltreatment in childhood. The Cronbach's alpha value of CTQ was 0.818 in this study.

Parental bonding

Parental bonding was assessed at Wave 5 by the Parental Bonding Instrument (PBI) which is a 50-item questionnaire measuring parental care and overprotection before 16 years of age. The PBI has been evaluated extensively for its psychometric properties (Parker, 1989, 1990). Each item is measured on a 4-point Likert Scale (1-very like, 4-very unlike). The total score of parental care ranged from 0 to 36, with higher scores indicating more parental neglect and rejection. The total score of parental overprotection ranged from 0 to 39, with higher scores indicating more severe overprotection. The Cronbach's alpha value was 0.932 for parental care and 0.888 for overprotection in this study.

Stressful life events

Life's Events Questionnaire (LEQ) at Wave 3 was used to measure stressful life events during the last 12 months (Laurin, 1998). The instrument of life events includes 21 items that can be further classified into five major themes: income, love, links with family and friends, housing, and experiences of aggression. Each item was measured on a 5-point Likert scale (0 = no event, 1 = experienced event but feel not stressful, 2 = feel a little stressful, 3 = feel quite stressful, 4 = feel very stressful). Two items (*deceased loved* and *seriously ill close*) were removed to increase the reliability of this study. The total score of stressful life events ranges from 0 to 76, with higher scores indicating higher levels of stress. The Cronbach's alpha value was 0.552 in this study.

2.2.2. Executive function

Executive function at Wave 6 was measured by the One Touch Stockings of Cambridge (OTS) and the Spatial Working Memory (SWM) from the Cambridge Neuropsychological Test Automated Battery (CANTAB®). CANTAB was developed by the University of Cambridge and has been widely used in many countries (Bento-Torres et al., 2017; Chamberlain et al., 2012; Lenehan et al., 2016; Robbins et al., 1998). OTS and SWM have demonstrated satisfactory psychometric properties to measure executive function (Heaton et al., 2014; Karlsen et al., 2020; Lowe and Rabbitt, 1998). Three key indicators were used in the present study: Problems Solved on First Choice (PSFC) from OTS, Between Errors 468 (BE468) from SWM, as well as Strategy (S) from SWM. The PSFC refers to the total number of assessed trials where the subject chose the correct answer on their first attempt and is calculated across all assessed trials. Lower scores indicate poorer performance. The BE468 is the number of times the subject incorrectly revisits a box in which a token has previously been found, which is calculated across all assessed four, six, and eight token trials. The S is the number of times a subject begins a new search pattern from the same box they started with previously. Subjects would be scored lower if they always begin a search from the same starting point, which indicates that the subject is employing a planned strategy for finding the tokens; whereas higher scores indicate that the subjects begin their searches from many different boxes. The S was calculated across assessed trials with 6 tokens or 8 tokens. The higher scores are indicative of the poorer performance of executive function.

2.2.3. Psychiatric disorders

Psychiatric disorders at Wave 4 were assessed by the Composite International Diagnostic Interview (CIDI), which is a structured diagnostic tool that generates psychiatric diagnoses according to the definitions and criteria of the International Classification of Diseases (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Kessler et al., 1998). In this study, psychiatric disorders included major depressive disorder (MDD), generalized anxiety disorder (GAD), and alcohol and drug use disorder (dependence and/or abuse).

2.2.4. Social Support

Social support at Wave 3 was measured by the Social Provision Scale (SPS) (Cutrona and Russell, 1987), including six subscales: reliable alliance, attachment, nurturance, social integration, reassurance of worth, and guidance (Weiss, 1974). This scale consists of 24 items in a 4-point Likert-type format (1-strongly disagree; 4-strongly agree). Higher scores indicate a greater degree of perceived support. SPS has demonstrated good psychometric properties and has been translated and validated in French and English (Caron, 1996). The Cronbach's alpha value of the SPS was 0.938 in this study.

