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COMPORTAMENTO

BÁRBARA TIETBOHL MARTINS QUADROS DOS SANTOS

**FATORES DE PROTEÇÃO ASSOCIADOS À TRAJETÓRIAS DE SAÚDE MENTAL
EM INDIVÍDUOS COM RISCO AUMENTADO PARA TRANSTORNO
DEPRESSIVO MAIOR**

**PROTECTIVE FACTORS ASSOCIATED WITH MENTAL HEALTH
TRAJECTORIES IN AT-RISK INDIVIDUALS FOR DEPRESSION**

Porto Alegre

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Tese apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul como requisito parcial para a obtenção do título de doutora em Psiquiatria e Ciências do Comportamento.

Orientador: Prof. Dr. Ives Cavalcante Passos, MD, PhD

Coorientador: Prof. Dr. Prof. Dr. Flávio Kapczinski, MD, PhD

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RESUMO

O transtorno depressivo maior (TDM) é um problema que envolve toda a população mundial devido à sua ampla prevalência e morbidade. Experiências adversas precoces (EAP) representam fatores de risco consistente para o desenvolvimento de depressão. Exemplos dessas experiências incluem pobreza na infância, doença mental dos pais, maus-tratos infantis e exposição à violência, a abuso de substâncias e/ou criminalidade.

No entanto, nem todos as pessoas expostas a fatores de risco desenvolverão TDM, e isso provavelmente se deve a características pessoais e fatores de proteção que afetam positivamente o desenvolvimento desses indivíduos. Isso enfatiza que influências específicas podem compensar trajetórias atípicas, estabelecendo trajetórias alternativas, mas igualmente funcionais. Fatores de proteção frequentemente discutidos na literatura incluem atributos individuais e várias categorias de relacionamentos que promovem suporte como família, vizinhança e escola.

Este projeto tem como objetivo avaliar como os fatores de proteção impactam indivíduos em risco de depressão por meio da análise de estudos de coorte. Ao elucidar quais fatores de proteção desempenham um papel importante nas trajetórias de desenvolvimento, podemos focar em intervenções personalizadas para essa população. Conseqüentemente, iniciamos uma revisão sistemática para explorar os fatores de proteção que influenciam o desenvolvimento do TDM em indivíduos em risco. Esta pesquisa buscou realizar uma revisão das evidências atuais, concentrando-se em uma abordagem preventiva e examinando exclusivamente artigos de coorte. Nossa análise envolveu 29 estudos com 62.405 participantes, identificando 38 fatores de proteção. Traços de personalidade positivos, religiosidade e fatores relacionados à família, ao relacionamentos com pares, à escola e à vizinhança foram associados à redução dos desfechos depressivos.

Subseqüentemente, nosso segundo estudo procurou aplicar os insights obtidos no nosso primeiro artigo a um subgrupo de uma coorte de jovens adultos, com o objetivo de testar a eficácia dos achados iniciais. Na primeira fase, os participantes tinham entre 18 e 24 anos, e na terceira fase, 31,94 anos (DP = 2,18). No grupo de alto risco, a incidência de TDM foi de 13,7% (n=24). O suporte paterno teve um efeito protetor sobre a incidência de TDM (OR = 0,366; IC 95% [0,137 a 0,955], p = 0,040) e sobre o risco de tentativa de suicídio (OR = 0,380; IC 95%

[0,150 a 0,956], $p = 0,038$). Pontuações mais altas de resiliência também foram protetoras (OR = 0,975; IC 95% [0,953 a 0,997], $p = 0,030$), correlacionando-se com reduções nas pontuações em escalas de depressão como o BDI ($r = 0,0484$; $B = -0,2202$; IC 95% [-0,3572 a -0,0738]; $p = 0,003$) e o MADRS ($r = 0,0485$; $B = -0,2204$; IC 95% [-0,3574 a -0,0741]; $p = 0,003$).

Em resumo, esta tese faz uma contribuição crucial ao ilustrar de maneira abrangente os fatores-chave para a prevenção de sintomas depressivos em indivíduos em risco por meio de estudos longitudinais. Os insights obtidos oferecem novas direções para intervenções eficazes voltadas a auxiliar essa população. É fundamental focar no ambiente familiar, especialmente no papel paterno, e ampliar a acessibilidade dos tratamentos de saúde mental para os pais e mães de crianças em risco.

Palavras-chave: Depressão; transtorno depressivo maior; prevenção; indivíduos em risco; crianças; adolescentes; fatores de proteção.

ABSTRACT

Major depressive disorder (MDD) is a global concern due to its widespread prevalence and morbidity. Early adverse experiences (EAE) represent consistent risk factors for the development of depression during childhood and adolescence and can increase the risk of developing MDD in adulthood. Examples of such experiences include childhood poverty, parental mental illness, exposure to violence, substance abuse or criminality, and child maltreatment. It is imperative to identify effective strategies to mitigate the impact of these negative exposures, thereby proactively preventing depressive outcomes on a global scale for future generations.

However, not all individuals at-risk will develop MDD, and this is likely attributable to unique characteristics and protective factors that positively affect their neurodevelopmental trajectory. This emphasizes the concept that specific influences can normalize atypical trajectories through compensatory mechanisms, establishing alternative yet equally functional trajectories. Protective factors frequently discussed in the literature encompass individual attributes and various categories of supportive relationships, such as those found within families, neighborhoods, and schools.

This project aims to evaluate how protective factors impact at-risk individuals for depression through analysing cohort studies. By elucidating which protective factors play a major role in developmental trajectories, we can focus our efforts on effective tailored interventions for this population. Consequently, we initiated a systematic review to explore protective factors influencing the development of MDD in individuals at-risk. This research endeavors to address a critical gap by providing a comprehensive review of existing evidence, concentrating on a preventive approach and exclusively scrutinizing papers with a longitudinal design. Our analysis comprised 29 studies with 62,405 participants, identifying 38 protective factors. Positive individual characteristics, family factors, peer relationships, school-related aspects, neighborhood characteristics and intrinsic religiosity were associated with reduced depressive outcomes.

