



Full Length Article

Childhood adversities and the comorbidity between mood and general medical disorders in adults: Results from the WHO World Mental Health Survey Portugal



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ABSTRACT

Objective: Childhood adversities have been linked to poor health outcomes in adults, including both mood and general medical disorders. Here we tested the hypothesis that childhood adversities specifically increase the risk of comorbidity between mood and general medical disorders, rather than increasing the risk of either one independently.

Methods: Mood disorders (DSM-IV major depressive, dysthymic and bipolar disorders), childhood adversities and general medical disorders were assessed in 2060 adults in the WHO World Mental Health Survey Portugal. Discrete-time survival analyses were used to investigate the association between mood disorders and subsequent first-onset general medical disorders and between general medical disorders and subsequent first-onset mood disorders, in adults. Discrete-time survival and multinomial regression analyses were used to test the influence of childhood adversities on the comorbidity between mood disorders and general medical disorders. Anxiety disorders were used as a psychiatric control.

Results: Adult-onset mood disorders were found to precede the onset of diabetes (OR:1.8; 95% CI:1.2–2.9), arthritis (OR:1.6; 95% CI:1.1–2.3) and seasonal allergies (OR:1.6; 95% CI:1.1–2.5) while adult-onset hypertension was found to precede the onset of mood disorders (OR:1.7; 95% CI:1.2–2.6). Maladaptive family functioning (abuse, neglect and parental maladjustment), was associated with mood disorders (OR:1.5; 95% CI:1.2–1.9), hypertension (OR:1.4; 95% CI:1.1–1.7), arthritis (OR:1.3; 95% CI:1.0–1.6) and seasonal allergies (OR:1.5; 95% CI:1.1–2.0) in adulthood. Finally, the effect of maladaptive family functioning in predicting comorbid mood disorders and arthritis significantly differed from its effect in predicting only arthritis ($p = 0.01$), which was not observed for other comorbidities. Maladaptive family functioning further predicted comorbid anxiety disorders and hypertension.

Conclusion: Childhood adversities may be a specific risk factor for comorbid mood disorders and arthritis in adults.

1. Introduction

The higher morbidity and mortality from general medical disorders among individuals with mental disorders is of significant concern (Scott et al., 2016; Chesney et al., 2014; Walker et al., 2015). These patients still

lag far behind the improvement achieved in health and life-expectancy worldwide, urging the need to understand the association between mental and physical illness and consider the role of risk factors in its prevention (Lawrence et al., 2013). In fact, among individuals diagnosed with a psychiatric disorder, not only are physical illnesses more

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prevalent, but also the mortality due to natural causes is 80% higher than in the general population (Walker et al., 2015).

Comorbidity is defined as two or more disorders existing simultaneously in the same individual. In patients with mood disorders, comorbid general medical disorders are suggested to exist as interacting illnesses (i.e., one being a risk factor for the subsequent), at least in what concerns metabolic and autoimmune disorders (Oliveira et al., 2018). Indeed, metabolic syndrome is prevalent in nearly one third of patients diagnosed with major depressive disorder or bipolar disorder (Vancampfort et al., 2015). Of remark, plasma glucose following an oral glucose load is already higher in drug-naïve first-episode patients with major depressive disorders or bipolar disorder, and non-depressed individuals meeting criteria for metabolic syndrome are twice as likely to develop depressive symptoms (Koponen et al., 2008; Garcia-Rizo et al., 2016). Autoimmune disorders have also been associated with subsequent hazard of a mood disorder, while individuals diagnosed with depression have a significantly higher hazard of subsequently developing an autoimmune disorder (Euesden et al., 2017; Andersson et al., 2015; Benros et al., 2013). It is often suggested that comorbidity between mood and physical disorders are explained by common risk factors, such as childhood adversity, acting through a common pathophysiological pathway, such as immune dysfunction (Nettis et al., 2020; Hosang et al., 2018). However, evidence to support this hypothesis is insufficient.

Childhood adversities are currently regarded as a foundational source of morbidity and premature all-cause mortality worldwide (Hughes et al., 2017; Kelly-Irving et al., 2013). In what concerns mood disorders, according to a previous study from the World Mental Health Survey Initiative that included data from 21 countries, the estimation of population-attributable risk proportions suggests that if childhood adversities are causal, their eradication alone would lead to a reduction of 22.9% in prevalence (Kessler et al., 2010). These studies and others, also demonstrate that childhood adversities act as a broad-spectrum risk factor for adult-onset of several non-psychiatric illnesses such as diabetes, asthma, arthritis, hypertension and cardiovascular disorders (Coelho et al., 2014; Stein et al., 2010; Scott et al., 2011). Interestingly, a joint analysis of data from 17 countries showed that mood disorders are a risk factor for the subsequent development of the abovementioned conditions (Scott et al., 2016). Nevertheless, while childhood adversities are risk factors for both mental and general medical disorders, it remains unclear if and how they may increase comorbidity through a common pathophysiological pathway, rather than inducing mere co-occurrence through distinct causal pathways.

The pathways that may lead from childhood adversity to disease, often several decades later, are still only faintly defined. Studying the routes linking childhood adversities with the development of disease faces several challenges, namely: i) a comprehensive and/or relevant repertoire of childhood adversities is not standardized; ii) childhood adversities commonly co-occur; iii) concurrent sociodemographic risk factors are often not considered; iv) these and other associated factors, both proximal and distal relative to exposure to childhood adversity, may exist and lead towards distinct pathological outcomes and; v) literature on assessment of multiple disease outcomes in the same population is lacking. The latter is necessary in hypothesis-driven studies, not only by allowing to parallel the associations between childhood adversities and diverse aftereffects in the same sample, but also to establish a “temporal sequence” between events of interest.