2.2.5. Coping strategies

Coping strategies at Wave 3 were evaluated from 14 items drawn from three scales used by the CCHS 1.2, including the Coping Strategies Indicator (CSI), the Ways of Coping-Revised (WOC-R), and the Coping Orientation to Problems Experienced (COPE) (Amirkhan, 1994; Carver et al., 1989; Clark et al., 1995; Vitaliano et al., 1985). Each item is scored in a 4-point Likert-scale (1-often; 4-never). Good psychometric qualities of these three instruments have been reported previously (Clark et al., 1995). Based on previous factor analytic work (Baetz and Bowen, 2008; Graff et al., 2009), principal component analysis (PCA) was used to derive a two-factor solution

specifying positive and negative coping strategies. Positive coping strategies included the following items: *speaking to others*, *looking on the bright side*, and *doing something enjoyable*. Negative coping strategies included *avoiding the company of others*, *sleeping more than usual*, *blaming oneself*, *changing eating habits*, and *more alcohol consumption*. Owing to the low anti-image coefficients (less than 0.5) (Kaiser and Rice, 1974), *physical exercise*, *spiritual help*, and *magical thinking* were removed from PCA. In addition, three items (*trying to solve the problem*, *more smoking*, *using drugs or medication*) were excluded because of low factor loadings on both factors (less than 0.4) (Dixon, 1993).

The total score of coping strategies was calculated by adding the reversed-item scores of positive coping strategies and the scores of negative coping strategies together, with higher scores indicating better coping skills. The Cronbach's alpha value in this study for coping strategies after PCA was 0.517. Details of PCA results are available upon request.

2.2.6. Sociodemographic characteristics

Sociodemographic characteristics at Wave 3 used in this study included age, sex, education (grade 10 or lower, grade 11 or higher), marital status (single, married/common-law, separated/divorced/widowed), and race (Caucasian, non-Caucasian).

2.3. Statistical analysis

2.3.1. Descriptive analyses

Descriptive analyses of the studied variables were used to understand the characteristics of the study sample. Mean ± standard deviation (SD) was used for continuous variables, whereas percentage and 95% CI for categorical variables. Differences in the outcomes were tested by analysis of variance (ANOVA) for continuous variables and Chi-squared tests (χ^2) for categorical variables.

2.3.2. Missing data

The missing data was tested by the Little's completely at random (MCAR) test and met the MCAR criterion for multiple imputations (χ^2=492.32, p=0.07). Multiple Imputations by Chained Equations (MICE) with 10 imputations were then used to handle the missing data (including emotional abuse, physical abuse, sexual abuse, family-related events, race, maternal care, maternal overprotection, paternal care, paternal overprotection, and coping strategies).

2.3.3. Cumulative psychosocial stressors

Because LPA and PCA cannot be run with imputed datasets (Olaya et al., 2017; Royston et al., 2009), so we conducted LPA and PCA based on non-imputed data. These two approaches were applied to assess psychosocial stressors: composite score and latent profile. First, a composite score of psychosocial stressors was created by aggregating the three standardized stress-related scales - CTQ, PBI, and LEQ. A greater composite score indicated a higher level of stress. Second, LPA was used to identify latent groups of stressors based on the standardized scores of the domains of psychosocial stressors. The goodness-of-fit was assessed by Akaike's information criterion (AIC) and Schwarz's Bayesian information criterion (BIC). Smaller values of AIC and BIC indicate better model fit (Akaike, 1987; Schwarz, 1978; Sclove, 1987). The final class model was selected

by considering values of AIC and/or BIC, at least 5% of the total sample size in each class as well as the interpretation of classes (Weller et al., 2020).

2.3.4. Neuropsychiatric comorbidities

For executive dysfunction, three indicators (PSFC in OTS, BE468, and S in SWM) were standardized to z-scores after adjusting for age, sex, and education status (Abbott et al., 2019). The standardized z-scores of BE468 and S were reversed to keep the same direction with PSFC. Lower scores indicated poorer performance. The LPA was then used to categorize the status of executive function (dysfunction vs. no dysfunction).

We considered those with both executive dysfunction and at least one of the studied psychiatric disorders (MDD, GAD, alcohol dependence/abuse, and drug dependence/abuse) as having neuropsychiatric comorbidities. Accordingly, the study cohort was grouped into four categories: healthy control (without psychiatric disorder or executive dysfunction), psychiatric disorders only, executive dysfunction only, and comorbidities of psychiatric disorder and executive dysfunction.

2.3.5. Roles of psychosocial stressors, social support, coping strategies in neuropsychiatric comorbidities

The relationship between psychosocial stressors and neuropsychiatric comorbidities was examined with multinomial logistic regression (MLR) analyses. We first ran a crude model to include only an indicator of stress. Adjusted models were then fitted to include covariates: age, sex, grade level, race, marital status, social support, and coping strategies. Risk ratio (RR) statistics with 95% CIs were used to assess the likelihood of outcomes.

All the analyses were conducted using Stata version 15.1 (StataCorp, College Station, Texas, USA).