Subsequently, our second study sought to operationalize the insights gained from our initial paper within a subset of a young adult cohort, with the objective of substantiating the efficacy of our findings. In the first wave (T1) participants were 18 to 24 years, while at the third wave

(T3), the average age of participants was 31.94 years (SD = 2.18). In the high-risk group, MDD incidence was 13.7% (n=24). Paternal support had a protective effect on MDD incidence (OR = 0.366; 95% CI [0.137 to 0.955], p = 0.040) and suicidal attempt risk (OR = 0.380; 95% CI [0.150 to 0.956], p = 0.038). Higher resilience scores were also protective (OR = 0.975; 95% CI [0.953 to 0.997], p = 0.030), correlating with reduced BDI (r = 0.0484; B = -0.2202; 95% CI [-0.3572 to -0.0738]; p = 0.003) and MADRS scores (r = 0.0485; B = -0.2204; 95% CI [-0.3574 to -0.0741]; p = 0.003).

In summary, this thesis makes a pivotal contribution by thoroughly illustrating key factors for preventing depressive symptoms in at-risk individuals through longitudinal studies. The insights gained offer new directions for effective interventions aimed at assisting this population. It is crucial to focus on the family environment, especially the role of fathers, and to enhance the accessibility of mental health treatments for parents.

Key words: Depression; major depressive disorder; prevention; at-risk individuals; children; adolescents, protective factors.

LISTA DE ABREVIATURAS E SIGLAS

CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
EAE	Early Adverse Experiences
MDD	Major Depressive Disorder

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1. INTRODUCTION

1.1. MAJOR DEPRESSIVE DISORDER

Major Depressive Disorder (MDD) stands out as one of the most prevalent mental disorders globally, impacting more than 300 million people across all age groups and carrying significant personal, societal, and economic consequences (Global Burden of Disease Study 2013 Collaborators, 2015). This concern becomes especially striking in the context of young individuals, not only because it manifests during the rapid progression of social, emotional, and cognitive development, along with critical life transitions but also due to a noteworthy surge in its prevalence among the youth in the past decade, specifically those aged 10–24 years, particularly in females (Vos et al., 2020).

MDD is defined by a variety of symptoms that encompass emotional, motivational, cognitive, and physiological domains. These symptoms include persistent sadness or low mood, loss of interest or pleasure, fatigue, and low energy, as well as disturbed sleep, poor concentration or indecisiveness, low self-confidence, changes in appetite, suicidal thoughts or acts, agitation, slowing of movements, guilt, or self-blame (Luxton & Kyriakopoulos, 2022). In addition, MDD displays significant heterogeneity. There are several combinations of depressive symptoms, as well as different levels of clinical severity, comorbidities, and ultimate outcomes (Thapar et al., 2022).

Furthermore, this disorder affects diverse populations with varying prevalences. The incidence of depression is significantly higher among individuals facing special educational needs or chronic health issues, as well as those hailing from socioeconomically disadvantaged households (*Mental Health of Children and Young People in England, 2017 [PAS]*, n.d.). Similar observations can be made regarding refugees and individuals exposed to war or terrorism (Lim et al., 2022). Moreover, it is crucial to consider the nearly universal exposure to the COVID-19 pandemic, which has led to a twofold increase in the prevalence of depression among young individuals compared to pre-pandemic estimates (Racine et al., 2021).

Gender represents another variable that can influence an individual's susceptibility to depression. The likelihood of developing MDD increases by 40%-180% for females, as revealed by a recent meta-analysis that scrutinized the heterogeneity of this prevalence across different countries (Gutiérrez-Rojas et al.,

2020). Nevertheless, females exhibit significantly higher lifetime prevalence rates of depression compared to males, with 21% of women meeting criteria for lifetime depression as opposed to 13% of males (Kessler et al., 1994). The origins of sex differences in depression can be traced back to adolescence and have been demonstrated across various ethnic groups and sampling criteria (Harold et al., 2014).

Over 20% of Americans will encounter depressive symptoms at least once in their lifetime (Gotlib & Joormann, 2010). The reported prevalence of MDD in children aged 1-7 years is relatively low at 1.1% (Vasileva et al., 2021). However, these figures escalate with age, potentially attributed to increased social demands, stressors, and hormonal changes influencing brain development (Thapar et al., 2022). While 34% of adolescents globally, aged 10-19 years, self-report depressive symptoms, the mean worldwide prevalence of depression in this population stands at 8% (Shorey et al., 2022). In addition, meta-analysis on depression estimated that approximately 20% of the adolescent population in the US would undergo at least one clinically significant depressive episode before reaching adulthood (Jane Costello et al., 2006). This holds paramount significance as early-life depression and anxiety pose threats to later physical and mental health, interpersonal relationships, educational attainment, and even later financial functioning (Wang et al., 2021).

Moreover, the presence of depressive symptoms in children and adolescents is particularly concerning as they signify an imbalance between risk and protective factors within the individual's environment, increasing the likelihood of MDD and other diagnoses in adulthood when there is an imbalance in these factors (Klasen et al., 2015). This underscores the need to identify protective factors in childhood to prevent trajectories towards mental disorders and depressive outcomes in adulthood. Given the substantial impact associated with adverse outcomes linked to depressive episodes and the disorder's high prevalence, it is crucial to deepen our understanding of the factors that contribute to and hinder its development, especially in young at-risk individuals.

1.2. AT-RISK POPULATIONS

A critical aspect in formulating effective prevention strategies for the onset of MDD involves accurately pinpointing the factors most closely associated with an elevated risk of developing the disorder. To achieve this, longitudinal studies are imperative, allowing for the observation of individuals exhibiting characteristics

previously linked to increased MDD incidence but who have not yet developed the disorder. These individuals are exposed to various adverse environmental factors that often co-occur, commonly referred to as Early Adverse Experiences (EAE). Examples of such experiences include childhood poverty, parental mental illness, exposure to violence, substance abuse or criminality, and child maltreatment. EAE stand out as the most robust and consistent risk factors for both depressive and anxious symptoms and disorders in children and adolescents (Petruccelli et al., 2019).