Here, we used a large cross-sectional population-based dataset to test the hypothesis that childhood adversity is a common risk factor for the development of mood disorders and general medical disorders of adult onset, increasing their comorbidity.

2. Methods

2.1. Sample

The WHO World Mental Health Survey Portugal is a community

survey administered between 2008 and 2009 in a probabilistic sample of the general Portuguese population (Antunes et al., 2018; Caldas de Almeida and Xavier, 2013). It is part of the WMH Survey Initiative, coordinated by Harvard University and the World Health Organization (WHO), based on a common methodology (<https://www.hcp.med.harvard.edu/wmh/>). The study was approved by the Ethics Committee of NOVA Medical School and by the Portuguese Data Protection Authority. Following a multi-stage, clustered probability sampling design, 3849 individuals (corresponding to a response rate of 57.3%, which is similar to the surveys in Belgium, France, Germany and The Netherlands) aged 18 years old or above, residing in permanent private dwellings in the country's mainland, were interviewed in their homes of residence by trained lay interviewers, after informed consent was obtained. The instrument used in the WHO World Mental Health Survey Portugal was the Portuguese version of the WHO Composite International Diagnostic Interview (CIDI), a validated fully structured lay-administered diagnostic interview.

2.2. Psychiatric diagnoses

The WHO Composite International Diagnostic Interview (CIDI), was used to assess the prevalence of a wide range of mental disorders according to the definitions and criteria of both the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV and the International Classification of Diseases (ICD)-10 (American Psychiatric Association, 2000; World Health Organization, 2004). Interviews were administered in two parts. Part 1 was a screening module administered to all 3849 individuals and included a core diagnostic assessment. Among the 3849 individuals screened, Part 2 was administered to those who met lifetime criteria for any Part 1 disorder, i.e., the screening module, and to a proportion of the remaining respondents (~25%), chosen randomly, in a total of 2060 respondents. Individuals were weighted by the inverse of their probability of being selected and this weight was used in statistical analyses to match the sample with known population sociodemographic distributions.

The number of individuals presenting at least one lifetime diagnosis of a mental disorder is 1300 (42.7% of the 2060; weighted analysis). For the purpose of the present study, cases were defined as individuals diagnosed with a first-onset of a mood disorder (major depressive disorder, dysthymic disorder, bipolar disorder type I and bipolar disorder type II) at age 18 or more, according to DSM-IV criteria, which corresponds to a total of 630 individuals (American Psychiatric Association, 2000). The control sample was defined as the remaining participants, corresponding to a total of 1430 individuals, and thus includes population-representative prevalences of any other mental disorder, including those of childhood onset. For control analyses, designed to assess specificity of the findings, we were interested in anxiety disorders, also according to DSM-IV, namely: generalized anxiety disorder (GAD), panic disorder (PD), social phobia (SP), agoraphobia (AP) and post-traumatic stress disorder (PTSD). A question sequence was used to retrospectively assess the age at onset of major depressive disorder, dysthymic disorder, bipolar disorders, GAD, PD, SP, AP and PTSD, as described previously (World Health Organization, 2004). The association of childhood adversities and general medical comorbidities with mental disorders, appears in recent literature as transnosological phenomena (McLaughlin et al., 2020; Walker and Druss, 2016). The objective of also performing the analyses using anxiety disorder as psychiatric control was to further verify this finding, in a similarly prevalent psychiatric diagnosis, but also test if any specific increased prevalence observed in comorbid mood and general medical disorders in association with childhood adversities is equally present in another diagnostic group, such as anxiety disorder.

2.3. Childhood adversities

The presence of eleven dichotomously scored childhood adversities

(i.e., occurring before the age of 18) was evaluated using the CIDI among respondents to part 2 of the interview, based on retrospective self-reports including child maltreatment (physical abuse, sexual abuse and neglect), interpersonal loss (parental death, parental divorce and other types of parental loss), parental maladjustment (mental illness, substance abuse, criminal behaviour and family violence) and economic adversity (Kessler et al., 2010). In what concerns family violence and physical abuse, the survey adopted a modified version of the Conflict Tactics Survey (Straus, 1990). Neglect was assessed using questions adopted from child welfare research about basic needs of children (e.g., nutrition, clothing, medical care), having inadequate supervision and exposure to age-inappropriate chores (Courtney et al., 2001). Sexual abuse was evaluated with questions regarding repeated fondling, attempted rape or rape (Molnar et al., 2001). Interpersonal loss, including both biological and non-biological parents, was evaluated with questions about childhood living conditions and included events such as death of a parent, parental separation or divorce, or parental absence of 6 months or longer due to other causes (e.g., imprisonment, lengthy hospitalization, respondent foster care placement). Parental mental illness, including major depressive disorder, generalized anxiety disorder, panic disorder and antisocial personality disorder, as well as substance misuse, were evaluated using the Family History Research Diagnostic Criteria Interview (Kendler et al., 1991; Endicott et al., 1978). Finally, parental criminality and economic adversity were evaluated with questions used in previous epidemiological surveys, namely the National Comorbidity Survey Replication I (Green et al., 2010).