3. Results

3.1. The study cohort and its characteristics

We compared the total sample (n=366) collected at Wave 6 of ZEPSOM and the study cohort (n=210) analyzed in this present study and found no significant difference in socio-demographic characteristics ($p>0.05$) (Details are available in Table S1). Table 1 summarizes the socio-demographic characteristics of the study cohort. Most of the subjects in this study cohort were females (67.6 %), averagely aged at 46.6 years (SD=10.1), married/common-law (71.4%), Caucasians (82.9%), and had 11 years or more of education (93.3%). A total of 59 (28.1%) participants had at least one psychiatric disorder. There were 99 (46.9%) subjects without any psychiatric disorders or executive dysfunction, followed by 34 (16.1%) subjects with at least one of the studied psychiatric disorders only, 52 (24.6%) subjects with executive dysfunction only, and 25 (11.8%) subjects with comorbidities of psychiatric disorders and executive dysfunction. The mean total scores for social support and coping strategies were 84.33 (SD= 9.13) and 18.74 (SD= 2.85), respectively. Both social support and coping strategies scores were higher in the healthy control and executive dysfunction groups, and lower in the psychiatric disorders and neuropsychiatric comorbidities groups.

3.2. Latent profiles of psychosocial stressors

We developed the latent profiles of psychosocial stressors and assessed model fit for 1-class through 4-class models (Table S2). The 2-class model was chosen based on the selection criteria. As illustrated in Figure 1, subjects in class 1 (N = 178, 84.76%) reported lower levels of stressors, including childhood maltreatment, parental bonding, and stressful life events. We labeled class 1 as "low stress". In contrast, individuals in class 2 (N = 32, 15.24%) had higher levels of stressors and were labeled as "high stress".

3.3. Latent profiles of executive function

For the latent profiles of executive function, we assessed model fit for 1-class through 4-class models (Table S2). The 2-class model had the smallest values of AIC and BIC and was consistent with the interpretation. As illustrated in Figure 2, the predicted mean of all indicators of executive function was lower than zero in class 1 (N = 77, 36.67%), thus it was labeled as "executive dysfunction". The predicted mean of all indicators was higher than zero in class 2 (N = 133, 63.33%), and it was considered as "no executive dysfunction".

3.4. Univariate analyses

We found that those with a higher level of social support had lower risks of developing neuropsychiatric comorbidities (p=0.001). Similarly, a higher level of coping strategies was associated with a lower risk of developing psychiatric disorders (p=0.016) and neuropsychiatric comorbidities (p=0.008). No statistical significances were identified in the relationships between sociodemographic characteristics (age, sex, race, marital status, and education level) and neuropsychiatric comorbidities (p>0.2).

3.5. Associations between cumulative stress and neuropsychiatric comorbidities

Table 2 summarizes the associations between cumulative stress and neuropsychiatric comorbidities. In the crude model, a larger cumulative stress score was associated with a higher risk of psychiatric disorders (RR=1.09, 95%CI=1.04-1.15) and neuropsychiatric comorbidities (RR=1.11, 95%CI=1.05-1.17). After adjusting for social support and coping strategies, the associations remained significant (RR=1.08, 95%CI=1.02-1.14 for psychiatric disorders; RR=1.08, 95%CI=1.01-1.15 for neuropsychiatric comorbidities). A higher level of social support was associated with a lower risk of developing neuropsychiatric comorbidities (RR=0.94, 95%CI=0.89-0.98). No statistical significance was identified between coping strategies and neuropsychiatric comorbidities (RR=0.87, 95%CI=0.73-1.05).

Consistently, we found those with "high stress" had a higher risk of developing psychiatric disorders (RR=2.88, 95%CI=1.07-7.72) and neuropsychiatric comorbidities (RR=5.33, 95%CI=1.93-14.74). After adjusting for social support and coping strategies, people exposed to "high stress" had a higher risk of developing neuropsychiatric comorbidities (RR=3.65, 95%CI=1.15-11.57, Figure 3). A higher level of social support was associated with a lower risk of comorbidities (RR=0.93, 95%CI=0.88-0.98). No statistical significance was identified between coping strategies and neuropsychiatric comorbidities (RR=0.88, 95%CI=0.73-1.06).

