



Population-attributable risk of adverse childhood experiences for high suicide risk, psychiatric admissions, and recurrent depression, in depressed outpatients

Sergio Gloger ^{a,b,c}, Pablo Martínez ^{a,c,d,e,f,g}, Alex Behn ^{c,h}, M. Victoria Chacón ^{a,c}, Marianne Cottin ^{c,h,i,j}, Dante Diez de Medina ^a and Paul A. Vöhringer ^{a,c,d,k,l}

^aPsicomédica, Clinical & Research Group, Santiago, Chile; ^bDepartamento de Psiquiatría y Salud Mental Campus Oriente, Facultad de Medicina, Universidad de Chile, Santiago, Chile; ^cANID, Millennium Science Initiative Program, Millennium Institute for Depression and Personality Research (MIDAP), Santiago, Chile; ^dDepartamento de Psiquiatría y Salud Mental, Hospital Clínico Universidad de Chile, Santiago, Chile; ^eANID, Millennium Science Initiative Program, Millennium Nucleus to Improve the Mental Health of Adolescents and Youths, Imhay, Santiago, Chile; ^fEscuela de Psicología, Facultad de Humanidades, Universidad de Santiago de Chile, Santiago, Chile; ^gCITIAPS, Universidad de Santiago de Chile, Santiago, Chile; ^hEscuela de Psicología, Pontificia Universidad Católica de Chile, Santiago, Chile; ⁱFacultad de Medicina, Universidad de Chile, Santiago, Chile; ^jEscuela de Psicología, Universidad Finis Terrae, Santiago, Chile; ^kMood Disorders Program, Tufts Medical Center, Boston, MA, USA; ^lDepartment of Psychiatry, Tufts University School of Medicine, Boston, MA, USA

ABSTRACT

Background: Population-attributable risk (PAR) may help estimate the potential contribution of adverse childhood experiences (ACEs) to serious clinical presentations of depression, characterized by suicidality, previous psychiatric admissions, and episode recurrence.

Objective: To determine the PAR of ACEs for serious clinical presentations of depression (high suicide risk, previous psychiatric admissions, and recurrent depression) in outpatients with ICD-10 clinical depression.

Method: Systematic chart review of 1,013 adults who were assessed and/or treated in a mental health clinic in Santiago, Chile for a major depressive episode. Data were collected on demographics and clinical characteristics of depression. Exposure to ACEs was determined with the Brief Physical and Sexual Abuse Questionnaire, assessing seven types of ACEs. Multivariable logistic regression analysis was used to assess the association between exposure to ACEs and suicidality, previous psychiatric admissions, and recurrence. Predicted probabilities were used for calculations of PAR.

Results: Of the 1,001 study participants with complete data, 53.3% had recurrent depression, 13.5% had high suicide risk, and 5.0% had previous psychiatric admissions. Exposure to at least one ACE was recorded for 69.0% of the sample. Exposure to at least one ACE and specific types of ACEs (i.e. childhood sexual abuse and traumatic separation from caregiver) were associated with serious clinical presentations of depression. A dose-response relationship was observed between cumulative exposure to ACEs and the most serious clinical presentations of depression. ACEs were attributed to a significant proportion of disease: 61.6% of previous psychiatric admissions, 45.0% of high suicide risk, and 14.5% of recurrent depression.

Conclusions: A substantial proportion of serious clinical presentations of depression among outpatients are associated with ACEs. Early detection of depressive episodes associated with ACEs, and tailored treatment for these patients, may potentially reduce the incidence of serious complications in this population.

Riesgo atribuible poblacional de experiencias adversas infantiles para alto riesgo suicida, hospitalizaciones psiquiátricas, y depresión recurrente, en pacientes deprimidos ambulatorios

Introducción: El riesgo atribuible poblacional (RAP) puede ayudar a estimar la potencial contribución de las experiencias adversas infantiles (EAI) a las presentaciones clínicas serias de la depresión, caracterizadas por riesgo suicida, hospitalizaciones psiquiátricas previas y recurrencia de episodios.

Objetivo: Determinar el RAP de las EAI para las presentaciones clínicas serias de la depresión (alto riesgo suicida, hospitalizaciones psiquiátricas previas y depresión recurrente) en pacientes deprimidos ambulatorios.

Método: Revisión sistemática de fichas clínicas de 1.013 adultos que fueron evaluados y/o tratados en una clínica de salud mental en Santiago, Chile por un episodio depresivo mayor. Se recolectaron datos demográficos y sobre características clínicas de la depresión. La exposición a EAI se determinó con el Brief Physical and Sexual Abuse Questionnaire, evaluándose siete tipos de EAI. Se usó análisis de regresión logística multivariada para evaluar la asociación entre exposición a EAI y riesgo suicida, hospitalizaciones psiquiátricas previas y recurrencia. Las probabilidades predichas fueron utilizadas para los cálculos de los RAP.

ARTICLE HISTORY

Received 11 February 2020
Revised 30 December 2020
Accepted 5 January 2021

KEYWORDS

Child abuse; major depressive disorder; affective disorders; psychiatric admissions; suicidal ideation; population attributable fraction

PALABRAS CLAVE

abuso infantil; trastorno depresivo mayor; trastornos afectivos; hospitalizaciones psiquiátricas; fracción atribuible poblacional

关键词

儿童虐待; 重度抑郁; 情感障碍; 精神病性住院; 自杀意念; 人口归因分数

HIGHLIGHTS

- In a sample of 1,001 depressed outpatients in Santiago, Chile, and according to population-attributable risk calculations, adverse childhood experiences contributed to nearly half of cases with high suicide risk and almost two thirds of those with previous psychiatric admissions.

Resultados: De 1.001 participantes del estudio con datos completos, 53,3% tuvieron una depresión recurrente, 13,5% tuvieron alto riesgo suicida, y 5,0% tuvieron hospitalizaciones psiquiátricas previas. La exposición a al menos un EAI se registró en 69,0% de la muestra. La exposición a al menos un EAI y tipos específicos de EAIs (i.e. abuso sexual infantil y la separación traumática del cuidador), se asociaron con presentaciones clínicas serias de la depresión. Se observó una relación dosis-respuesta entre la exposición acumulativa a EAIs y las presentaciones clínicas más serias de la depresión. Las EAIs se atribuyeron una proporción significativa de la enfermedad: 61,6% de las hospitalizaciones psiquiátricas previas, 45,0% del alto riesgo suicida, y 14,5% de depresión recurrente.

Conclusiones: Una proporción sustancial de presentaciones clínicas serias de la depresión en pacientes deprimidos ambulatorios se asocian con EAIs. La detección temprana de los episodios depresivos asociados con EAIs y el tratamiento a la medida para estos pacientes podrían potencialmente reducir la incidencia de complicaciones serias en esta población.