2.4. Chronic conditions

The CIDI was also used, among respondents to part 2 of the interview, to inquire about lifetime diagnoses of general medical disorders, including heart disease, hypertension, diabetes, arthritis, seasonal allergies and asthma, selected for this study for being metabolic- or immune-related. The selection of the chronic conditions was among the diagnoses identified by the CIDI, with exclusion of conditions that were: i) not metabolic nor immune-related; ii) very unspecific for the purposes of the proposed analysis (e.g., “Any other chronic lung disease, like COPD or emphysema”). Specifically, participants were asked: “The next few questions are about health problems you might have had at any time in your life. Have you ever had any of the following: (...)”? The general medical disorders of interest were specified as follows: “heart disease?”, “high blood pressure?”, “diabetes or high blood sugar?”, “arthritis or rheumatism?”, “seasonal allergies like hay fever?” and “asthma?”. The question “arthritis or rheumatism?” does not differentiate between rheumatoid arthritis and osteoarthritis while the question regarding “asthma” is not specific for allergic asthma and may include other subtypes. Participants were also asked: “How old were you the first time you had (...)”? to estimate the age at onset of each chronic condition. The remaining questions regarding general medical disorders included in the CIDI ask about “An ulcer in your stomach or intestine”, “Chronic back or neck problems”, “Frequent or severe headaches”, “Any other chronic pain”, “A stroke”, “Tuberculosis”, “Any other chronic lung disease, like COPD or emphysema”, “HIV infection or AIDS”, “Epilepsy or seizures” and “Cancer”.

2.5. Statistical analyses

In preliminary analyses, tetrachoric correlations between childhood adversities and an exploratory factor analysis using promax rotation was performed, similarly to previous analyses of data from the WMH Surveys, in order to define main factors for use in further analyses (Kessler et al., 2010; Knäuper et al., 1999). A person-year file was then created for adult-onset mood disorders, and a model in a discrete-time survival framework was computed to estimate the association between main factors for childhood adversities and adult-first onset of a mood disorder (Willett and Singer, 1993). The model was adjusted for person-year, age,

sex, years of education, marital status, employment status, income category and other psychiatric disorders with onset at 17 years of age or younger, namely SP, PD, obsessive-compulsive disorder (OCD), AP, PTSD, GAD, anorexia, bulimia and binge eating disorder (BED), as well as attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD) and intermittent explosive disorder (IED). This variable was meant to adjust for the direct effects of childhood adversities on early-onset psychiatric disorders, which in turn, predict adult-first onset of mood disorders. A similar model was used to estimate the association between childhood adversities and the adult-onset of anxiety disorders. In this case the analysis was also adjusted for other psychiatric disorders with onset at 17 years of age or younger, namely child- and adolescent-onset mood disorders, anorexia, bulimia and BED as well as ADHD, ODD, CD and IED.

Discrete-time survival analysis was additionally used to estimate the association between several other pairs of variables, namely between: childhood adversities and the adult-onset of a general medical disorder; adult-first diagnosis of general medical disorders and the subsequent first-onset of a mood disorder; adult-onset of mood disorder and the subsequent first diagnosis of a general medical disorder; adult-first diagnosis of a general medical disorder and the subsequent first-onset of an anxiety disorder; adult-onset of an anxiety disorder and the subsequent first diagnosis of a general medical disorder. All such analyses were adjusted for person-year, age, sex, years of education, marital status, employment status and income category. Specifically studying the association between childhood adversities, i.e., events occurring before the age of 18 years, and the adult first-onset of mood and of general medical disorders prevent the possibility that these disorders precede childhood adversities, thus allowing to extract potential causal relationships.

Finally, multinomial logistic regression analyses were performed in order to separately test the association between childhood adversities and: (i) adult-onset mood disorder without comorbid adult-onset general medical disorders, (ii) adult-onset general medical disorders without comorbid adult-onset mood disorder and, (iii) adult-onset comorbid mood disorder and adult-onset general medical disorders. Likewise, multinomial logistic regression analyses were performed in order to test the association between childhood adversities and: (i) adult-onset anxiety disorders without comorbid adult-onset general medical disorders, (ii) adult-onset general medical disorders without comorbid adult-onset anxiety disorders and, (iii) adult-onset comorbid anxiety disorders and adult-onset general medical disorders. Multinomial logistic regression analyses were adjusted for age, sex, years of education, marital status, employment status and income category. In each analysis, cases were defined as individuals diagnosed with mood disorders, anxiety disorders or a general medical disorder, i.e., composed of all participants presenting with an adult first-onset of a specific disorder, and may thus present comorbidities with other mental or physical disorders.

3. Results

Across the 3849 members of the study cohort, lifetime prevalence of adult-onset mood disorders was 14.7%, including 571 respondents with major depressive disorder (13.3%), 51 with dysthymia (1.2%) and 24 with bipolar disorder (0.6%). Sociodemographic characteristics of the population with and without mood disorders (respectively ‘cases’ and ‘controls’) are reported in Table 1, corresponding to the 2060 individuals interviewed in part 2.

Regarding childhood adversities, 42.0% of the study sample reported having experienced at least one, parental death being the most common (12.0%). Other common childhood adversities were family violence (11.7%), physical abuse (10.5%) and neglect (9.2%). Economic adversity, parental criminal behaviour and sexual abuse were reported less frequently: 3.5%, 2.4% and 1.1%, respectively. Childhood adversities frequently co-occurred, with 42.4% of those with childhood adversities reporting more than one. Their prevalence also differed significantly

Table 1
Sociodemographic characteristics of the study population.