4. Discussion

The present study provides one of the first pieces of evidence on the relationship between cumulative effects of multiple stressors and subsequent neuropsychiatric comorbidities. This study identified three major findings: (1) Compared to those with a lower level of stress, people exposed to a higher level of stress were at an elevated risk of developing neuropsychiatric comorbidities; (2) an increase in composite stress score was linked with a higher risk of psychiatric disorders and neuropsychiatric comorbidities; (3) social support buffered the negative consequences of multiple stressors on neuropsychiatric comorbidities.

In line with the literature, cumulative stress was associated with an increased risk of psychiatric disorders. Copeland and his colleagues found that cumulative childhood trauma exposure was associated with a higher risk of adult psychiatric disorders in a prospective population-based cohort study (Copeland et al., 2018). The more adverse childhood exposures experienced the higher likelihood developed psychiatric disorders (for instance, depression and anxiety) and/or developmental challenges (speech or other language problems and learning disability, etc.) (Bright et al., 2016). Adverse childhood experiences not only increased the risk of subsequent psychiatric disorders (Green et al., 2010) but also negatively influenced certain neurocognitive characteristics, such as verbal learning, memory, and cognitive flexibility (Padua, 2021). Furthermore, stressful life events also increased the risk of psychiatric disorders (depressive disorders and anxiety disorders, etc.) (McLaughlin et al., 2010) and psychological distress (Caron and Liu, 2011). These findings could be partially explained by the brain development hypothesis. This hypothesis suggests that early adverse experiences may interrupt the maturity of neural circuits that control the hypothalamic-pituitary-adrenal (HPA) axis and form pathological neural circuits, resulting in psychiatric disorders in later life (Atrooz et al., 2019; Fatemi and Folsom, 2009).

We also found that cumulative effects of multiple stressors across the lifespan elevated the risk of developing neuropsychiatric comorbidities. Keers and his colleagues found that depressed patients with exposures to childhood adversities tend to suffer from cognitive decline (Keers et al., 2010). There are several potential mechanisms involved in the relationship between cumulative stress and neuropsychiatric comorbidities. First, the activated HPA axis can interfere with the normal function of prefrontal cortex (Arnsten et al., 2015; Herringa et al., 2013), which is associated with numerous forms of psychopathology (Sullivan and Gratton, 2002). Prefrontal cortex is critical for both psychiatric disorders and executive dysfunction. The impairment of prefrontal cortex is a central feature of psychiatric disorders (Gamo and Arnsten, 2011; Treadway et al., 2015) and core performance of executive dysfunction (Baker et al., 1996; Manes et al., 2002; Owen et al., 1990). Additionally, the brain-derived neurotrophic factor (BDNF) pathway in the hippocampus and prefrontal cortex may be impaired (Jin et al., 2019), which can lead to neuropsychiatric comorbidities (Jakovljević and Ostojić, 2013).

The risk of neuropsychiatric comorbidities can be modified by social support. Conclusive evidence has been published to support the correlation between social support and mental health (Harandi et al., 2017; Moulin et al., 2017) and the correlation between social support and cognition (Costa-Cordella et al., 2021). Moreover, social support was negatively associated with trajectories

of physical and psychiatric comorbidities (Pugh et al., 2018). Accumulated evidence has identified that social support is positively correlated with the right medial prefrontal cortical thickness (Sherman et al., 2015). Prefrontal cortical thinning was significantly correlated with higher cortisol levels, (Kremen et al., 2010) which is linked to multiple neuropsychiatric disorders (Dziurkowska and Wesolowski, 2021). The findings of the present study corroborate the protective role of social support in neuropsychiatric comorbidities.

Positive coping strategies did not show a significant protective effect on neuropsychiatric comorbidities. Although several studies showed that psychiatric comorbidities were significantly associated with avoidance-focused coping strategies (Chung et al., 2011), it is likely that positive (or adaptive) and negative (or maladaptive) coping strategies may play different roles in different mental health outcomes. Positive coping strategies may be more critical for positive mental health (Meng and D'Arcy, 2016; Miller Smedema et al., 2010; Moulin et al., 2017), whereas negative coping strategies associated with psychiatric disorders and comorbidities (Adan et al., 2017; Curran et al., 2021). Additionally, other factors may either mediate or moderate the role of coping strategies in psychiatric disorders. For instance, self-worth, self-esteem, and psychological distress could mediate the effects of coping strategies on mental health and well-being (Miller Smedema et al., 2010; Peláez-Fernández et al., 2021; Pereira-Morales et al., 2018).