抑郁门诊患者的童年期不良经历对于高自杀风险, 精神病性住院和复发性抑郁的人群归因危险度

背景: 人群归因危险度 (PAR) 可能有助于估计童年期不良经历 (ACE) 对以自杀, 先前的精神病性住院和发作复发为特征的严重抑郁临床表现的潜在作用。

目的: 在ICD-10临床抑郁患者中确定ACEs对于严重抑郁临床表现 (高自杀风险, 既往精神病性住院和复发性抑郁) 的 PAR。

方法: 系统图表综述了1,013名在一家智利圣地亚哥心理健康诊所接受评估和/或治疗的成人的重症抑郁发作。收集了人口统计学和抑郁相关临床特征的数据。通过简短版身体和性虐待问卷确定了ACE暴露情况, 评估了七类ACE。多变量逻辑回归分析用于评估ACEs暴露与自杀, 先前的精神病性住院和复发之间的关联。预测的概率用于计算PAR。

结果: 在1001名有完整数据的研究参与者中, 53.3%有复发性抑郁, 13.5%具有高自杀风险, 5.0%有既往精神病性住院。记录到样本中69.0%至少暴露于一种ACE。至少有一种ACE暴露且为特定类型的ACEs (即童年期性虐待和与照顾者的创伤性分离) 与严重抑郁临床表现有关。观察到ACEs的累积暴露与最严重的抑郁临床表现之间存在剂量反应关系。疾病很大一部分被归因于ACEs:既往精神病性住院的61.6%, 高自杀风险的45.0%, 复发性抑郁的14.5%。

结论: 门诊患者中很大比例的严重抑郁临床表现与ACEs有关。对ACEs相关抑郁发作的早期识别, 以及针对这些患者量身定制的治疗, 可能会降低该人群严重并发症的发生率。

1. Introduction

Adverse childhood experiences (ACEs) are prevalent in individuals with depression. For instance, a meta-analysis of 46 studies found that 45.6% of individuals with depression reported any exposure to ACEs (Nelson, Klumparendt, Doebler, & Ehring, 2017). Up to 40% of cases of depression in high-income countries might be attributable to exposure to ACEs (Bellis et al., 2019), thus supporting the association between early traumatic events and adult psychopathology (Nemeroff, 2016; Putnam, Harris, & Putnam, 2013). Patients with depression who were exposed to ACEs are at risk for serious clinical presentations, including chronic treatment-resistant depressive episodes and suicide attempts throughout their lives (Dube et al., 2001; Fuller-Thomson, Baird, Dhrodia, & Brennenstuhl, 2016; Nanni, Uher, & Danese, 2012; Nelson et al., 2017; Tokuda et al., 2018). ACEs might also be partly responsible for the higher health care costs and poorer functional outcomes in severely depressed populations (Ekman, Granström, Omérov, Jacob, & Landén, 2013; Johnston, Powell, Anderson, Szabo, & Cline, 2019; Kraus, Kadriu, Lanzenberger, Zarate, & Kasper, 2019).

The Latin American population is among the most affected by depressive disorders and child abuse and neglect worldwide (Viola et al., 2016; World Health

Organization, 2017), though the impact of ACEs upon serious clinical presentations of depression in this region have been poorly studied to date. Research conducted in Chile and Brazil has demonstrated that depression severity might be related to the extent of exposure to ACEs (Novelo et al., 2018; Vitriol, Cancino, Ballesteros, Potthoff, & Serrano, 2017), in line with the cumulative risk hypothesis. According to this hypothesis, the deleterious developmental effects of the accumulation of childhood adversities follow a dose-response relationship, with higher exposure leading to greater clinical and social problems over the lifespan (Appleyard, Egeland, van Dulmen, & Sroufe, 2005; Charak et al., 2016; Dube et al., 2001). However, some types of ACEs might be more 'toxic' than others (Charak, Tromp, & Koot, 2018), as noted by Novelo et al.'s (2018), who found that emotional abuse had a more severe influence on depressive symptoms, in comparison to other ACEs.

The population-attributable risk (PAR) might be a particularly useful measure for evaluating the precise impact of ACEs in patients with serious clinical presentations of depression. PAR quantifies the burden of disease attributable to a certain risk factor in a population and, in this sense, can be viewed as the potentially preventable proportion of disease – if risk factors are controlled – which means that is an important indicator for prioritizing the potential impact of

public health policies (Northridge, 1995). PAR differs from traditional measures of effect size, such as odds ratios, that are commonly used to estimate the magnitude of associations between ACEs and major depression (see meta-analyses by Nanni et al. [2012] and Nelson et al. [2017]). To our knowledge, no previous study has explored to what extent serious clinical presentations of depression, such as recurrence, suicidal ideation, and history of psychiatric admissions, might be attributed to ACEs exposure.

In light of the cumulative, long-lasting, and deleterious effects of ACEs on physical and mental health (Appleyard et al., 2005; Charak et al., 2016; Dube et al., 2001; Nemeroff, 2016), the main objective of the current study is to determine the PAR of ACEs for high suicide risk, previous psychiatric admissions and recurrent depression in outpatients with ICD-10 clinical depression. We hypothesize that a significant proportion of cases of serious clinical presentations of depression are attributed to ACEs. Additionally, we expect to find that: (1) exposure to ACEs will be significantly higher in patients with most serious clinical presentations of depression; (2) specific types of ACEs will be differentially associated with serious clinical presentations; and (3) a dose-response relationship between higher rates of ACEs exposure and more serious clinical presentations of depression will be observed.

2. Methods

2.1. Study sample

A systematic chart review was carried out, with information from a sample of 1,013 adult outpatients between the ages of 18 and 85 years, who met ICD-10 criteria for a major depressive episode (World Health Organization, 2004), and who were assessed and/or treated for depression at a mental health clinic in Santiago, Chile, from 2013 to 2014. Semi-structured diagnostic interviews and follow-up visits for the treatment of depression were conducted by psychiatrists and physicians with mental health training, as part of their usual clinical practice. Data extraction from the clinical charts was performed by a trained clinical psychologist (MC), with the assistance of a standardized data extraction form and subsequent quality assurance checks carried out by the rest of the research team. The Institutional Review Board of Psicomédica, Clinical & Research Group, approved the study. Since this study involved the use of existing and de-identified data, informed consent requirement was waived.

2.2. Measures

Measures of serious clinical presentations of depression were chosen. Suicidality, especially high suicide

risk, has been extensively recognized as a strong predictor of poor prognosis and serious clinical presentations of depression (Dold et al., 2018). Similarly, psychiatric admissions – a reliable and objective outcome – are robustly associated with poor prognosis and complex illness trajectories (BALANCE investigators and collaborators et al., 2010). Finally, current evidence suggests that the recurrence of mood episodes is also closely related to prognosis (Ghaemi, 2019; Goodwin, Jamison, & Ghaemi, 2007).

On this basis, the following measures were obtained from the clinical charts:

2.2.1. High suicide risk

Suicidality was determined by using the total score of the suicidality module of the Mini International Neuropsychiatric Interview (MINI), Spanish version 5.0.0 (Bobes, 1998), with scores above 9 indicating high suicide risk. The MINI is a valid, reliable, and short structured diagnostic interview, based on the DSM-IV and ICD-10 criteria (Sheehan et al., 1998).

2.2.2. Previous psychiatric admissions

Prior psychiatric hospitalizations were registered through a series of questions ('Have you ever been admitted to a psychiatric hospital/unit?', 'How many times have you been admitted to a psychiatric hospital/unit?', and 'The last time you were admitted, how many days or months were you hospitalized?').

2.2.3. Recurrent depression

Recurrent courses of depression were assessed according to ICD-10 criteria for recurrent depressive disorder (World Health Organization, 2004).