Connections between these early experiences and the emergence of depressive symptoms may be attributed to several factors, encompassing disruptions in parent-child attachment (Nolte et al., 2011) and modifications in the development of affect regulation and stress response systems (Morris et al., 2007). Neurodevelopmental alterations in brain circuits regulating fear, stress reactivity, cognition, and reward sensitivity have been observed in the offspring of rodents and nonhuman primates exposed to low levels of parental care (A & JH, 2012). This sheds crucial light on the mechanisms through which parental care and early life experiences can exert a lasting impact on neurodevelopment and subsequent adult behavior (Franklin et al., 2012; Morris et al., 2007).

Certain subgroups face an elevated risk of Early Adverse Experiences (EAE) compared to others. Notably, individuals who are female, belong to ethnic minorities, and reside in developing countries present risk profiles associated with a higher likelihood of encountering EAE exposures (Hunt et al., 2017). Moreover, ethnic minority groups exhibit increased susceptibility to specific EAE, with Black children more prone to parental incarceration, and Hispanic children more likely to witness domestic violence in comparison to their White counterparts (Hunt et al., 2017; Wang et al., 2021). Furthermore, children born into low-income families are at a heightened risk of experiencing various types of EAE from birth to age three (Choi et al., 2019). Consequently, economically disadvantaged ethnic minority children are more prone to living with EAE, thereby amplifying their risks for adverse outcomes in later stages of life (Wang et al., 2021). Indeed, youth residing in disadvantaged communities face an elevated risk for a spectrum of health and behavioral challenges in their later years, encompassing substance abuse, anti-social behavior, depressive symptoms, heightened vulnerability to further victimization, and increased exposure to violence (Kuper & Turanovic, 2019; Ross, 2000; Sharkey, 2018).

Few childhood adversities are believed to pose as significant a threat to healthy development as physical abuse, particularly when inflicted by caregivers during the early years of life. Such abuse can profoundly violate a child's sense of safety and control, exerting adverse effects on brain structure and function (Anda et al., 2006; Bremner, 2006; Kuper & Turanovic, 2019). A meta-analysis has shown that individuals exposed to one or more types of abuse are 1.5 to 3.5 times more likely to experience a depressed mood and 1.3 to 6.8 times more likely to report anxiety (Petruccelli et al., 2019) in adulthood. Additionally, there is data indicating that adolescents who have experienced physical abuse are at a higher risk of developing depression and anxiety compared to their counterparts (Lee et al., 2020).

The literature corroborates that individuals who have experienced abuse not only endure more severe depressive symptoms but also encounter significantly more episodes of depression throughout early adulthood (Nilsson et al., 2017), with these episodes typically commencing at an earlier stage in life (Widom et al., 2007). Furthermore, it is well-established that childhood physical abuse heightens the likelihood of various adverse outcomes later in life. Adults who underwent childhood physical abuse are documented to face numerous health issues (such as diabetes, cardiovascular problems, lung disease, malnutrition, and vision problems), engage in violent and criminal behaviors, and grapple with a broad spectrum of psycho-emotional difficulties (Widom et al., 2007, 2018). Consequently, childhood physical abuse is recognized as a traumatic experience that can compromise one's overall well-being across the life span (Kuper & Turanovic, 2019).

Parental mental health problems stand as a well-established risk factor for child psychopathology (Ramchandani & Psychogiou, 2009). Extensive research highlights that the progeny of depressed mothers face an elevated risk of psychological and social maladjustment (Goodman et al., 2011). Moreover, children with depressed parents are more prone to experiencing depression, phobias, panic disorders, and substance misuse during adolescence (Weissman et al., 2006). The interplay of genetic factors and the family environment makes noteworthy contributions to the heritability of depression (Thapar & McGuffin, 1994) and other mental disorders (Caspi et al., 2020; Schaefer et al., 2017). Understanding the complex interplay between genetic predispositions and environmental factors is crucial for comprehending the transmission of mental health vulnerabilities within families and tailoring effective interventions to mitigate the impact on children's psychological well-being.

1.3. PROTECTIVE FACTORS

Protective factors can be viewed as positive environmental influences that can facilitate healthy development. Regarding their role, they do not inherently promote normal evolution in the absence of risk factors. However, their substantial impact becomes evident in scenarios where risk factors exert influence (Brasso et al., 2021). This underscores the notion that certain influences possess the capacity to normalize an atypical neurodevelopmental trajectory through compensatory mechanisms, establishing an alternative yet equivalent functional trajectory (Salum et al., 2010). The protective factors predominantly discussed in the literature include individual attributes and various categories of supportive relationships such as family, neighborhood, peers, and school.

1.3.1. Family

Family life emerges as one of the extensively examined factors across various dimensions. Establishing a robust connection with one's family is a potent protective element for young individuals facing exposure to EAE (Morris et al., 2007). Numerous studies reveal positive health outcomes for children raised in functional families, characterized by close emotional ties between parents and children, mutual support, and shared quality time (Haavet et al., 2004; HAAVET et al., 2005). Resilient children likely benefit from increased guidance and supervision within well-functioning family dynamics (HAAVET et al., 2005). As identified by Crouch et al. in 2018, when children maintain a secure, stable, and nurturing bond with their parents, coupled with the fulfillment of their basic needs, they exhibit a reduced likelihood of reporting mental distress, such as depression and emotional problems, irrespective of heightened EAE exposure (Crouch et al., 2018). Moreover, Haavet et al. in 2005 demonstrated that specific family-related attributes, such as the family's regard for the young person's opinions and their motivation for their child's education, emerged as the most frequently associated risk-reducing factors, correlating with lower incidences of illness and healthcare system utilization (HAAVET et al., 2005). Remarkably, this risk-reducing effect appeared more pronounced in the presence of multiple risk factors (HAAVET et al., 2005).