This study used a longitudinal population-based cohort to examine the association between psychosocial stressors and subsequent risk of neuropsychiatric comorbidities. This study covered a wide range of stressful events from childhood to adulthood and originally applied two approaches to quantify the cumulative effects of multiple stressors in neuropsychiatric comorbidities. However, there are several limitations to be noted. First, the sample size was not large. It limited the possibilities of exploring other psychosocial attributes that may be also linked with the outcome. The generalizability of the findings may be limited. Second, baseline executive function was not collected, therefore the analyses cannot consider the status of baseline neuropsychiatric comorbidities. The effect of baseline neuropsychiatric comorbidities on the associations between cumulative stress and subsequent neuropsychiatric comorbidities was not studied. Third, self-reported measurements of stressors, especially early life stressful events (childhood maltreatment and parental bonding), may not accurately capture the true experience due to recall bias (Cohen et al., 1988; Hardt and Rutter, 2004). Finally, the status of executive dysfunction was not a clinical diagnosis. The interpretations of the study results should take this fact into account.

5. Conclusion

The present study discovered the associations between cumulative stressors and subsequent neuropsychiatric comorbidities. Higher levels of social support attenuated the negative consequences of cumulative stressors on neuropsychiatric comorbidities. The findings of the study not only direct clinical management to pay more attention to neuropsychiatric comorbidities among those who experienced multiple stressors but also advocate prevention and intervention programs to target modifiable stressors, such as preventing childhood maltreatment and promoting child-parent bonding, to minimize the occurrence of neuropsychiatric comorbidities. Training programs and family financial support (e.g., family-friendly work policies and an increase in family

supplements) could be feasible solutions to promote healthy family relationships. Promoting a warm social environment and strengthening social connections could be viable solutions to decrease the negative consequences when stressful events are inevitable.

Author Contributions

WWR, ML, and XM designed the research, ML, XM, and JC collected the data, WWR conducted the data analysis and prepared the first draft of this manuscript, with ML and XM's feedback on all steps of analysis, interpretation, and manuscript drafting. YTX contributed to the interpretations of the results. All authors agreed the final version of the manuscript.

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Declaration of Competing Interests

We have no conflicts of interest to declare.

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Table 1. Characteristics of the study cohort[#]

Characteristics	All participants n=210	HC n=99	PDO n=34	EDO n=52	CPDED n=25	F/χ^2	*p* value
Sociodemographic characteristic							
Age, M (SD)	46.62 ± 10.051	46.57 ±10.566	44.91 ± 10.393	46.46 ± 8.930	49.48 ± 9.653	1.007	0.390
Sex n (%, 95%CI)						0.182	0.980
Male	68 (32.4, 26.4-39.0)	33 (33.3, 24.8-43.1)	10 (29,4, 16.8-46.2)	17 (32.7, 21.5-46.2)	8 (32.0, 17.2-51.6)		
Female	142 (67.6, 61.0-73.6)	66 (66.7, 56.9-75.2)	24 (70.6, 53.8-83.2)	35 (67.3, 53.8-78.5)	17 (68.0, 48.4-82.8)		
Marital status, n (%, 95%CI)						6.114	0.416
Single	34 (16.2, 11.8-21.8)	14 (14.1, 8.6-22.4)	8 (23.5, 12.4-40.0)	5 (9.6, 4.2-20.6)	7 (28.0, 14.3-47.6)		
Married/Common-law	150 (71.4, 65.0-77.1)	72 (72.7, 63.2-80.5)	22 (64.7, 47.9-78.5)	41 (78.8, 66.0-87.8)	15 (60.0, 40.7-76.6)		
Separated/Divorced/Widowed	26 (12.4, 8.6-17.5)	13 (13.1, 7.8-21.2)	4 (11.8, 4.7-26.6)	6 (11.5, 5.4-23.0)	3 (12.0, 4.2-30.0)		
Race, n (%, 95%CI)						6.604	0.087
Caucasian	174 (82.9, 77.2-87.4)	82 (82.8, 74.2-89.0)	32 (94.1, 80.9-98.4)	39 (75.0, 61.8-84.8)	21 (84.0, 65.4-93.6)		
Non-Caucasian	31 (14.8, 10.6-20.2)	14 (14.1, 8.6-22.4)	1 (2.9, 0.5-14.9)	12 (23.1, 13.7-36.1)	4 (16.0, 6.4-34.7)		
Missing	5 (2.4, 1.0-5.5)	3 (3.0, 1.0-8.5)	1 (2.9, 0.5-14.9)	1 (1.9, 0.3-10.1)	0 (0.0)		
Education status, n (%, 95%CI)						2.048	0.571
Grade 10 and lower	14 (6.7, 4.0-10.9)	6 (6.1, 2.8-12.6)	1 (2.9, 0.5-14.9)	4 (7.7, 3.0-18.2)	3 (12.0, 4.2-30.0)		
Grade 11-13	196 (93.3, 89.1-96.0)	93 (93.9, 87.4-97.2)	33 (97.1, 85.1-99.5)	48 (92.3, 81.8-97.0)	22 (88.0, 70.0-95.8)		
Social Support, M (SD)	84.33 ± 9.125	86.00 ± 7.858	83.32 ± 9.562	84.40 ± 8.216	78.92 ± 12.665	4.375	**0.005**
Coping strategies, M (SD)	18.74 ± 2.852	19.15 ± 2.537	17.72 ± 2.963	19.37 ± 2.596	17.20 ± 3.651	4.705	**0.003**