Additionally, the following measures were also recorded from the clinical charts, per study objectives:

2.2.4. Adverse childhood experiences (ACEs)

Exposure to ACEs was determined with the Brief Physical and Sexual Abuse Questionnaire (BPSAQ) developed by Marshall et al. (2000), a brief screening interview that has been validated and previously used in Chilean mental health settings (Cuneo et al., 2005; Weil et al., 2004). The BPSAQ assesses exposure to seven types of ACEs: (1) traumatic separation from one's father, mother, and/or primary caregiver for more than 1 month; (2) experiences of harsh physical punishment; (3) physical injury resulting from harsh punishment; (4) witnessing physical violence between parents and/or caregivers; (5) having a family member with substance abuse issues at the home; (6) forced sexual contact with a relative; and (7) forced sexual contact with a non-relative.

2.2.5. Demographics

Sex (male/female), age (in years) at the time of the clinical interview, and occupation (i.e. employed,

housekeeper, student, unemployed, independent, or retired), as registered in the clinical charts, were also considered for the analyses.

2.3. Statistical approach

To conduct a first exploratory analysis, the study sample was stratified into three groups by clinical presentation of depression, based on the presence/absence of high suicide risk, previous psychiatric admission, and/or recurrent depression. Thus, the 'least-serious' comparison group had none of the above characteristics, 'serious' cases had one of these characteristics, and the 'most serious' group possessed two or more of these attributes. Arithmetic means (M) and standard deviations (SD) were reported for continuous variables, and frequencies (n) with their respective percentages (%) for dichotomous or categorical variables. Features of the stratified study sample were compared using one-way analysis of variance for continuous variables, and Chi χ^2 or Fisher's exact tests for binary variables.

Multivariable logistic regression analyses were conducted to assess the magnitude of the association between exposure to ACEs and features of serious clinical presentations of depression. Main predictors reflected the following types of exposures to ACEs: (1) at least one ACE; (2) specific types of ACEs, testing the differential importance of each type of ACEs; and (3) cumulative exposure to ACEs, using a 0- to 7-point range to evaluate the presence of a possible dose-response relationship. With regards to the last exposure, and in accordance with a threshold effect model of cumulative risk (Appleyard et al., 2005; Dube et al., 2001), we partitioned ACEs scores into three groups to reflect no exposure ('0'), mild to moderate exposure ('1 to 3'), and severe exposure ('4 to 7') to childhood adversities. The three previously presented clinical markers of serious presentations of depression – high suicide risk, previous psychiatric admissions, and recurrent depression – were the considered outcomes. Additionally, we tested whether there was a dose-response relationship between ACEs score and the 'most serious' (vs. 'serious' or 'least-serious') clinical presentations of depression. Statistically significant demographic covariates were selected through stepwise regression. Further adjustments for all types of ACEs were carried out by testing the differential importance of each type of ACEs. Multivariable-adjusted odds ratios (aORs) were used as effect size measures, with their respective 95% CIs.

Finally, to estimate the proportion of depressed cases with serious clinical presentations that might be attributed to different ACEs exposures, multivariable-adjusted predicted probabilities from the previously fitted logistic regression models were used for to

calculate PAR (and 95% CI), in line with a current Stata's user written package agreement for estimating scenario means and comparisons (Newson, 2013). All the analyses were performed with the statistical software Stata 14 (StataCorp, 2015). The data set is publicly available at <https://osf.io/ux2e5>.

3. Results

3.1. Clinical characteristics of the study sample

As the proportion of missing data was negligible (1.2%, $n = 12$), all calculations were done with the sample of users with no missing data ($n = 1,001$). Of the 1,001 study participants, 53.3% ($n = 533$) had experienced recurrent depression, 13.5% ($n = 135$) had high suicide risk, and 5.0% ($n = 50$) had previous psychiatric admissions. Characteristics of study participants in terms of clinical presentation of depression (least serious, serious, and most serious) are shown in Table 1. Men were less likely to have serious and most serious clinical presentations of depression ($\chi^2[1] = 19.0$, $p < .001$, and $\chi^2[1] = 5.4$, $p = .020$, respectively). Unemployment rates were higher ($\chi^2[1] = 6.5$, $p = .011$) in patients with the most serious clinical presentation of depression.

3.2. Adverse childhood experiences

In the study sample, 69.0% ($n = 691$) had at least one ACE, and the ACEs score had a mean of 1.4 (SD = 1.4). As per specific types of ACEs, the most common ACEs were having a family member with substance abuse issues at home (32.5%, $n = 325$), a traumatic separation from one's father, mother, and/or primary caregiver for more than 1 month (30.5%, $n = 305$), witnessing physical violence between parents and/or caregivers (29.6%, $n = 296$), and experienced harsh physical punishment (29.6%, $n = 296$). Table 1 also reports detailed information about the clinical presentation of depression for each of the studied ACEs exposures. Analysis of χ^2 tests for between group comparisons showed that those most-serious clinical presentation of depression were more likely of having had the following types of ACEs exposures: (1) a traumatic separation from their primary caregiver for more than 1 month ($\chi^2[1] = 13.4$, $p < .001$, and $\chi^2[1] = 6.5$, $p = .011$, respectively); (2) hard physical punishment ($\chi^2[1] = 11.7$, $p = .001$, and $\chi^2[1] = 8.0$, $p = .005$, respectively); (3) physical injury resulting from harsh punishment ($\chi^2[1] = 8.4$, $p = .004$, and $\chi^2[1] = 11.1$, $p = .001$, respectively); and (4) forced sexual contact with a non-relative ($\chi^2[1] = 23.5$, $p < .001$, and $\chi^2[1] = 28.0$, $p < .001$, respectively). There was a graded relationship between the levels of seriousness of clinical presentations of depression and having had at least one ACE (non-serious vs. serious clinical presentations of

Table 1. Characteristics of study participants stratified by clinical presentation of depression ($n = 1,001$).

Characteristic	Least serious [†]	Serious [‡]	Most serious [§]	P-values [§]
	($n = 418$)	($n = 466$)	($n = 117$)	
	N (%) / mean (SD)	N (%) / mean (SD)	N (%) / mean (SD)	
Age, mean (SD)	39.3 (12.8)	42.0 (12.7)	39.1 (11.9)	.002
Male	171 (40.9)	126 (27.0)	34 (29.1)	< .001
<i>Occupation</i>				
Employed	324 (77.5)	343 (73.6)	77 (65.8)	.033
Housekeeper	38 (9.1)	58 (12.5)	17 (14.5)	.145
Student	35 (8.4)	26 (5.6)	12 (10.3)	.119
Unemployed	9 (2.2)	21 (4.5)	8 (6.8)	.035
Independent	7 (1.7)	12 (2.6)	3 (2.6)	.619
Retired	5 (1.2)	6 (1.3)	0 (0.0)	.694
<i>ACEs exposures</i>				
At least one ACE	260 (62.2)	331 (71.0)	100 (85.5)	< .001
Traumatic separation from caregiver, 1+ month	109 (26.1)	145 (31.1)	51 (43.6)	.001
Harsh physical punishment	95 (22.7)	118 (25.3)	45 (38.5)	.003
Physical injury from harsh punishment	36 (8.6)	36 (7.7)	21 (18.0)	.002
Witnessing violence between caregivers	118 (28.2)	140 (30.0)	38 (32.5)	.642
Family member with substance abuse	128 (30.6)	151 (32.4)	46 (39.3)	.207
Forced sexual contact, relative	32 (7.7)	55 (11.8)	22 (18.8)	.002
Forced sexual contact, non-relative	21 (5.0)	21 (4.5)	22 (18.8)	< .001
ACEs score, mean (SD)	1.3 (1.4)	1.4 (1.4)	2.1 (1.7)	< .001

Abbreviations: ACEs, adverse childhood experiences.