The family's impact on a child's mental well-being has been systematically assessed using various tools and scales. Substantial evidence suggests that family routines, defined as regularly repeated interactions involving instrumental communication among family members, can emerge as a robust protective factor against depressive symptoms (Doyle et al., 2003). This is attributed to their role in establishing a foundational setting for nurturing closeness and a sense of belonging (Doyle et al., 2003), providing a reliable context for fostering positive familial interactions (Spagnola & Fiese, 2007; Thakur & Cohen, 2022). Additionally, Uddin et al. in 2020 found that family resilience, characterized by collaborative efforts among family members in planning for the future and engaging in effective problem-solving, is correlated with a decreased likelihood of adolescents experiencing mental health concerns. This correlation holds true even after adjusting for sociodemographic characteristics (Uddin et al., 2021).

Moreover, positive parenting behaviors, such as expressing warmth toward children, and active co-parenting involving a high level of father involvement during early childhood, exhibited positive associations with subsequent child outcomes (Crandall et al., 2020; Wang et al., 2021). In addition, the significance of high-quality family attachments in fostering healthy development cannot be overstated (Kuper & Turanovic, 2019). This was also shown in an interesting meta-analysis focused specifically on maltreated children that was able to link resilience to healthy family environment and supportive relationships. Similarly, robust family attachments during adolescence were identified as contributors to a diminished likelihood of depressive symptoms and low self-esteem in early adulthood among abuse victims (Kuper & Turanovic, 2019). Lastly, it has been demonstrated that the family climate can act as a moderating factor, mitigating the adverse impact of parental psychopathology on a child's depressive symptoms (Klasen et al., 2015).

1.3.2. School and peers

Positive peer relationships and favorable childhood experiences at school exert a significant impact on child development, demonstrating the ability to foster positive mental health outcomes and shield children from adversities (Crouch et al., 2019). In a study by Jain et al. in 2012, the presence of positive peers was identified as increasing the likelihood of emotional resilience for all youth, surpassing the influence of

individual and neighborhood risks (Jain et al., 2012). This observation aligns with other studies emphasizing the crucial role of positive friendships, especially during the adolescent years (Leffert et al., 1998). Additionally, several investigations have documented the advantages of organized activity participation in adolescents, contributing to both academic and behavioral improvements (Eccles et al., 2003; Fredricks & Eccles, 2006; Hartmann & Massoglia, 2007). Organized activities such as afterschool programs and school clubs can be particularly beneficial for at-risk adolescents, offering psychosocial resources that may be lacking in their home environment (Ungar, 2011). These activities present opportunities for adolescents to forge social connections and develop interpersonal competence in relationships with both peers and adults, engaging participants in goal-oriented activities within structured settings (Kwak et al., n.d.).

Moreover, school connectedness, delineated by students' perceptions of acceptance, respect, inclusion, and support within school environments, emerges as a potential protective factor (Goodenow, 1993). This construct encapsulates both a sense of belonging and social support, each individually linked to reduced levels of depressive symptoms (Ibarra-Rovillard & Kuiper, 2011; Marroquín, 2011; Walton & Cohen, 2011). Consequently, the recurrent association of school connection with diminished depressive symptoms comes as no surprise (Jose & Lim, 2014; Markowitz A.J., 2017; Shochet et al., 2006). A comprehensive longitudinal study demonstrated that elevated school connectedness significantly reduces the likelihood of adolescent depression and anxiety one year later, even after accounting for previous mental health conditions (Shochet et al., 2006). Notably, prior research investigating school connection and depressive symptoms in normative samples found no gender differences in its efficacy as a protective factor (Oesterle et al., 2010).

1.3.3. Neighborhood

Social support and neighborhood conditions exert considerable influence on children's mental health and their families (Cohen et al., 2000; Ibarra-Rovillard & Kuiper, 2011). Social support, characterized by having individuals outside the family, such as friends, peers, teachers, or other caregivers, who listen and provide assistance, has consistently demonstrated protective effects on mental health in various cross-sectional studies (Ezzell et al., 2000; Klasen et al., 2015; Schwarzer & Knoll, 2007).

While literature suggests that females may derive more benefits from social support than males (Kendler et al., 2005), nurturing relationships within the neighborhood correlate with reduced mental distress for parents and children of both genders (Choi et al., 2021; Solmi et al., 2017). Moreover, studies indicate that a heightened level of neighborhood efficacy, characterized by factors like high closeness and trust among neighbors, is associated with decreased instances of family adverse experiences, parenting stress, and peer bullying victimization. These factors, in turn, contribute to positive outcomes in adolescents (Choi et al., 2021; Wang et al., 2020, 2021).

Likewise, neighborhood social cohesion, characterized by trust and support among individuals in a community (Kawachi & Berkman, 2001), plays a pivotal role in cultivating a sense of belonging and safety. An individual's sense of belonging reflects their integration into a social system and fulfills a fundamental need for connection (Ibarra-Rovillard & Kuiper, 2011). This feeling of belongingness correlates with elevated levels of self-esteem and overall well-being, establishing an inverse relationship between a sense of belonging and the manifestation of depressive symptoms (Markowitz A.J., 2017).

1.3.4. Individual characteristics

Intelligence may serve as a mitigating factor against adverse outcomes, including violent behavior, depression, and low self-esteem (Kuper & Turanovic, 2019; Meldrum et al., 2017). Specifically, higher intelligence is associated with the cultivation of self-control in youth, exerting a robust influence on overall life success. This success encompasses engaging in prosocial behavior, accumulating wealth, and achieving economic stability (Meldrum et al., 2017). Additionally, intelligence plays a crucial role in emotional and behavioral regulation, enhancing inhibitory control and the pursuit of long-term goals (Meldrum et al., 2017). Moreover, intelligence contributes to problem-solving skills (Widom et al., 2007) and the ability to communicate effectively (Boland & Ross, 2010). Elevated intelligence levels may facilitate more efficient problem-solving and coping strategies, ultimately reducing depressive symptoms in adulthood (Kuper & Turanovic, 2019).