Cumulative psychosocial stress							
Cumulative stress	-0.56 ± 6.900	-1.67 ± 6.272	2.463 ± 6.842	-2.78 ± 5.090	5.72 ± 8.995	10.637	**<0.001**
LPA-derived psychosocial stress clusters							
High Stress, n (%, 95%CI)	32 (15.2, 11.0-20.7)	11 (11.1, 6.3-18.8)	9 (26.5, 14.6-43.1)	2 (3.8, 1.1-13.0)	10 (40.0, 23.4-59.3)	21.719	**<0.001**
Low stress, n (%, 95%CI)	178 (84.8, 79.3-89.0)	88 (88.9, 81.2-93.7)	25 (73.5, 56.9-85.4)	50 (96.2, 87.0-98.9)	15 (60.0, 40.7-76.6)		
Note: HC=healthy control, PDO=psychiatric disorder only, EDO=executive dysfunction only, CPDED=comorbidity of psychiatric disorders and executive dysfunction, LPA=latent profile analysis. Bold: $P<0.05$. [#]Presenting with non-imputed data							

Table 2. Relationships between cumulative stressors and neuropsychiatric comorbidities

Multiple stressors	Status of neuropsychiatric comorbidities	Crude Model			Adjusted Model[a]		
		RR	95%CI	*P value*	RR	95%CI	*P value*
Composite stress score	HC	1	-	-	1	-	-
	PDO	1.09	1.04-1.15	**0.001**	1.08	1.02-1.14	**0.010**
	EDO	0.96	0.90-1.01	0.136	0.95	0.89-1.01	0.121
	CPDED	1.11	1.05-1.17	**<0.001**	1.08	1.01-1.15	**0.019**
LPA-derived psychosocial stress groups (High Stress vs. level stress**)**	HC	1	-	-	1	-	-
	PDO	2.88	1.07-7.72	**0.036**	1.95	0.65-5.86	0.231
	EDO	0.32	0.07-1.50	0.149	0.33	0.07-1.60	0.169
	CPDED	5.33	1.93-14.74	**0.001**	3.65	1.15-11.57	**0.028**

Note: HC=healthy control, PDO=psychiatric disorder only, EDO=executive dysfunction only, CPDED=comorbidity of psychiatric disorders and executive dysfunction, LPA=latent profile analysis. Bold: $P<0.05$.