[†]Least serious clinical presentation of depression defined as the absence of recurrent depression, high suicide risk, and previous psychiatric admissions.

[‡]Serious clinical presentation of depression defined as having one of the following characteristics: recurrent depression, high suicide risk, and previous psychiatric admissions.

[§]Most serious clinical presentation of depression defined as having two or more of the following characteristics: recurrent depression, high suicide risk, and previous psychiatric admissions.

[§]P-values for χ^2 test for categorical variables – Fisher's exact test used when at least one cell had a value less than 5 – and one-way analysis of variance for continuous variables.

depression: $\chi^2[1] = 7.8$, $p = .005$; serious vs. most-serious clinical presentations of depression: $\chi^2[1] = 10.1$, $p = .001$, or, specifically, having had forced sexual contact with a relative (non-serious vs. serious clinical presentations of depression: $\chi^2[1] = 4.3$, $p = .039$; serious vs. most-serious clinical presentations of depression: $\chi^2[1] = 4.0$, $p = .046$).

3.3. Association of adverse childhood experiences and recurrent depression, high suicide risk, and previous psychiatric admissions

Tables 2–4 show the association of ACEs and features of serious clinical depression (recurrent depression,

high suicide risk, and previous psychiatric admissions) before and after adjustment for covariates. In adjusted models, it was observed that exposure to at least one ACE increased the likelihood of having a recurrent depression by 57%, high suicide risk by 125%, and previous psychiatric admissions by more than 3-fold.

Regarding specific types of ACEs, having had a traumatic separation from one's father, mother, and/or primary caregiver for more than 1 month, and having been a victim of forced sexual contact (either with a relative or non-relative), independently contributed to an elevated risk of having serious clinical presentations of depression in adulthood (Tables 2–4).

Table 2. Associations between exposure to ACEs and recurrent depression; unadjusted and adjusted estimates, with population-attributable risk for adjusted estimates ($n = 1,001$).

Exposure	Unadjusted estimates [†]	Adjusted estimates [‡]	Population-attributable risk (%)
At least one ACE	1.57 (1.20, 2.06)	1.60 (1.21, 2.12)	14.5 (5.4, 22.7)
Specific types of ACEs[§]			
Traumatic separation from caregiver, 1+ month	1.40 (1.07, 1.84)	1.42 (1.07, 1.89)	4.7 (0.8, 8.4)
Harsh physical punishment	1.33 (1.00, 1.78)	1.36 (0.94, 1.97)	3.5 (−0.7, 7.5)
Physical injury from harsh punishment	1.07 (0.70, 1.65)	0.74 (0.44, 1.25)	−1.2 (−3.3, 0.9)
Witnessing violence between caregivers	1.09 (0.83, 1.43)	0.94 (0.67, 1.25)	−0.8 (−5.2, 3.3)
Family member with substance abuse	1.16 (0.89, 1.51)	1.09 (0.80, 1.47)	1.2 (−3.2, 5.4)
Forced sexual contact, relative	1.52 (1.01, 2.29)	1.29 (0.84, 1.98)	1.2 (−0.8, 3.2)
Forced sexual contact, non-relative	1.50 (0.89, 2.53)	1.36 (0.79, 2.34)	0.8 (−0.6, 2.3)
Cumulative exposure to ACEs			
No ACEs (0)			
Mild to moderate exposure to ACEs (1–3)	1.54 (1.17, 2.03)	1.58 (1.19, 2.11)	14.5 (5.4, 22.7)
Severe exposure to ACEs (4 or more)	1.77 (1.14, 2.76)	1.70 (1.08, 2.69)	-

Abbreviations: ACEs, adverse childhood experiences.

[†]Unadjusted odds ratios with their 95% confidence intervals.

[‡]Adjusted odds ratios with their 95% confidence intervals. All models were adjusted by sex, age, and occupation.

[§]Model adjusted by sex, age, occupation, and all types of ACEs.

Table 3. Associations between exposure to ACEs and high suicide risk; unadjusted and adjusted estimates, with population-attributable risk for adjusted estimates ($n = 990$).

Exposure	Unadjusted estimates [†]	Adjusted estimates [‡]	Population-attributable risk (%)
At least one ACE	2.25 (1.42, 3.58)	2.48 (1.53, 4.00)	45.0 (22.0, 61.3)
Specific types of ACEs[§]			
Traumatic separation from caregiver, 1+ month	1.52 (1.04, 2.21)	1.38 (0.93, 2.06)	8.6 (−3.0, 18.9)
Harsh physical punishment	1.72 (1.17, 2.52)	1.42 (0.86, 2.37)	8.5 (−4.5, 19.8)
Physical injury from harsh punishment	2.22 (1.32, 3.73)	1.87 (0.97, 3.62)	6.1 (−0.8, 12.5)
Witnessing violence between caregivers	0.96 (0.64, 1.43)	0.70 (0.43, 1.14)	−9.4 (−23.2, 2.8)
Family member with substance abuse	1.03 (0.70, 1.52)	0.98 (0.63, 1.53)	−0.5 (−13.2, 10.8)
Forced sexual contact, relative	2.50 (1.56, 4.02)	2.33 (1.40, 3.87)	9.8 (2.8, 16.2)
Forced sexual contact, non-relative	2.71 (1.52, 4.82)	2.32 (1.26, 4.28)	6.1 (0.8, 11.1)
Cumulative exposure to ACEs			
No ACEs (ref)			
Mild to moderate exposure to ACEs (1–3)	2.04 (1.27, 3.28)	2.24 (1.37, 3.65)	42.2 (21.6, 57.4)
Severe exposure to ACEs (4 or more)	3.51 (1.91, 6.48)	3.93 (2.09, 7.38)	-

Abbreviations: ACEs, adverse childhood experiences.

[†]Unadjusted odds ratios with their 95% confidence intervals.

[‡]Adjusted odds ratios with their 95% confidence intervals. All models were adjusted by sex, age, and occupation.

[§]Model adjusted by sex, age, occupation, and all types of ACEs.

Table 4. Associations between exposure to ACEs and previous psychiatric admissions; unadjusted and adjusted estimates, with population-attributable risk for adjusted estimates ($n = 968$).