High self-efficacy, a personality trait characterized by a belief in personal competence and the ability to manage stress (Luszczynska et al., 2005), has demonstrated its efficacy as a protective factor for mental health, particularly in the

context of depression (Tahmassian & Jalali Moghadam, 2011). In a study by Klasen et al., self-efficacy emerged with the highest direct beneficial effect on depressive symptoms in children and adolescents even when compared to environmental protective factors like family climate and social support (Klasen et al., 2015). Furthermore, a cross-sectional study of Finnish adolescents revealed a correlation between self-efficacy, physical activity, and higher-quality bonds with parents and peers. These correlated factors, in turn, were associated with fewer depressive symptoms (HAAVET et al., 2005).

Recent evidence suggests that religiosity/spirituality also plays a moderating role in the impact of stressful life events on depressive symptoms (Ahmed et al., 2011), particularly among females (Desrosiers & Miller, 2007). Intrinsic religiosity, characterized by personal religious commitment or motivation—pursuing religion as an end in itself, is linked to lower levels of depressive symptoms and reduced suicide risk in adolescents (Kim et al., 2020). Religiosity is multifaceted, serving as both an individual and environmental factor, with its moderating effects potentially linked to faith-based social support (Herzog et al., 2020). Religious involvement is also associated with broader social networks, increased perceived social support, and greater satisfaction with the levels of support received (Ellison & George, 1994; Helms et al., 2015). However, a study by Helms et al. (2015) revealed that intrinsic religiosity moderated the longitudinal relationship between peer victimization and depressive symptoms, even after accounting for the frequency of religious attendance (Helms et al., 2015).

1.2. THE RESILIENCE CONSTRUCT

Resilience to mental disorders, a neurobiological construct encompassing neurobehavioral and emotional features, has garnered increasing attention in recent years (Franklin et al., 2012). There are various approaches to assess this phenomenon; some authors measure it solely as the absence of a mental health diagnosis, while other studies describe resilience as a cluster of characteristics, treating it as a trait. The latter approach overlooks the crucial balance between stressor load and environmental factors that could enhance resilience, neglecting the significance of this equilibrium in discussions about mental disorder trajectories (Shrivastava & Desousa, 2016). This oversight has been observed by other authors who demonstrated that individuals

exposed to more stressors are less likely to exhibit resilience to negative outcomes, even when considering personal strengths (Kuper & Turanovic, 2019). Thus, in the study of resilience, it is imperative to consider protective factors that provide individuals with coping resources and support, while also moderating with risk factors that amplify the negative impact of trauma on well-being (Wright et al., 2019).

2. JUSTIFICATION

In medicine and psychiatry, there has been a historical emphasis solely on the disorders themselves, neglecting the individuals beyond their diagnoses (Insel & Wang, 2010). A shift in perspective is imperative, aiming to comprehend the characteristics and environments that play a protective role for vulnerable individuals. This change is crucial in reshaping how we approach the treatment and prevention of mental disorders. Furthermore, this project adopts an outlook that views mental illness as an outcome resulting from a developmental trajectory. This reinforces the significance of exploring how these factors interact during the formative years of individuals' lives. Coupled with a focus on longitudinal designs, this approach seeks to provide a more accurate understanding of how these factors act to prevent the development of mental disorders. Defining which factors have a major impact on resilience could be the differential between preventing new disorders and just treating individuals that have mental disease trajectories with chronic and relapsing mental disorders.

Given the diverse presentations and widespread comorbidity of mental disorders, it is expected that multiple factors influencing resilience or risk are relevant across various disorders. Unfortunately, investigating all these factors is beyond the current scope of this project. Consequently, depression was selected as a model to examine the outcome of insufficient resilience in at-risk subjects, owing to its well-established and extensively studied biological, behavioral, and psychological impacts. By focusing on this specific subject, this research proposal serves as a crucial initial step in developing preventive strategies that concentrate on enhancing protective factors and fostering resilient trajectories. Furthermore, this project could potentially serve as a model for exploring how protective factors impact other mental disorders, paving the way for broader applications in the field.

3. OBJECTIVES

The primary objective of this study is to explore the construct of resilience concerning Major Depressive Disorder (MDD) in at-risk individuals, aiming to identify the factors with the most substantial impact on preventing depression.

The specific objectives are as follows:

- a) Initially, we will conduct a comprehensive literature review to gather existing evidence on protective factors associated with depressive symptoms and MDD in at-risk populations, focusing exclusively on longitudinal studies. This phase will contribute to the creation of a systematic review and may potentially lead to a meta-analysis of the gathered data.
- b) Subsequently, we will delve into the identified protective factors from the aforementioned review using data obtained from a cohort specifically structured to monitor the incidence of psychiatric disorders. Our aim is to assess whether these factors exert an influence on the development of depression in at-risk individuals. The investigation will scrutinize both the interactive and independent contributions of each protective factor in preventing depression.

4. HYPOTHESES

Our primary hypothesis suggests that there is evidence supporting the existence of protective factors in longitudinal studies and their impact on mental health trajectories in at-risk individuals. Additionally, we anticipate that the presence of these protective factors will correlate with a reduced incidence of major depressive episodes in at-risk young adults during the third wave of a cohort specifically designed to examine the incidence of mental disorders.

5. ETHICAL ASPECTS

This project exclusively utilizes pre-existing data gathered from other studies. In the literature review, our examination will focus on verifying the ethical alignment of all selected studies with their respective institutions. Regarding our second paper, the data from the cohort adhered to the guidelines set forth by the Research Ethics

Committee of the Universidade Católica de Pelotas, protocol number 2008/118. Written consent was secured from participants who possessed the ability to read, write, and comprehend the written consent. For those who did not, verbal agreement was obtained. It is imperative to emphasize that information concerning the cohort's participants will be utilized solely and exclusively for the academic and scientific purposes outlined in this project.

6. PAPERS

6.1. ARTICLE 1

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Protective factors against depression in high-risk children and adolescents: a systematic review of longitudinal studies

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TITLE PAGE

Protective factors against depression in high-risk children and adolescents: a systematic review of longitudinal studies

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ABSTRACT

Background: Depression is a significant global disability, and early adverse experiences (EAE) represent consistent risk factors in children. However, protective factors play a vital role in promoting healthy development and mitigating these risks.