[a]Adjusted for social support and coping strategies

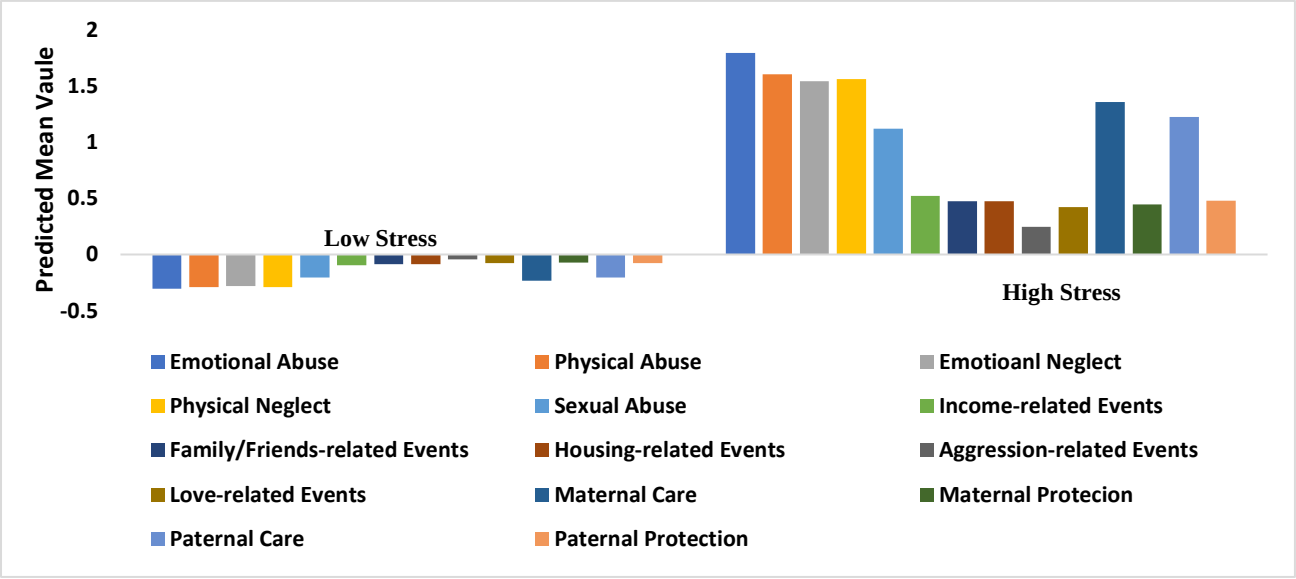

Figure 1. Predicted mean of experienced childhood maltreatment, child-parent bonding, and stressful events across latent profiles

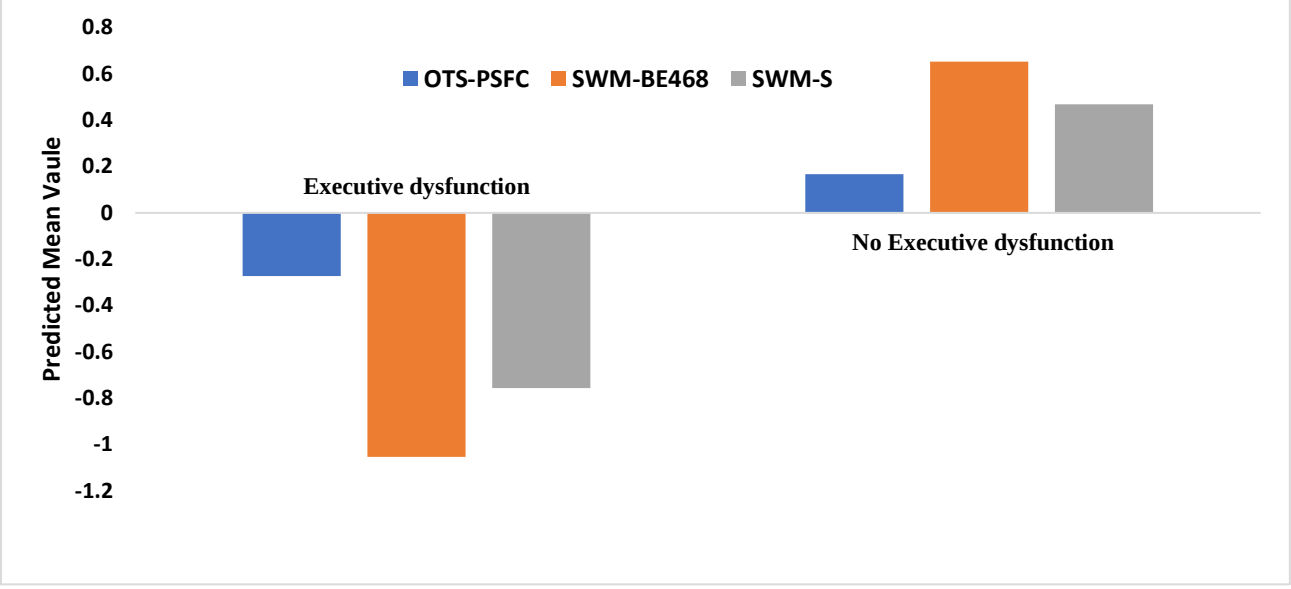

Figure 2. Predicted mean of each indicator of One Touch Stockings of Cambridge (OTS) and the Spatial Working Memory (SWM) across latent profiles