| | Cases (n = 630) | Controls (n = 1430) | OR (95% CI) | p |
|----------------------------|--------------------|------------------------|--------------------|--------|
| <i>n</i> (%) or Mean ± SD | | | | |
| Sex (female) | 457 (67.1) | 1760 (49.0) | 2.1 (1.8–2.6) | <0.001 |
| Age at interview | 45.7 ± 15.2 | 46.5 ± 17.2 | 0.997 (0.99–1.003) | 0.3 |
| Age at onset | 32.5 ± 11.9 | – | – | – |
| Years of education | 9.21 ± 4.58 | 8.67 ± 4.83 | 1.02 (0.99–1.05) | 0.07 |
| Marital Status | | | | |
| Never married | 109 (17.8) | 642 (21.0) | REF | |
| Married/Cohabiting | 381 (65.0) | 2189 (70.0) | 1.1 (0.9–1.4) | 0.4 |
| Separated/Widowed/Divorced | 140 (17.1) | 388 (9.0) | 2.3 (1.7–3.1) | <0.001 |
| Income | | | | |
| Low | 252 (37.4) | 563 (40.1) | REF | |
| Low-average | 169 (27.4) | 411 (28.9) | 1.02 (0.8–1.4) | 0.9 |
| High-average | 146 (24.6) | 344 (23.1) | 1.1 (0.8–1.5) | 0.4 |
| High | 63 (10.6) | 112 (7.9) | 1.5 (0.95–2.2) | 0.08 |
| Employment | | | | |
| Working | 384 (62.1) | 890 (59.2) | REF | |
| Student | 14 (2.5) | 76 (6.0) | 0.4 (0.2–0.8) | 0.01 |
| Homemaker | 26 (3.7) | 61 (4.5) | 0.8 (0.4–1.4) | 0.4 |
| Retired | 125 (19.9) | 267 (22.0) | 0.9 (0.6–1.2) | 0.3 |
| Other | 81 (11.8) | 136 (8.2) | 1.4 (0.9–2.0) | 0.1 |

SD: standard deviation; OR: odds ratio; CI: confidence interval; REF: reference. Cases are defined as individuals diagnosed with an adult first-onset of a mood disorder (major depressive disorder, dysthymic disorder or bipolar disorder).

Table 2
Prevalence of childhood adversities in the World Mental Health Survey Portugal.

| | Total (n = 2060) | | Cases (n = 630) | | Controls (n = 1430) | | OR (95% CI) ^a | p | OR (95% CI) ^b | p |
|---|---------------------|------|--------------------|------|------------------------|------|--------------------------|--------|--------------------------|--------|
| | n | % | n | % | n | % | | | | |
| I Maltreatment | | | | | | | | | | |
| Neglect | 233 | 9.2 | 77 | 11.8 | 156 | 8.8 | 1.1 (0.8–1.6) | 0.5 | 1.5 (1.0–2.1) | 0.03 |
| Physical abuse | 260 | 10.5 | 79 | 11.8 | 181 | 10.2 | 1.1 (0.8–1.5) | 0.7 | 1.2 (0.9–1.8) | 0.2 |
| Sexual abuse | 37 | 1.1 | 12 | 1.6 | 25 | 1.0 | 2.5 (1.0–6.0) | 0.04 | 1.5 (0.6–3.7) | 0.4 |
| II Parental maladjustment | | | | | | | | | | |
| Parental mental illness | 217 | 7.7 | 81 | 12.5 | 136 | 6.8 | 2.1 (1.5–2.9) | <0.001 | 1.7 (1.2–2.4) | 0.002 |
| Parental substance disorder | 147 | 5.3 | 49 | 8.1 | 98 | 4.8 | 1.6 (1.1–2.4) | 0.02 | 1.6 (1.0–2.3) | 0.04 |
| Parental criminal behaviour | 64 | 2.4 | 22 | 3.4 | 42 | 1.7 | 1.7 (0.9–3.1) | 0.1 | 1.8 (1.0–3.2) | 0.06 |
| Family violence | 323 | 11.7 | 106 | 15.6 | 217 | 11.0 | 1.6 (1.2–2.2) | 0.002 | 1.4 (1.0–1.9) | 0.03 |
| III Interpersonal loss | | | | | | | | | | |
| Parental death | 234 | 12.0 | 51 | 8.1 | 183 | 12.7 | 0.5 (0.3–0.7) | 0.001 | 0.7 (0.5–1.0) | 0.06 |
| Parental divorce | 116 | 4.5 | 37 | 5.6 | 79 | 4.3 | 1.7 (1.1–2.8) | 0.02 | 1.2 (0.7–2.0) | 0.4 |
| Other parental loss | 119 | 5.2 | 29 | 5.0 | 90 | 5.3 | 1.0 (0.6–1.7) | 1.0 | 0.9 (0.5–1.5) | 0.7 |
| IV Other childhood adversities | | | | | | | | | | |
| Economic adversity | 69 | 3.5 | 22 | 3.7 | 47 | 3.4 | 1.1 (0.6–1.9) | 0.8 | 1.4 (0.8–2.6) | 0.2 |
| V Factors ^c | | | | | | | | | | |
| Factor 1 – Maladaptive family functioning | 737 | 29.9 | 244 | 38.3 | 493 | 28.4 | 1.4 (1.1–1.8) | 0.002 | 1.5 (1.2–1.9) | <0.001 |
| Factor 2 – Other | 454 | 21.1 | 117 | 19.0 | 337 | 21.4 | 0.8 (0.6–1.1) | 0.1 | 0.9 (0.7–1.1) | 0.3 |
| VI Childhood adversities | | | | | | | | | | |
| Any | 975 | 42.0 | 306 | 48.3 | 669 | 40.8 | 1.2 (1.0–1.5) | 0.08 | 1.3 (1.1–1.6) | 0.02 |
| One | 514 | 24.2 | 164 | 26.5 | 350 | 23.7 | 1.2 (0.9–1.5) | 0.3 | 1.2 (0.9–1.6) | 0.1 |
| Two | 247 | 10.2 | 74 | 11.8 | 173 | 9.9 | 1.1 (0.8–1.6) | 0.5 | 1.3 (0.9–1.9) | 0.2 |
| Three | 104 | 3.9 | 36 | 5.0 | 68 | 3.6 | 1.4 (0.8–2.3) | 0.2 | 1.5 (0.9–2.7) | 0.1 |
| Four or more | 110 | 3.8 | 32 | 5.0 | 78 | 3.6 | 1.7 (1.0–2.9) | 0.04 | 1.7 (1.0–2.9) | 0.06 |

OR: odds ratio; CI: confidence interval. Individuals were weighted by the inverse of their probability of being selected thus matching the sample with population sociodemographic characteristics. Cases are defined as individuals diagnosed with an adult first-onset of a mood disorder (major depressive disorder, dysthymic disorder or bipolar disorder).