Methods: We conducted a thorough literature search on Pubmed, APA, Emcare, and EMBASE from 1946 to August 25, 2023. We included longitudinal studies analyzing protective factors for depressive symptoms in high-risk children or adolescents, excluding cross-sectional studies, reviews, and pre-clinical studies.

Outcomes: Our analysis comprised 29 studies with 62,405 participants, identifying 38 protective factors. Positive individual characteristics, family factors, peer relationships, school-related aspects, neighborhood characteristics and intrinsic religiosity were associated with reduced depressive outcomes.

Interpretation: These findings have important implications for developing preventive strategies in this population. Addressing protective factors can contribute to preventing depression and enhancing mental well-being across the lifespan.

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Keywords: protective factors, systematic-review, high-risk population, depression.

INTRODUCTION

Since 1990, depressive disorders have consistently held a significant position among the top ten causes of disability-adjusted life-years (DALYs) across various age groups, maintaining this status for ages 10–49, as reported by The Global Burden of Diseases.¹ In 2019, depressive disorders, along with anxiety disorders, ranked among the top three causes of DALYs among females, underscoring their enduring impact on health burdens.¹ In particular, childhood and adolescence are critical periods for brain development and the subsequent emergence of depressive symptoms.² Approximately one in five adolescents is anticipated to experience a diagnosable depressive episode by the age of 18, underscoring the imperative need to identify at-risk young individuals and mitigate the long-term impact of this disorder.³ Risk factors for mental disorders in childhood are often discussed in the literature as a combination of negative environmental exposures that typically co-occur. Early Adverse Experiences (EAE), such as childhood poverty, parental mental illness, family instability, exposure to violence, substance abuse or criminality, and child maltreatment, stand out as the strongest and most consistent risk factors for both depressive and anxious symptoms.⁴ These early experiences can disrupt parent-child attachment⁵ and alter the development of affect regulation and stress response systems.⁶

However, it is crucial to emphasize the significant role that protective factors play in fostering healthy development and alleviating the impact of risk factors.⁷ These factors can be regarded as positive influences in the environment that facilitate healthy development. While they may not necessarily promote normal progression in the absence of risk factors, they can make a notable difference when risk factors come into play.⁸ Understanding the intricate interplay between risk factors, protective factors, and the development of depressive symptoms enhances our comprehension of depression's etiology, guiding effective interventions for its prevention. Identifying protective factors is crucial to promote resilience and enhance mental well-being, particularly for individuals vulnerable to depressive symptoms. Hence, this study aims to adopt a preventive perspective by examining the literature, focusing on longitudinal studies investigating protective factors for the development of depressive symptoms in high-risk children and adolescents.

METHODOLOGY

This article presents a literature search conducted in accordance with the PRISMA guidelines - Key Items for Reporting Systematic Reviews and Meta-analyses⁹, and the PRISMA checklist is available in Suppl_Table 1. To ensure transparency of our methodology, the study protocol and search strategy are detailed in the supplemental material. Table 1 provides a comprehensive and objective overview of our inclusion and exclusion criteria. Our focus was on longitudinal studies investigating protective factors for depression in high-risk children and adolescents (18 years old or younger). High-risk criteria were defined by the presence of at least one of the following risk factors: low socioeconomic status, parental psychiatric disorders, or a history of maltreatment. We excluded studies that did not specifically explore protective factors in high-risk populations aged 18 years or younger. Additionally, review articles, preclinical studies, cross-sectional, case-control studies, and clinical trials were excluded.

We conducted a comprehensive search for studies spanning PubMed/Medline, Embase, Emcare, and APA from 1946 to December 15, 2022, encompassing cohort studies published in any language. In instances where language posed a barrier, we proactively engaged translation services to ensure inclusivity. The primary outcome sought was a reduction in the incidence of depressive symptoms or diagnosis. On August 25th, 2023, we executed an updated search to maintain the utmost currency of information for our study. Six investigators were paired to conduct both primary and secondary screenings independently. Initially, the primary screening involved evaluating titles and abstracts. Subsequently, PDFs of potentially eligible articles were obtained, and each pair conducted a secondary screening independently. Any discrepancies that emerged during the primary or secondary screenings were resolved through consensus among the pairs.

After the screening phase, the six authors were paired to systematically extract diverse data points from each article. This encompassed crucial information such as the sample's population type, geographical location, publication year, sample size per group, follow-up duration, gender distribution, mean baseline age, and types of risk factors (e.g., low socioeconomic level, parental psychiatric history, or maltreatment). We also extracted details on the tools used to measure risk and protective factors, the authors' key conclusions, and the studied outcome in each article. The outcomes ranged

from depressive symptoms, major depressive disorder (MDD) diagnosis, internalizing and externalizing problems, to emotional and behavioral issues, alongside the corresponding measurement tools. This systematic approach to study outcomes was adopted due to the varied assessment methods used for depressive symptomatology during childhood and adolescence. Furthermore, Figure 1 offers a comprehensive overview of the systematic literature search process.

QUALITY ASSESSMENT

The methodological quality of the included studies was determined using a heat map created through the Research Triangle Institute (RTI) item bank, which assesses representativeness and sample size, comparability between groups, the thoroughness of statistical reports, and the determination of outcomes and protective factors. Further information on the questions included is presented in Suppl_Table S2. Each study was given a score based on the number of applicable RTI items met and subsequently graded as low (0–.40), moderate (.41–.70), or high (.71–1) for methodological quality/risk of bias. The critical appraisal was carried out independently by two authors, with discrepancies being resolved by discussion. We utilized the GRADE criteria (Grading of Recommendations, Assessment, Development, and Evaluations) to evaluate the evidence quality (classified as high, moderate, low, or very low) for each association. This assessment resulted in an overarching score assigned to each paper. In the process of constructing the Evidence Map (Suppl_Table S4) we calculated the mean of the individual scores from each paper that explored the corresponding protective factor.