Exposure	Unadjusted estimates [†]	Adjusted estimates [‡]	Population-attributable risk (%)
At least one ACE	3.42 (1.44, 8.12)	3.53 (1.47, 8.47)	61.6 (19.1, 81.7)
Specific types of ACEs[§]			
Traumatic separation from caregiver, 1+ month	2.18 (1.23, 3.87)	2.00 (1.10, 3.68)	22.1 (−0.5, 39.6)
Harsh physical punishment	1.27 (0.68, 2.38)	0.63 (0.26, 1.53)	−14.0 (−45.5, 10.7)
Physical injury from harsh punishment	2.36 (1.11, 5.04)	2.25 (0.79, 6.42)	8.9 (−3.9, 20.0)
Witnessing violence between caregivers	1.24 (0.68, 2.27)	0.96 (0.46, 2.00)	−1.2 (−26.3, 18.9)
Family member with substance abuse	1.54 (0.86, 2.74)	1.45 (0.74, 2.83)	11.7 (−12.4, 30.7)
Forced sexual contact, relative	2.50 (1.24, 5.05)	1.88 (0.89, 3.99)	9.0 (−4.1, 20.5)
Forced sexual contact, non-relative	4.79 (2.32, 9.91)	4.05 (1.87, 8.74)	15.2 (3.3, 25.7)
Cumulative exposure to ACEs			
No ACEs (0)			
Mild to moderate exposure to ACEs (1–3)	3.10 (1.29, 7.47)	3.20 (1.31, 7.80)	56.3 (20.6, 76.0)
Severe exposure to ACEs (4 or more)	5.29 (1.87, 14.95)	5.41 (1.89, 15.54)	-

Abbreviations: ACEs, adverse childhood experiences.

[†]Unadjusted odds ratios with their 95% confidence intervals.

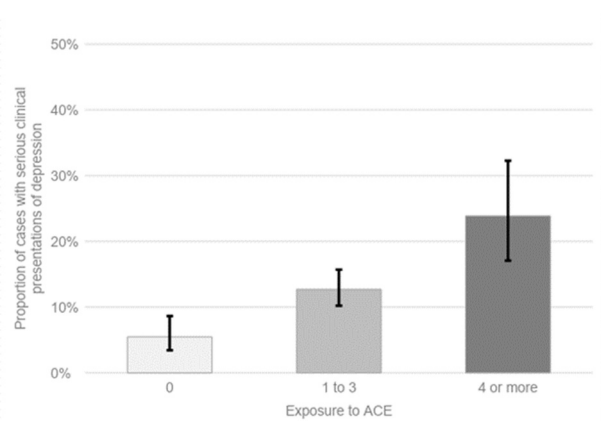
[‡]Adjusted odds ratios with their 95% confidence intervals. All models were adjusted by sex, age, and occupation.

[§]Model adjusted by sex, age, occupation, and all types of ACEs.

In addition, evaluation of the cumulative risk hypothesis revealed that increased exposure to ACEs was associated with a graded, greater, and statistically significant likelihood for all features of serious clinical presentations of depression (Tables 2–4). Consistently, a dose-response relationship was observed between cumulative exposure to ACEs and the ‘most serious’ clinical presentations of depression (Figure 1), where mild to moderate exposure to ACEs (aOR 2.51, 95% CI: 1.45 to 4.34) was followed in magnitude by severe exposure to ACEs (aOR 5.54, 95% CI: 2.86 to 10.74), as compared with no exposure.

3.4. Calculation of PAR of adverse childhood experiences for recurrent depression, high suicide risk, and previous psychiatric admissions

As shown in Tables 2–Tables 4, PAR of exposure to at least one ACE for recurrent depression was 14.5%, for high suicide risk was 45.0% and for previous psychiatric admissions was 61.6%. Furthermore, PAR of specific types of ACEs showed statistically

**Figure 1.** Cumulative exposure to ACEs and the ‘most serious’ clinical presentations of depression ($n = 117$).

Vertical error bars represent normal-based 95% confidence intervals after 200 bootstrap replications.

significant potential reductions in the burden of psychiatric admissions for depressed outpatients, of up to 15.2% (as observed in the case of having had sexual forced contact with a non-relative). Lastly, reducing the cumulative exposure to ACEs from the sample

mean to an alternative scenario with no exposure to ACEs (i.e. ACEs score = 0), resulted in PAR of up to 56.3% (as in the case for previous psychiatric admissions).

4. Discussion

The study results supported our hypotheses. Firstly, as a result of the high prevalence of exposure to ACEs in the sample, and the strong associations between ACEs and serious clinical presentations of depression, ACEs were attributed to a significant proportion of disease in this patient population: up to two thirds of previous psychiatric admissions, nearly a half of cases with high suicide risk, and close to fifteen percent of cases with recurrent depression. Secondly, our study demonstrated the relevance of specific types of ACEs, such as childhood sexual abuse (i.e. being a victim forced sexual contact) and traumatic separation from the primary caregiver, with having been a victim of sexual abuse by a non-relative potentially attributing around fifteen percent of previous psychiatric admissions in this patient population. Finally, results also confirmed a dose-response relationship between higher rates of ACEs exposure and more serious clinical presentations of depression, in accordance with the cumulative risk hypothesis.

The prevalence of exposure to ACEs in our study sample was greater than that reported for individuals with depression (45.6%) in a meta-analysis on child abuse and depression in adulthood (Nelson et al., 2017). Although this might be attributed to measurement differences, this is in line with the high prevalence of exposure to ACEs found by a Chilean study conducted in patients with depression treated in primary health care facilities (Vitriol et al., 2017). It should be emphasized that in the aforementioned study (Vitriol et al., 2017), one third of their participants were exposed to child sexual abuse, in contrast to 16.1% of the subjects in our study. These differences may potentially be related to greater rurality and lower socioeconomic status in the sample of Vitriol et al.'s study (2017), both of which are factors that have been associated with increased reporting of childhood sexual abuse (Beatriz, Salhi, Griffith, & Molnar, 2018).

Our finding that exposure to ACEs increases the risk of a more serious clinical presentation of depression is consistent with the literature. ACEs is a known risk factor for having early onset depression, more severe depressive symptoms, and chronic, treatment-resistant depression (Nanni et al., 2012; Nelson et al., 2017; Tokuda et al., 2018). Moreover, in the present study, we purposefully selected the most objective clinical measures of serious clinical presentations of depression (Velentgas, Dreyer, & Nourjah, 2013),

such as high suicide risk and previous psychiatric hospitalizations. The guidelines of the National Institute of Excellence in Health and Care (NICE), of the United Kingdom, argue that depressive episodes with these characteristics should be considered 'complex and severe,' as they pose a significant risk to life and demand greater specialized mental health resources, involving additional direct and indirect costs (NICE, 2009).

Regarding high suicide risk, the landmark ACEs study, conducted with members of a health maintenance organization (HMO), found a dose-response gradient between exposure to child abuse and neglect and suicide attempts throughout the lifespan (Dube et al., 2001; Felitti, 2002). In addition, other studies have indicated that childhood trauma confers a high risk for suicidal ideation and suicide attempts among depressed mothers with low-income (Ammerman et al., 2019), depressed outpatients and inpatients (Andover, Zlotnick, & Miller, 2007; Brodbeck et al., 2018; Johnstone et al., 2016), and patients with chronic depression (Ernst et al., 2019). In the present study, we have replicated these findings in a sample of depressed outpatients, observing the gradual dose-response effect of cumulative exposure to ACEs on high risk of suicide, as in Dube et al. (2001), and the particular relevance of child sexual abuse for this elevated risk, as has also been demonstrated by Andover et al. (2007), and Ernst et al. (2019).