^a Discrete-time survival models in a logistic regression framework with person-year as the unit of analysis were used to predict adult first-onset of mood disorders (major depressive disorder, dysthymic disorder or bipolar disorder type I and type II) according to the presence of childhood adversities.

^b The association between childhood adversities and mood disorders were further adjusted for gender, years of education, marital status, employment status, income category and other psychiatric diagnoses with an onset before the age of 18.

^c Factor 1: neglect, physical abuse, sexual abuse, parental mental disorder, parental substance disorder, parental criminal behaviour and family violence; Factor 2: parental death, parental divorce, other parental loss and economic adversity.

between cases (48.3%) and controls (40.8%), with the former reporting more frequently neglect, parental mental illness, parental substance misuse and family violence (Table 2).

Correlations between pairs of childhood adversities were mostly statistically significant, and among these, all of them were positive, with coefficients ranging from 0.14 to 0.59 (Supplementary Table 1). The strongest correlations were observed between: neglect and physical abuse (0.59), family violence and parental substance use (0.57) and, family violence and physical abuse (0.54). Exploratory factor analysis with promax rotation was subsequently used to identify meaningful factors in the distribution of childhood adversities, as described previously (McGrath et al., 2017). We found very similar results to those obtained with WMH Survey data from 17-countries, that included data from Portugal (McGrath et al., 2017). We retained a two-factor solution, with neglect, physical abuse, sexual abuse, parental mental disorder, parental substance use, parental criminal behaviour and family violence loading significantly on the first factor. Although parental divorce also loaded on the first factor, it was classified in the second factor, with parental death and other parental loss, since these are all adversities related with interpersonal loss, and for consistency with previous literature (Supplementary Table 2) (McGrath et al., 2017). We also preserved the labels of maladaptive family functioning (MFF) for Factor 1, and other CAs for Factor 2 (Kessler et al., 2010; McGrath et al., 2017).

Discrete-time survival analyses showed that maladaptive family functioning, but not other childhood adversities, significantly predicted the subsequent diagnosis of several adult-onset disorders, namely mood disorders, hypertension, arthritis and seasonal allergies, with odds ratios ranging from 1.3 (arthritis) to 1.5 (mood disorders and seasonal allergies; Table 3).

We further found that adult-first onset of a mood disorder was

significantly associated with subsequent onset of diabetes, arthritis and seasonal allergies, while hypertension was the only adult-onset general medical disorder associated with subsequent diagnosis of a mood disorder. Maladaptive family functioning, as well as other childhood adversities, were found to be significant predictors of subsequent adult-first onset anxiety disorders, increasing their odds by approximately 50% in both cases. However, in additional discrete-time survival analyses, adult-first onset of an anxiety disorder was not associated with subsequent onset of any of the general medical disorders tested here, while adult-onset heart disease or hypertension were significantly associated with subsequent diagnosis of an anxiety disorder (Supplementary Table 3).

Maladaptive family functioning was thus a common risk factor for mood disorders, as well as hypertension, arthritis and seasonal allergies, 3 general medical disorders found to precede or follow diagnosis of a mood disorder. To test associations between this childhood adversity and comorbidities between mood disorders and general medical disorders, and also to compare such associations with those observed for non-comorbid diagnoses, we performed multinomial regression analyses. We found that maladaptive family functioning was associated with comorbidities between mood disorders and hypertension, as well as arthritis, but not between mood disorders and seasonal allergies. However, the effect of maladaptive family functioning in predicting comorbid mood disorders and hypertension did not differ from its effect in predicting only mood disorder ($\chi^2 = 0.65, p = 0.4$) or only hypertension ($\chi^2 = 1.57, p = 0.2$). On the other hand, the effect of maladaptive family functioning in predicting co-morbidity between mood disorders and arthritis differed significantly from its effect in predicting only arthritis ($\chi^2 = 6.68, p = 0.01$), although it was only borderline distinct from its effect in predicting only mood disorders ($\chi^2 = 3.15, p = 0.08$; Table 4).

Maladaptive family functioning was also a common risk factor for anxiety disorders and hypertension, that was found to precede an anxiety disorder diagnosis (Supplementary Table 3). Importantly, we found that maladaptive family functioning was associated with the comorbidity between anxiety disorders and hypertension (Supplementary Table 4), and that this effect differed significantly from its effect in predicting only hypertension ($\chi^2 = 6.47, p = 0.01$), but was only borderline distinct from its effect in predicting only anxiety disorders ($\chi^2 = 3.38, p = 0.07$).