The methodological quality of the included studies was assessed using a heat map generated through the Research Triangle Institute (RTI) item bank.¹⁰ This comprehensive evaluation considers factors such as representativeness and sample size, comparability between groups, the thoroughness of statistical reports, and the determination of outcomes and protective factors.¹⁰ For detailed information on the design of our quality assessment scale, please refer to Suppl_Table S2. Each study received a score based on the number of applicable RTI items met and was subsequently categorized as low (0–.40), moderate (.41–.70), or high (.71–1) for methodological quality/risk of bias. Two authors conducted the critical appraisal independently,

resolving discrepancies through discussion. To gauge evidence quality, we applied the GRADE criteria (Grading of Recommendations, Assessment, Development, and Evaluations), classifying it as high, moderate, low, or very low for each association.¹¹ This assessment yielded an overarching score for each paper. To develop the Evidence Map (Suppl_Table S4), we computed the mean individual scores from each paper, subsequently arranging them from low to high risk of bias.

RESULTS

We identified 29 publications that reported a total of 38 protective factors, spanning the years 2002 to 2023. The participant count per study varied from 72 to 14,694, culminating in a total of 62,405 included individuals. The predominant focus was on studies conducted in the USA (n=20), while others were from the UK (n=2), Germany (n=3), Australia (n=1), Spain (n=1), Sweden (n=1), and China (n=1). The median follow-up duration was 4 years (IQR 2.06–10 years), and the mean age at baseline was 9.75 years (IQR 6.53–14 years). To define high-risk populations, certain studies took a comprehensive approach, considering multiple risk factors simultaneously as their criteria. The most frequently employed criteria for high-risk populations in longitudinal studies were childhood maltreatment (n=13), followed by socio-economic risks (n=12), and parental mental health problems (n=9). For detailed information on each article, refer to Table 2. The majority of studies received a low overall risk-of-bias score (i.e., overall risk-of-bias scoring $\leq 40\%$), with a mean overall risk of bias at 15.70%. The heat map, generated using the studies' RTI-bank scores, is presented in Suppl_Table S3. Out of the 38 protective factors identified, 18 factors (47.36%) had high evidence certainty according to GRADE, as illustrated in the Evidence Map on Suppl_Table S4. A comprehensive list of the protective factors is provided in Table 3, categorized as follows:

INDIVIDUAL CHARACTERISTICS

In 11 studies, significant associations were established between 11 distinct characteristics and reduced depressive outcomes.^{12–22} The most prevalent protective factor identified was intelligence and executive function, assessed through various measures, encompassing high cognitive skills¹³, higher IQ^{19,21}, verbal intelligence¹⁹, and reading comprehension¹³. Subsequently, self-efficacy^{22–24} and self-esteem^{13,14,21} emerged as frequently cited protective factors, each highlighted in three different papers. Nevertheless, one study was unable to find a significant association between IQ and depressive symptoms.¹³ Additionally, positive correlations were observed between adaptive stress responses^{18,20}, easy temperament^{12,13}, strong social functioning^{22,25,26}, intrinsic religiosity^{27,28}, and diminished depressive symptoms, while another study associated higher striving¹⁶ with decreased depressive tendencies. However, other

studies were unable to find a significant association between self-esteem²⁹ and internal locus of control¹³ and depressive symptoms. Another study was also unable to determine a protective effect for easy temperament against internalizing symptoms.¹² Furthermore, a study connected ego-resiliency¹⁵ to lower depressive symptoms. Notably, a specific study illustrated that possessing a particular genotype for the serotonin receptor (5-HTTLPR genotype) led to improved mental health outcomes in high-risk children.¹² Moreover, ethnic identity and an optimistic view of the future were not found to be significantly protective.²⁷

PARENTING AND FAMILY CHARACTERISTICS

The family environment emerged as the focal point in research exploring protective factors for children and adolescents, investigated across various dimensions (n=22)^{12-14,17-19,21,22,24,27,29-40}. Attachment between parental figures was a key focus, with seven studies highlighting its preventive impact on depression^{21,24,26,34,39-41}. We also found three studies that emphasized maternal attachment^{31,33,35}, while one underscored the significance of paternal attachment⁴⁰. Intriguingly, while caregiver involvement and aspects like positive parenting³² exhibited preventive tendencies in some papers, they were inconclusive¹³ or even deemed risk factors in another study³⁵. Additionally, the caregiver's emotional regulation and sense of coherence emerged as influential protective factors for a child's mental well-being^{12,18}. The overall household atmosphere was examined in three studies^{14,17,22}, with two of them employing the Family Environment Scale⁴². Feeling supported^{27,36} and accepted¹⁸ within the family context was significantly associated with depression prevention, documented in three separate studies. Investigations also delved into the family structure's impact on depression prevention, highlighting the protective effects of a two-parent household²⁴, higher parental educational levels²⁴, and lower perception of marital discord²⁹. Positive sibling relationships were also identified as a contributing factor to future mental health¹³ as well as having a family routine^{24,30,40}.

SCHOOL, COMMUNITY, AND RELATIONSHIPS OUTSIDE THE FAMILY

The quality of individuals' personal relationships was investigated by 12 studies^{13,14,22,24,26,27,32,33,36,39,40}, with only one¹³ failing to demonstrate a significant protective effect for having supportive friendships against depressive symptoms. Five authors found a significant protective association between positive school experiences and depressive symptoms.^{13,26,27,40,43} Notably, one of these authors identified a significant protective effect for a positive perception of school but did not find the same associations with high school engagement and school attendance in relation to lower depression symptom scores.¹³ Additionally, two studies demonstrated the preventive power of regular participation in extracurricular activities^{13,41}, while one study failed to show this association³⁶.

Experiencing support^{14,23}, particularly from individuals outside the immediate family³⁶, has been established as a protective factor. However, it is noteworthy that one study did not identify a statistically significant protective effect with supportive friendships¹³, while another study did not demonstrate a significant impact for teacher support²⁷. Notably, three studies underscored the importance of neighborhood social cohesion^{18,24,38} as a protective factor, although two other investigations^{30,36} did not establish a clear association. Similarly, the role of religious attendance yielded mixed results, with one study revealing a significant protective effect⁴⁴, while two others failed to substantiate this finding^{13,28}. In addition, service provision²¹, a perceived high socioeconomic level²⁴, and strong academic performance²⁹ did not emerge as statistically significant factors in the examined studies.