It has also been reported that exposure to ACEs is related to adverse health outcomes and health-harming behaviours in adulthood (Bellis et al., 2019; Dube et al., 2001; Felitti, 2002). Along the same line, in a sample of relatively deprived and ethnically diverse individuals in the United Kingdom, ACEs was related to a greater probability of general hospital stays (Bellis, Lowey, Leckenby, Hughes, & Harrison, 2014). Likewise, the 'complex and severe' characterization of depressed populations exposed to ACEs (Nanni et al., 2012; Nelson et al., 2017; Tokuda et al., 2018), paired with high suicide risk (Andover et al., 2007; Ernst et al., 2019), is also associated with a greater chance of psychiatric hospitalization, as the present study suggests. In this regard, the only similar result found in the literature was the study by Rytälä-Manninen et al. (2014), which compared hospitalized adolescents with severe psychiatric conditions (mostly mood disorders), with healthy controls from the general population, to find a higher risk of psychiatric hospitalization based on cumulative exposure to ACEs.

After reviewing the literature, to the best of our knowledge, this is the only study that has determined the PAR of ACEs for high suicidal risk, previous psychiatric hospitalizations and recurrent depression, in a sample of patients with depression. A recently published meta-analysis by Bellis et al. (2019) and a report

from the Centers for Disease Control and Prevention (Merrick et al., 2017) have highlighted the important contribution of ACEs to depressive disorders in general, with PARs of 40 and 44.1%, respectively. Previous studies, using nationally representative data from the United States and Canada (Afifi et al., 2008, 2016; Choi, DiNitto, Marti, & Segal, 2017), have confirmed that ACEs are strongly associated with the burden of suicidal ideation and suicide attempts in these countries. For instance, suicide ideation would have been reduced in the general Canadian population by more than 50% if ACEs exposure had not occurred. Likewise, Dube et al. (2001), in the seminal ACEs study, found an even larger PAR value for suicide attempts (64%) in members of the HMO. These studies have used population-representative samples. As our study used a patient sample, our results are not comparable with previous literature. However, its interpretation also highlights the mental health burden attributed to ACEs, as high suicide risk and psychiatric hospitalizations would potentially have been reduced by almost half and up to two thirds, respectively, if this group of patients with depression had not been exposed to child abuse and neglect. The aforementioned finding supports the current evidence with respect to both the high prevalence of ACEs among this clinical population, as well as the robust association of ACEs with high suicide risk and previous psychiatric hospitalizations.

Our findings have important implications for clinical practice. The results illustrate the overwhelming impact that experiences of child abuse and neglect have on mental health in adulthood, given that a substantial percentage of cases with serious clinical presentations of depression were found to be largely attributable to ACEs. This is an argument for the prioritization of early prevention strategies for ACEs, such as parenting programmes (Chen & Chan, 2016), as well as palliative interventions, aimed at addressing the consequences of ACEs in a timely manner, by offering training on coping and stress management skills (Korotana, Dobson, Pusch, & Josephson, 2016; Sheffler, Piazza, Quinn, Sachs-Ericsson, & Stanley, 2019). This is of particular importance for Latin America, which is among the regions that are most afflicted by child abuse and neglect (Viola et al., 2016).

The evidence accumulated to date on the serious consequences of ACEs in adulthood and, in particular, their link with most 'complex and severe' presentations of depression, as confirmed by our study, serves emphatic warning of the need to actively inquire about ACEs when working with depressed adults. Moreover, as suggested by clinically-oriented studies, it is very likely that individuals with ACEs exposure will not respond well to first-line antidepressant treatment (Tokuda et al., 2018; Williams,

Debattista, Duchemin, Schatzberg, & Nemeroff, 2016). In this regard, an important recommendation found in the literature is that these patients should be subject to more personalized attention, such as trauma-informed and resilience-oriented care (Leitch, 2017; Oral et al., 2016), which might avoid retraumatization, improve response to treatment, and reduce associated health care costs. In Chile, for instance, the clinical guidelines for depression do not include ACEs exposure as a contributor to serious clinical presentations of depression, in stark contrast to findings by Vitriol, Ballesteros, Florenzano, Weil, and Benadof (2009), who demonstrated that a trauma-focused intervention was more effective in the treatment of Chilean depressed women with a history of ACEs exposure, than the standard treatment for depression.

Our study results reinforce the need to implement screening strategies for ACEs in mental health and psychiatry services. Nevertheless, the literature reveals that in clinical contexts this is the exception, not the rule, and health care providers acknowledge that their competencies and knowledge regarding the detection and treatment of patients with ACEs are quite limited (Weinreb et al., 2010). Therefore, any intention to promote ACEs screening should raise awareness among clinicians about the scope and prevalence of this public health problem, provide guidance on how to ask for this sensitive information, and provide the patients with affordable and effective treatment alternatives (Becker-Blease & Freyd, 2006; Edwards, Dube, Felitti, & Anda, 2007; Lee, Coles, Lee, & Kulkarni, 2012). Moreover, standard assessment tools, such as the one used in this study (BPSAQ, Marshall et al., 2000), could be readily implemented in mental health and psychiatry services for screening purposes.

There were a few limitations of the study that should be addressed. First, the data was obtained through systematic chart reviews of structured interviews conducted by psychiatrists or physicians with mental health training. Thus, as it might be affected by recall bias, a future study should consider the development of a protocol for the systematic collection of data in prospective fashion, by independent observers. Second, the questionnaire used to assess exposure to ACEs (BPSAQ, Marshall et al., 2000) does not allow for a detailed evaluation of early trauma exposure. However, this questionnaire has been validated and used in other studies in Chile (Cuneo et al., 2005; Vitriol et al., 2017; Weil et al., 2004), with the advantage of being short and quite useful for a first exploration of exposure to ACEs in clinical practice. In a future study, a fine-grained assessment of ACEs should be performed, including a detailed evaluation of child abuse and neglect, a thorough appraisal of exposure 'doses' (e.g. frequency and duration), along with the

patients' subjective judgement of the impact of ACEs on the principal functional life domains. Third, as this study recruited a large sample from a single mental health clinic, future replication studies might support the generalization of the present findings, and additionally, comorbidities (particularly, other mental disorders) or other important explanatory factors (e.g. coping strategies) should be considered for a more accurate estimation of the contribution of ACEs to the 'complex and severe' presentations of depression. This is important, as such unmeasured explanatory factors may have overestimated the contribution of ACEs.

In summary, this study supports the very frequent presence of ACEs in depressed adults and its deleterious consequences for the severity of their condition. The seemingly elevated PAR values we found suggest that preventing ACEs exposure may potentially have a high, clinically-meaningful impact in the proportion of patients with serious clinical presentations of depression (e.g. high suicide risk, previous psychiatric admission, and recurrent episodes) in mental health clinics. Therefore, it seems advisable to suggest that policy steps should be taken to prevent this exposure during childhood or provide early detection and treatment interventions, in order to improve the well-being of the exposed population throughout the lifespan.

Acknowledgments

The authors would like to thank the administrative personnel, health providers, and patients from Psicomedica, Clinical & Research Group. Authors would also like to thank the ANID Millennium Science Initiative/Millennium Institute for Research on Depression and Personality-MIDAP ICS13_005 and ANID - Millennium Science Initiative Program - NCS17_035.

Data availability statement

The data that support the findings of this study are openly available in OSF at <https://osf.io/ux2e5>, file name ZEPT-2020-0029R2.csv.

Disclosure statement

No potential conflicts of interest were reported by the authors.