4. Discussion

Precise identification of factors increasing the predisposition for the development of general medical comorbidities among individuals

Table 3

Prevalence of adult-onset mood disorders and chronic general medical disorders in the World Mental Health survey Portugal and their association with childhood adversities.

| | Lifetime prevalence | | MFF | | Other CAs | | Mood → Physical | | Physical → Mood | |
|--------------------|---------------------|-------|----------------|-------|---------------|-----|-----------------|-------|-----------------|-------|
| | % | (SE) | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p | OR (95% CI) | p |
| Mood disorders | 14.7 | (0.6) | 1.5 (1.2–1.9)* | 0.001 | 0.9 (0.7–1.1) | 0.3 | – | – | – | – |
| Heart disease | 5.4 | (0.5) | 1.1 (0.8–1.7) | 0.5 | 1.0 (0.6–1.5) | 0.9 | 1.1 (0.6–1.9) | 0.9 | 1.3 (0.6–2.8) | 0.4 |
| Hypertension | 22.1 | (0.9) | 1.4 (1.1–1.7)* | 0.002 | 1.1 (0.9–1.3) | 0.5 | 1.2 (0.9–1.6) | 0.2 | 1.7 (1.2–2.6)* | 0.008 |
| Diabetes | 6.7 | (0.6) | 1.2 (0.8–1.7) | 0.3 | 1.2 (0.8–1.8) | 0.3 | 1.8 (1.2–2.9)* | 0.009 | 1.1 (0.5–2.5) | 0.9 |
| Arthritis | 15.5 | (0.8) | 1.3 (1.0–1.6)* | 0.047 | 0.8 (0.6–1.1) | 0.2 | 1.6 (1.1–2.3)* | 0.01 | 1.4 (1.0–2.1) | 0.08 |
| Seasonal allergies | 10.5 | (0.7) | 1.5 (1.1–2.0)* | 0.005 | 1.0 (0.7–1.3) | 0.8 | 1.6 (1.1–2.5)* | 0.02 | 1.3 (0.9–2.0) | 0.2 |
| Asthma | 2.5 | (0.3) | 1.2 (0.6–2.1) | 0.6 | 1.3 (0.7–2.4) | 0.5 | 1.2 (0.5–3.1) | 0.7 | 0.9 (0.3–2.4) | 0.8 |

MFF: maladaptive family functioning; CAs: childhood adversities; OR: odds-ratio; CI: confidence interval; SE: standard error.

Heart disease: 6 missing, 19 childhood onset; High blood pressure: 26 missing, 12 childhood onset; Diabetes: 4 missing, 11 childhood onset; Arthritis: 40 missing, 54 childhood onset; Seasonal allergies: 46 missing, 132 childhood onset; Asthma: 13 missing, 79 childhood onset.

Discrete-time survival models in a logistic regression framework with person-year as the unit of analysis were used to predict adult first-onset of mood disorders (major depressive disorder, dysthymic disorder or bipolar disorder type I and type II) or adult first-diagnosis of a general medical disorder according to the presence of childhood adversities. The same method was used to: (i) test the association between the first episode of adult-onset of a mood disorder and the subsequent first diagnosis of a chronic medical disorder and, (ii) test the association between first diagnosis of the adult-onset of a chronic medical disorder and the subsequent first episode of an adult-onset mood disorder. These analyses were adjusted for age at interview, gender, employment status, income category, marital status and years of education. The association between childhood adversities and mood disorders were further adjusted for other psychiatric diagnoses with an onset before the age of 18. Individuals were weighted by the inverse of their probability of being selected thus matching the sample with population sociodemographic characteristics.

diagnosed with a mood disorder is of paramount importance. While both mood and physical adverse outcomes have been linked to childhood adversity, evidence supporting an increase in comorbidity between the two in those exposed is lacking. Here, we confirm the pervasive harm associated with childhood adversities throughout the life-course providing evidence supporting that: (i) childhood adversities are similarly associated with mood disorders and general medical disorders (i.e. hypertension, seasonal allergies and arthritis); (ii) adult-onset mood disorders are associated with the subsequent onset of a general medical disorder, and *vice versa*; (iii) maladaptive family functioning is a potential risk factor for adult-onset comorbidity between arthritis and mood disorders and; (iv) childhood adversities do not increase the likelihood of comorbidity between most of the other mental and general medical disorders studied.

Maladaptive family functioning, a cluster of adversities related to neglect, abuse and parental mental and behavioural changes, is identified here as having the highest number of associations. The described associations with mood disorders and general medical disorders are in agreement with published literature, except for adult-onset of seasonal allergies, which is a novel result (Kessler et al., 2010; Stein et al., 2010; Scott et al., 2011; Vallerand et al., 2019; Spitzer et al., 2013). Not only events were studied sequentially, considering only adult-onset mental

Table 4

Association of maladaptive family functioning childhood adversities and comorbid mood and general medical disorders.

| | OR | 96% CI | p-value |
|------------------------------------|-----|---------|---------|
| I. Hypertension | | | |
| Only mood disorder | 1.7 | 1.3–2.3 | <0.001 |
| Only hypertension | 1.5 | 1.2–2.0 | 0.001 |
| Mood disorder & hypertension | 2.1 | 1.3–3.4 | 0.002 |
| II. Arthritis | | | |
| Only mood disorder | 1.5 | 1.1–2.0 | 0.006 |
| Only arthritis | 1.2 | 0.9–1.7 | 0.3 |
| Mood disorder & arthritis | 2.5 | 1.5–4.2 | <0.001 |
| III. Seasonal allergies | | | |
| Only mood disorder | 1.8 | 1.3–2.4 | <0.001 |
| Only seasonal allergies | 1.8 | 1.3–2.5 | 0.001 |
| Mood disorder & seasonal allergies | 1.6 | 0.9–2.9 | 0.1 |

OR: odds ratio; CI: confidence interval.

Multinomial regression analyses were adjusted for age at interview, gender, employment status, income category, marital status and years of education.

and general medical disorders, also analyses were adjusted for the presence of child and adolescent psychopathology (often neglected in published literature) as well as several adult sociodemographic characteristics, known to be correlated with poor health outcomes in adults exposed to childhood adversities (Kessler et al., 2010; Mock and Arai, 2010). Importantly, associations were estimated simultaneously, thus confirming that childhood adversities are widely associated with increased adult morbidity, with comparable odds-ratios of association across diverse illnesses. This result is consistent with current multiple-hit models of complex human disorders, and highlights childhood adversity as a potential preventable cause of adult morbidity (Coelho et al., 2014).