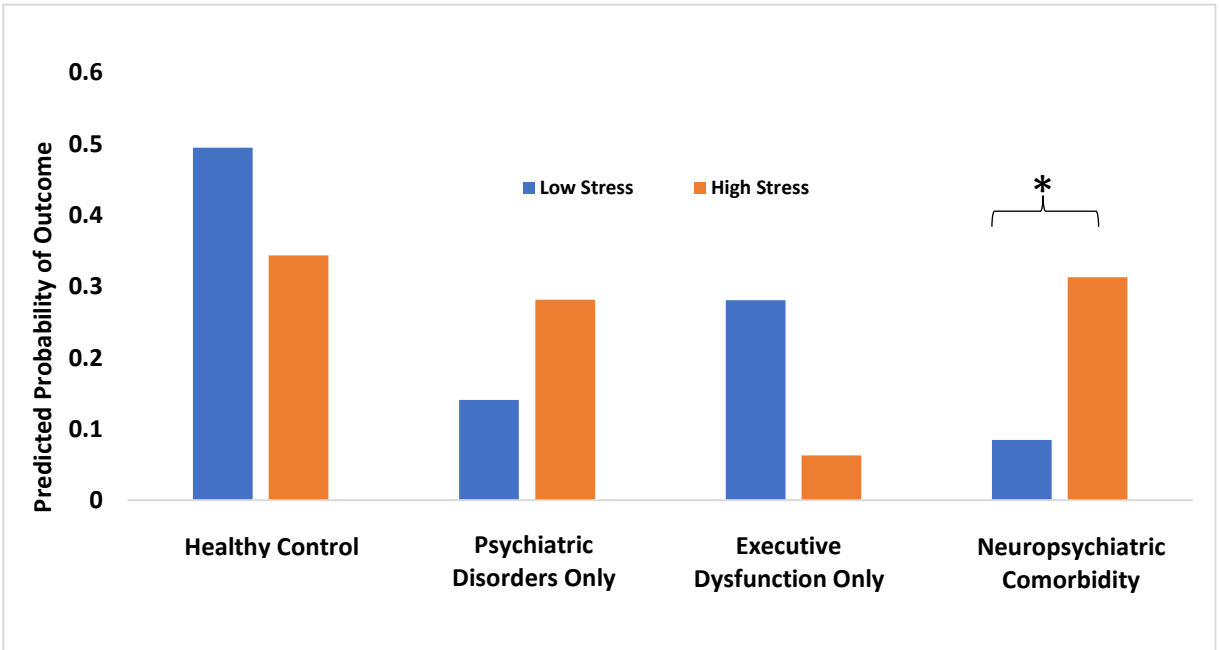

Figure 3. Predicted probabilities of outcomes by different levels of stress, adjusting for social support and coping strategies

Table S1. Comparison between the target sample and the analyzed study cohort at Wave 4

Characteristics	All the targeted samples (n=366)	The study cohort (n=210)	t/χ^2/Fisher	*p* value
Sociodemographic characteristic				
Age, M (SD)	48.31 ± 11.025	47.86 ±9.986	0.490	0.624
Sex n (%, 95%CI)				
Male	112 (30.6, 26.1-35.5)	68 (32.4, 26.4-39.0)	0.197	0.709
Female	254 (69.4, 64.5-73.9)	142 (67.6, 61.0-73.6)		
Marital status, n (%, 95%CI)				
Single	53 (14.5, 11.2-18.5)	28 (13.3, 9.39-18.6)		
Married/Common-law	251 (68.6, 63.7-73.1)	156 (74.3, 68.0-79.7)	3.198	0.360
Separated/Divorced/Widowed	61 (16.7, 13.2-20.8)	25 (11.9, 8.2-17.0)		
Missing	1 (0.13, 0.1-1.5)	1 (0.5, 0.1-2.7)		
Education status, n (%, 95%CI)				
Grade 10 and lower	26 (7.1, 4.9-10.2)	10 (4.8, 2.6-8.5)	1.636	0.417
Grade 11-13	339 (92.6, 89.5-94.9)	199 (94.8, 90.9-97.1)		
Missing	1 (0.3, 0.1-1.5)	1 (0.5, 0.1-2.7)		

Table S2. Goodness of fit indices for latent profile analyses (multiple stressors and executive function)

Number of classes	1	2	3	4
Multiple stressors				
AIC	8249.106	7666.309	7556.802	7391.755
BIC	8342.825	7810.235	7650.935	7636.094
Executive function				
AIC	1762.795	1649.619	1613.771	1600.437
BIC	1782.878	1683.09	1660.63	1660.685

Note: AIC= Akaike's information criterion; BIC= Schwarz's Bayesian information criterion