ORCID

Sergio Gloger  <http://orcid.org/0000-0002-8674-1306>
 Pablo Martínez  <http://orcid.org/0000-0003-4482-7993>
 Alex Behn  <http://orcid.org/0000-0003-2070-7866>
 M. Victoria Chacón  <http://orcid.org/0000-0002-7438-8031>
 Marianne Cottin  <http://orcid.org/0000-0002-9460-7190>

Dante Diez de Medina  <http://orcid.org/0000-0001-7084-1778>

Paul A. Vöhringer  <http://orcid.org/0000-0002-2460-4680>

Funding

This study was not financed by a specific grant or funding agency from the public, commercial, or not-for-profit sectors.

References

- Afifi, T. O., Enns, M. W., Cox, B. J., Asmundson, G. J. G., Stein, M. B., & Sareen, J. (2008). Population attributable fractions of psychiatric disorders and suicide ideation and attempts associated with adverse childhood experiences. *American Journal of Public Health, 98*(5), 946–952.
- Afifi, T. O., Taillieu, T., Zamorski, M. A., Turner, S., Cheung, K., & Sareen, J. (2016). Association of child abuse exposure with suicidal ideation, suicide plans, and suicide attempts in military personnel and the general population in Canada. *JAMA Psychiatry, 73*(3), 229–238.
- Ammerman, R. T., Scheiber, F. A., Peugh, J. L., Messer, E. P., Van Ginkel, J. B., & Putnam, F. W. (2019). Interpersonal trauma and suicide attempts in low-income depressed mothers in home visiting. *Child Abuse & Neglect, 97*, 104126.
- Andover, M. S., Zlotnick, C., & Miller, I. W. (2007). Childhood physical and sexual abuse in depressed patients with single and multiple suicide attempts. *Suicide and Life-threatening Behavior, 37*(4), 467–474.
- Appleyard, K., Egeland, B., van Dulmen, M. H., & Sroufe, L. A. (2005). When more is not better: The role of cumulative risk in child behavior outcomes. *Journal of Child Psychology and Psychiatry, 46*(3), 235–245.
- BALANCE investigators and collaborators, Geddes, J. R., Goodwin, G. M., Rendell, J., Azorin, J. M., Cipriani, A., & Juszczak, E. (2010). Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): A randomized open-label trial. *The Lancet, 375*, 385–395.
- Beatriz, E. D., Salhi, C., Griffith, J. L., & Molnar, B. E. (2018). Urbanicity matters in self-reported child maltreatment prevalence: Findings from a nationally representative study. *Child Abuse & Neglect, 79*, 371–383.
- Becker-Blease, K. A., & Freyd, J. J. (2006). Research participants telling the truth about their lives: The ethics of asking and not asking about abuse. *The American Psychologist, 61* (3), 218–226. doi:10.1037/0003-066X.61.3.218.
- Bellis, M. A., Hughes, K., Ford, K., Ramos Rodríguez, G., Sethi, D., & Passmore, J. (2019). Life course health consequences and associated annual costs of adverse childhood experiences across Europe and North America: A systematic review and meta-analysis. *The Lancet Public Health, 4*(10), e517–e528.
- Bellis, M. A., Lowey, H., Leckenby, N., Hughes, K., & Harrison, D. (2014). Adverse childhood experiences: Retrospective study to determine their impact on adult health behaviours and health outcomes in a UK population. *Journal of Public Health, 36*(1), 81–91.
- Bobes, J. (1998). A Spanish validation study of the Mini-international neuropsychiatric interview. *European Psychiatry, 13*(S4), 198s–199s.
- Brodbeck, J., Fassbinder, E., Schweiger, U., Fehr, A., Späth, C., & Klein, J. P. (2018). Differential associations between patterns of child maltreatment and comorbidity

- in adult depressed patients. *Journal of Affective Disorders*, 230, 34–41.
- Charak, R., Byllesby, B. M., Roley, M., Claycomb, M. A., Durham, T. A., Ross, J., ... Elhai, J. D. (2016). Latent classes of childhood poly-victimization and association with suicidal behavior among adult trauma victims: Moderating role of anger. *Child Abuse & Neglect*, 62, 19–28.
- Charak, R., Tromp, N. R., & Koot, H. M. (2018). Associations of specific and multiple types of childhood abuse and neglect with personality pathology among adolescents referred for mental health services. *Psychiatry Research*, 270, 906–914.
- Chen, M., & Chan, K. L. (2016). Effects of parenting programs on child maltreatment prevention: A meta-analysis. *Trauma Violence Abuse*, 17, 88–104. doi:10.1177/1524838014566718
- Choi, N. G., DiNitto, D. M., Marti, C. N., & Segal, S. P. (2017). Adverse childhood experiences and suicide attempts among those with mental and substance use disorders. *Child Abuse & Neglect*, 69, 252–262.
- Cuneo, C., González, I., Jara, M., Palomares, L., Rammasy, C., & Cruz, C. (2005). Validación externa de la escala de trauma de Marshall. In R. Florenzano, P. Weil, C. Carvajal, & C. Cruz (Eds.), *Trauma infanto-juvenil y psicopatología adulta* (p. 145). Santiago: Editorial Corporación de Promoción Universitaria.
- Dold, M., Bartova, L., Fugger, G., Kautzky, A., Souery, D., Mendlewicz, J., ... Kasper, S. (2018). Major depression and the degree of suicidality: Results of the European group for the study of resistant depression (GSRD). *International Journal of Neuropsychopharmacology*, 21(6), 539–549.
- Dube, S. R., Anda, R. F., Felitti, V. J., Chapman, D. P., Williamson, D. F., & Giles, W. H. (2001). Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span: Findings from the adverse childhood experiences study. *JAMA*, 286(24), 3089–3096.
- Edwards, V. J., Dube, S. R., Felitti, V. J., & Anda, R. F. (2007). It's ok to ask about past abuse. *The American Psychologist*, 62(4), 327–328.
- Ekman, M., Granström, O., Omérov, S., Jacob, J., & Landén, M. (2013). The societal cost of depression: Evidence from 10,000 Swedish patients in psychiatric care. *Journal of Affective Disorders*, 150(3), 790–797.
- Ernst, M., Kallenbach-Kaminski, L., Kaufhold, J., Negele, A., Bahrke, U., Hautzinger, M., ... Leuzinger-Bohleber, M. (2019). Suicide attempts in chronically depressed individuals: What are the risk factors? *Psychiatry Research*, 287, 112481.
- Felitti, V. J. (2002). The relation between adverse childhood experiences and adult health: Turning gold into lead. *The Permanente Journal*, 6(1), 44–47.
- Fuller-Thomson, E., Baird, S. L., Dhrodia, R., & Brennenstuhl, S. (2016). The association between adverse childhood experiences (ACEs) and suicide attempts in a population-based study. *Child: Care, Health and Development*, 42(5), 725–734.
- Ghaemi, N. S. (2019). *Clinical psychopharmacology: Principles and practice*. New York: Oxford University Press.
- Goodwin, F. K., Jamison, K. R., & Ghaemi, S. N. (2007). *Manic-depressive illness: Bipolar disorders and recurrent depression*. New York: Oxford University Press.
- Johnston, K. M., Powell, L. C., Anderson, I. M., Szabo, S., & Cline, S. (2019). The burden of treatment-resistant depression: A systematic review of the economic and quality of life literature. *Journal of Affective Disorders*, 242, 195–210.
- Johnstone, J. M., Carter, J. D., Luty, S. E., Mulder, R. T., Frampton, C. M., & Joyce, P. R. (2016). Childhood predictors of lifetime suicide attempts and non-suicidal self-injury in depressed adults. *Australian & New Zealand Journal of Psychiatry*, 50, 135–144.
- Korotana, L. M., Dobson, K. S., Pusch, D., & Josephson, T. (2016). A review of primary care interventions to improve health outcomes in adult survivors of adverse childhood experiences. *Clinical Psychology Review*, 46, 59–90.
- Kraus, C., Kadriu, B., Lanzenberger, R., Zarate, C. A., Jr, & Kasper, S. (2019). Prognosis and improved outcomes in major depression: A review. *Translational Psychiatry*, 9(1), 127.
- Lee, A., Coles, J., Lee, S., & Kulkarni, J. (2012). Primary healthcare practitioners' screening practices and attitudes towards women survivors of child abuse. *Mental Health in Family Medicine*, 9(3), 181–189.
- Leitch, L. (2017). Action steps using ACEs and trauma-informed care: A resilience model. *Health & Justice*, 5(1), 5.
- Marshall, R. D., Schneier, F. R., Lin, S.-H., Simpson, H. B., Vermes, D., & Liebowitz, M. (2000). Childhood trauma and dissociative symptoms in panic disorder. *The American Journal of Psychiatry*, 157(3), 451–453. doi:10.1176/appi.ajp.157.3.451.
- Merrick, M. T., Ports, K. A., Ford, D. C., Afifi, T. O., Gershoff, E. T., & Grogan-Kaylor, A. (2017). Unpacking the impact of adverse childhood experiences on adult mental health. *Child Abuse Negl*, 69, 10–19. doi:10.1016/j.chiabu.2017.03.016
- Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *The American Journal of Psychiatry*, 169(2), 141–151.
- National Institute for Health and Care Excellence. (2009). *Depression in adults: Recognition and management*. London. Retrieved from <https://www.nice.org.uk/guidance/cg90>
- Nelson, J., Klumpp, A., Doebler, P., & Ehring, T. (2017). Childhood maltreatment and characteristics of adult depression: Meta-analysis. *The British Journal of Psychiatry*, 210(2), 96–104.
- Nemeroff, C. B. (2016). Paradise lost: The neurobiological and clinical consequences of child abuse and neglect. *Neuron*, 89(5), 892–909.
- Newson, R. B. (2013). Attributable and unattributable risks and fractions and other scenario comparisons. *The Stata Journal: Promoting Communications on Statistics and Stata*, 13(4), 672–698.
- Northridge, M. E. (1995). Public health methods – Attributable risk as a link between causality and public health action. *American Journal of Public Health*, 85(9), 1202–1204.
- Novelo, M., von Gunten, A., Behr Gomes Jardim, G., Spanemberg, L., de Lima Argimon, I. I., & Nogueira, E. L. (2018). Effects of childhood multiple maltreatment experiences on depression of socioeconomic disadvantaged elderly in Brazil. *Child Abuse & Neglect*, 79, 350–357. doi:10.1016/j.chiabu.2018.02.013.
- Oral, R., Ramirez, M., Coohey, C., Nakada, S., Walz, A., Kuntz, A., ... Peek-Asa, C. (2016). Adverse childhood experiences and trauma informed care: The future of health care. *Pediatric Research*, 79(1–2), 227–233.