Regarding the sequential occurrence of mood disorders and general medical disorders, we observed that among the general medical disorders associated with maladaptive family functioning, mood disorders predated the diagnosis of arthritis and seasonal allergies. This raises the possibility for a common pathway of vulnerability, linking maladaptive family functioning to arthritis and/or seasonal allergies, through the occurrence of mood disorders. Adult-onset hypertension, also linked to maladaptive family functioning, was significantly associated with subsequent mood disorders, suggesting, in this case, a pathway where stress in childhood precedes the onset of hypertension during adulthood, that may then be a risk factor for subsequent occurrence of mood disorders. Taking these results into account, we tested the hypothesis that maladaptive family functioning would increase the likelihood of comorbidity between mood disorders and general medical disorders. While maladaptive family functioning did not increase the risk of comorbidity with seasonal allergies, the likelihood of comorbid adult-onset mood disorders and hypertension, as well as mood disorders and arthritis, were significantly increased. However, only for arthritis, but not hypertension, association with the comorbid diagnoses was stronger than that for non-comorbid diagnoses, namely arthritis-only. Of remark, a meta-analysis of prospective studies (Gao et al., 2015) provided evidence to support that depression is associated with a 43% increased hazard of developing adult-onset asthma, but not of the reverse association. Also, recent meta-analyses suggest a bidirectional association between depression and cardiovascular disorders (Hare et al., 2014). Several reasons may underlie the fact that these findings were not replicated in this dataset, among them limitations in the ability to fully ascertain general medical disorders, due to the nature of the CIDI questionnaire, as well as real differences that are particular to the population analysed in this study. Furthermore, our survival analyses were adjusted to several socio-demographic variables that potentially mediate these associations, and the restriction of analyses to adult first-onset of all of these diagnoses may also have an impact.

The fact that maladaptive family functioning was associated with adult-onset mood disorders with or without comorbid arthritis, but not with adult-onset arthritis without a comorbid mood disorder, is of particular interest. This is consistent with the finding that adult-first onset of a mood disorder was associated with subsequent onset of arthritis, but that the reverse was not true. In fact, immune dysfunction is a possible contributor to the aetiopathogenesis of major depressive disorder and bipolar disorder, which is supported by studies demonstrating that peripheral C-reactive protein and cytokines such as IL-6 are increased in patients when compared with controls (Oliveira et al., 2018). Arthritis, in the other hand, is a well-known chronic inflammatory disease, also characterized by up-regulation of C-reactive protein and cytokines such as IL-6, probably due to dysfunctional innate and adaptive immunity, that start long before the onset of detectable joint inflammation (Demoruelle et al., 2014). Moreover, childhood adversities have been consistently associated with increased C-reactive protein and other peripheral markers of inflammation in adults, thus being a candidate early primer of persistent immune dysfunction in adults (Coelho et al., 2014). Shared mechanistic pathways involving the immune system thus seem biologically plausible. However, this particular association between childhood adversities and comorbid mood disorders and arthritis, but not other chronic conditions, may in fact be due to promotion of dysfunction

of a specific biological pathway. One hypothesis is dysregulation of IL6 signalling, a pivotal pathway implicated in the pathogenesis of arthritis, that may be involved in the development of depressive symptoms in these patients (Li et al., 2019; Favalli, 2020). Interestingly, IL6 has been shown not only to be increased in adults exposed to childhood adversity and to play an important role in stress response but also to be increased in patients with mood disorders in whom it is associated with worst prognosis and therapeutic response (Tursich et al., 2014; Carpenter et al., 2010; Osimo et al., 2020; Ting et al., 2020). It remains however uncertain if childhood adversity acts through disruption of this or other additional inflammatory pathways or even if this association is restricted to arthritis or widens to other chronic inflammatory disorders.

Our findings are consistent with recent evidence that depressive episodes predate the onset of arthritis and are associated with a more detrimental disease outcome (Vallerand et al., 2019; Egede, 2008). However, the hypothesis that depression may be associated with inflammation in the pre-articular phase of arthritis has not been explored. Moreover, childhood adversities, and mood disorders themselves, may also mediate behavioural causal pathways towards arthritis, for example by interfering with coping mechanisms and through lifestyle-related factors (Vallerand et al., 2019; Miller et al., 2011). Finally, a potential contributor to the association between childhood adversity, depression and arthritis, may be pain. Childhood adversities are associated with the subsequent development of chronic pain, following a dose-response relationship (Stickley et al., 2015; Edwards et al., 2016). Moreover, among individuals with a current physical condition, those exposed to childhood abuse report more pain, independently of depression, which suggests the existence of biological mechanisms linked to pain perception or to the pathophysiology of the disorder itself (Sachs-Ericsson et al., 2007). It is also known that chronic pain is an independent contributor to the association between medical illnesses and depression, which also suggests that, in addition to inflammation, long-standing pain predating the diagnosis of arthritis may be an important factor to consider in the present results (Sharpe et al., 2017).

On the other hand, prior evidence that arthritis may be a risk factor for mood disorders, thus establishing a bidirectional relationship between the two, was not reproduced in our study (Vallerand et al., 2019). While the data collected here is insufficient to clarify the reasons for this negative finding, several reasons can be pointed out: i) the benefits achieved with targeted immune therapies for arthritis, not only for articular disease but potentially also on depression by also targeting inflammation-related depression; ii) the statistical analyses were adjusted for several sociodemographic factors such age, sex, marital status, income and education level; iii) the diagnoses of arthritis in this survey is self-reported and does not necessarily differentiate between rheumatoid arthritis and osteoarthritis which are governed by distinct mechanisms (Martel-Pelletier et al., 2016; Smolen et al., 2018; Kappelmann et al., 2018).