- Putnam, K. T., Harris, W. W., & Putnam, F. W. (2013). Synergistic childhood adversities and complex adult psychopathology. *Journal of Traumatic Stress, 26*(4), 435–442.
- Ryttilä-Manninen, M., Lindberg, N., Haravuori, H., Kettunen, K., Marttunen, M., Joukamaa, M., & Fröjd, S. (2014). Adverse childhood experiences as risk factors for serious mental disorders and inpatient hospitalization among adolescents. *Child Abuse & Neglect, 38*(12), 2012–2032.
- Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., ... Dunbar, G. C. (1998). The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry, 59*, 22–33.
- Sheffler, J. L., Piazza, J. R., Quinn, J. M., Sachs-Ericsson, N. J., & Stanley, I. H. (2019). Adverse childhood experiences and coping strategies: Identifying pathways to resiliency in adulthood. *Anxiety, Stress, and Coping, 32* (5), 594–609.
- StataCorp. (2015). *Stata statistical software (Release 14)*. College Station, TX: Author.
- Tokuda, T., Yoshimoto, J., Shimizu, Y., Okada, G., Takamura, M., Okamoto, Y., ... Doya, K. (2018). Identification of depression subtypes and relevant brain regions using a data-driven approach. *Scientific Reports, 8*(1), 14082.
- Velentgas, P., Dreyer, N. A., & Nourjah, P. (2013). Chapter 6: Outcome definition and measurement. In P. Velentgas, N. A. Dreyer, P. Nourjah, S. R. Smith, & M. M. Torchia (Eds.), *Developing a protocol for observational comparative effectiveness research: A user's guide* (pp. 71–92). Rockville, MD: Agency for Healthcare Research and Quality (US).
- Viola, T. W., Salum, G. A., Kluwe-Schiavon, B., Sanvicente-Vieira, B., Levandowski, M. L., & Grassi-Oliveira, R. (2016). The influence of geographical and economic factors in estimates of childhood abuse and neglect using the childhood trauma questionnaire: A worldwide meta-regression analysis. *Child Abuse & Neglect, 51*, 1–11. doi:10.1016/j.chiabu.2015.11.019.
- Vitriol, V., Ballesteros, S., Florenzano, R. U., Weil, K. P., & Benadof, D. F. (2009). Evaluation of an outpatient intervention for women with severe depression and a history of childhood trauma. *Psychiatric Services, 60* (7), 936–942.
- Vitriol, V., Cancino, A., Ballesteros, S., Potthoff, S., & Serrano, C. (2017). Factors associated with greater severity of depression in Chilean primary care patients. *The Primary Care Companion for CNS Disorders, 19*(3). doi:10.4088/PCC.16m02051
- Weil, K., Florenzano, R., Vitriol, V., Cruz, C., Carvajal, C., Fullerton, C., ... Muñoz, C. (2004). Trauma infantojuvenil y psicopatología adulta: Un estudio empírico. *Revista médica de Chile, 132*(12), 1499–1504. doi:10.4067/S0034-98872004001200007.
- Weinreb, L., Savageau, J. A., Candib, L. M., Reed, G. W., Fletcher, K. E., & Hargraves, J. L. (2010). Screening for childhood trauma in adult primary care patients: A cross-sectional survey. *Primary Care Companion to the Journal of Clinical Psychiatry, 12*(6), PCC.10m00950. doi:10.4088/PCC.10m00950blu.
- Williams, L. M., Debattista, C., Duchemin, A. M., Schatzberg, A. F., & Nemeroff, C. B. (2016). Childhood trauma predicts antidepressant response in adults with major depression: Data from the randomized international study to predict optimized treatment for depression. *Translational Psychiatry, 6*(5), e799. doi:10.1038/tp.2016.61.
- World Health Organization. (2004). *ICD-10: International statistical classification of diseases and related health problems: Tenth revision* (2nd ed.). Geneva: WHO.
- World Health Organization. (2017). *Depression and other common mental disorders: Global health estimates*. Geneva: WHO.