When analyses were performed for anxiety disorders, we found that they are associated with maladaptive family functioning as well as with other childhood adversities, with similar odds ratios. However, anxiety disorders were not associated with subsequent diagnosis of any of the studied general medical disorders, suggesting that the described association between mood disorders and arthritis are specific. Besides the well-known association between inflammation and depression or anxiety, in agreement with this finding, recent evidence suggests that specific inflammatory and metabolic changes are associated with depression, and discriminate these patients from those diagnosed with anxiety disorders (Osimo et al., 2020; Zou et al., 2020; de Kluiver et al., 2021; Costello et al., 2019). Interestingly, adult-onset hypertension was associated with subsequent anxiety disorders, which is in accordance with the existing literature (Grimsrud et al., 2009). However, we did not confirm the opposite association, which is more often discussed in literature, possibly due to adjustment to several sociodemographic factors and/or because child and adolescent onset of anxiety disorders were not considered in

the analysis (Pan et al., 2015). In this respect, it is noteworthy that early-onset anxiety disorders have been particularly well-associated with later onset of hypertension (Stein et al., 2010, 2014). Moreover, the fact that, in our study, maladaptive family functioning had, in adults, a more significant effect on the anxiety-hypertension comorbidity than on the diagnosis of hypertension only, suggests that early exposure to psychosocial stress may pave the way towards this comorbidity through common pathways, such as alterations in sympathoadrenal, neurotransmitter or inflammatory activities (Pan et al., 2015).

The study results should, nevertheless, be interpreted in the context of the study design. Specifically, while we evaluated a wide range of childhood adversities on a large population-representative sample, collection of data regarding childhood bullying was not performed, despite its association with adult inflammation (Copeland et al., 2014). Moreover, sensitivity to stress derived from objective and subjective ratings of its severity, a measure currently being adopted as a reliable stress-related variable, should be included in future studies (Ho et al., 2017). Furthermore, besides potential limitations of the WMH-CIDI in accurately establishing psychiatric diagnoses, like in many epidemiological studies, the WMH-CIDI was administered by lay people, which may negatively impact the reliability and concordance of the diagnosis of mental disorders (Trinh and Chen, 2019). In what concerns the diagnosis of general medical disorders, the age at onset of mental and general medical disorders and the occurrence of childhood adversities, information is based on retrospective self-reports, rather than clinical records or other equivalent documents, and thus may be subject to recall bias (Silman et al., 2018). Also, the WMH-CIDI is limited in the number of chronic conditions evaluated, which restricts the current analysis to the existing information. In this regard, and in view of the present results, future epidemiological studies should explore a wider range of chronic immune-related disorders, such as for example, other allergies, inflammatory bowel diseases or multiple sclerosis. Furthermore, some diagnoses lack specificity, such as the case of asthma, which does not allow for the distinction between allergic and other causes, as well as arthritis, that does not allow for the distinction between rheumatoid arthritis and osteoarthritis, clearly with distinct etiologies. Moreover, in order to test the hypothesis that childhood adversity is associated with comorbid mood and general medical disorders that are related to immune and/or metabolic mechanisms, other physical conditions were not included in the analysis, which precludes conclusions regarding other disease outcomes and exploration of other potentially relevant pathways. Finally, measurement of body mass index across time should be considered as an important variable in longitudinal comorbidity studies, as it can be associated with childhood adversities and some mood and general medical disorders. While weight and height have been registered at one time point, i.e., at inclusion, this variable could not be selected for the current analysis due to several reasons: i) this measure of body mass index can be several years or decades distant from the onset of the mood and general medical disorders studied, providing no reliable information on its true temporal relationship with the development of these conditions; ii) the possibility that obesity precedes the occurrence of childhood adversities themselves cannot be excluded; iii) information regarding current weight and height is not informative on its trajectory meaning that normal current body mass index does not exclude the possibility that individuals had obesity in the past.

For futures studies, even though a reliable trauma-related marker has not yet been identified, having supplementary biological data (e.g., markers of inflammation) could help narrow the “arthritis-related” mood disorder phenotype. Future studies should also widen the spectrum of general medical disorders, including obesity, to further explore the possibility of a specific increase of comorbidity between mood and inflammatory disorders in relation to exposure to childhood adversities. In this regard, finally, it would be worthy to account for the effect of treatments, including psychological, anti-inflammatory and others, as they may become relevant therapeutic targets.

In conclusion, childhood adversities are highly prevalent and a shared

risk factor for the adult-onset of psychiatric and non-psychiatric disorders, namely mood and anxiety disorders, hypertension, arthritis and seasonal allergies. Maladaptive family functioning may be a specific risk factor for comorbid mood disorders and arthritis and comorbid anxiety disorders and hypertension. Future research should explore the shared mechanisms in their aetiology, as childhood adversity may represent a preventable cause of morbidity.

Declaration of competing interest

AJO-M was national coordinator for Portugal of a non-interventional study (EDMS-ERI-143085581, 4.0) to characterize a Treatment-Resistant Depression Cohort in Europe, sponsored by Janssen-Cilag, Ltd (2019–2020), is recipient of a grant from Schuhfried GmbH for norming and validation of cognitive tests, and is national coordinator for Portugal of trials of psilocybin therapy for treatment-resistant depression, sponsored by Compass Pathways, Ltd (EudraCT number 2017-003288-36 and 2020-001348-25), and of esketamine for treatment-resistant depression, sponsored by Janssen-Cilag, Ltd (EudraCT NUMBER: 2019-002992-33). The remaining authors declare that they have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbih.2021.100329>.

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