DISCUSSION

Through a comprehensive exploration of longitudinal studies focusing on protective factors, this review unveils a wealth of positive influences that can lead to a decrease in depressive outcomes among high-risk children and adolescents. By understanding and harnessing these factors, we may pave the way for a more proactive and optimistic approach to preventing and promoting mental well-being in the vulnerable youth.

While certain identified protective factors, such as IQ, temperament, intrinsic religiosity, or genotype, may be inherently non-modifiable, the majority of our findings suggest that targeted programs could influence various protective factors. Interventions

emphasizing the development of self-efficacy and healthy coping strategies have demonstrated positive effects on overall well-being in children and adolescents ^{45,46}. Notably, increased self-efficacy, reflecting a belief in personal competence and stress management abilities ⁴⁷, has proven to be a protective factor for mental health ⁴⁸, particularly in the context of major depression ⁴⁹. It is of note that there were multiple individual characteristics that were not proven to significantly protect against depression in our review. This may be attributed to the potential deficiency in positive intrinsic characteristics among high-risk individuals, leading to their dependency on their environments for support. For instance, children exposed to maltreatment may exhibit lower self-esteem, self-efficacy, and IQ⁵⁰⁻⁵².

Low IQ has been recognized as a risk factor for depressive symptoms across various clinical and population samples ^{53,54}. Consequently, it is reasonable to expect that individual traits linked to higher cognitive capacity, such as higher IQ, advanced cognitive skills, and superior reading comprehension, have been found to act as protective factors against the onset of depressive symptoms our study ^{13,16,19,21}. While one paper in our review did not demonstrate a significant relationship between overall IQ scores and resilience, other measures of cognitive abilities, such as high cognitive skills and advanced linguistic abilities, were identified as protective factors in the same study. This may suggest a potential bias in the testing methodology used in that specific paper.¹³ Nonetheless, intelligence has been associated with emotional and behavioral regulation, greater inhibitory control, better problem-solving skills, and effective communication abilities, enabling individuals to cope with stressors in ways that may reduce depressive symptoms in adulthood.^{19,55,56}

Numerous cross-sectional studies have consistently shown positive health outcomes for children raised in functional families, characterized by close emotional relationships between parents and children, mutual support, and quality time spent together ⁵⁷⁻⁶⁰. Our review further corroborated these findings, despite the heterogeneous measurement of family environments in the studies involving children and adolescents. It became evident that a more structured and cohesive family environment appears to be more protective. Parents who are actively involved with their young ones and display enhanced emotional regulation seem to have a lower incidence of depression in their offspring. Interestingly, one study indicated that spending more

time with a mother with mental health issues increased the likelihood of the participant experiencing depression at follow-up. This underscores the significance of interventions aimed at preventing and treating parents' mental disorders to mitigate the risk of depression in their children. Such interventions should focus on enhancing attachment, promoting positive parenting techniques, and developing emotional regulation skills in parents, as well as effectively treat parents who are in need of mental health support.

In our review, multiple studies highlighted the particularly protective role of quality peer relationships against depressive symptoms in children and adolescents, alongside a positive perception of school. These findings align with cross-sectional studies underscoring the significance of positive friendships, particularly during adolescence.⁶¹ Focusing interventions within school settings to nurture improved peer relationships may yield additional benefits, simultaneously enhancing both school environments and peer support. This dual enhancement could exert an additional preventive effect against depression in children and adolescents. Positive school experiences, encapsulated by a broader concept like school connection^{40,43}, were explored in a systematic review. The findings indicated that higher levels of school connectedness in children and adolescents predict lower levels of depressive and/or anxiety symptoms in both population-based and intervention studies during adulthood.⁶²

Moreover, the findings related to participation in structured activities were inconsistent, with an equal number of papers demonstrating these factors as significantly protective and others not. This discrepancy may arise from other aspects of extracurricular activities contributing to the prevention of depressive symptoms, rather than the activities themselves. A parallel observation was made by Cahill et al., where a positive perception of school had a protective effect, but high school engagement and school attendance did not exhibit the same statistical significance in a population of maltreated children and adolescents¹³. Also of note, was that teacher support did not prove to be significant in a large study of children at psychosocial risk, while other types of support were protective.²⁷ It is possible that teachers in socioeconomically deprived areas are less available to offer their students emotional support, leading children and adolescents to seek help from other sources.

While positive neighborhood factors have demonstrated a safeguarding impact on individuals' mental health in another review ⁶³, our findings regarding neighborhoods as a protective factor were inconsistent. This inconsistency may stem from two studies where participants faced the risk factor of maltreatment, and neighborhood connection was identified as protective ^{24,38}. This suggests that, in these instances, communities might have functioned as a protective factor. Nevertheless, individuals at psychosocial risk may not experience as much benefit from their community in alleviating depressive symptoms, as indicated by other studies ^{30,36}. Given the ample evidence that an individual's neighborhood could act as a protective⁶⁴ or a risk factor⁶⁵ concerning mental health outcomes in children, more studies should be conducted in high-risk children to understand how the interaction of positive neighborhood traits influences risk factors such as maltreatment and psychosocial risk.

Religiosity emerges as a factor contributing to a child's resilience against depression, mirroring observations in studies involving maltreated children where religiosity demonstrated protective effects on internalizing and externalizing symptomatology.⁶⁶ Notably, higher rates of spiritual/religious well-being seem to reduce the likelihood of depressive symptoms and risk-taking behaviors in children and adolescents.⁶⁷ However, the significance of religious attendance remains inconclusive in our review, with two papers failing to establish its significance. Interestingly, one author found that service attendance was protective, while religious importance was not.⁴⁴ This discrepancy may stem from the context of the studies, where the paper affirming attendance as protective focused on children with parental mental health issues, while those disputing its significance targeted populations with psychosocial risk and maltreatment. This suggests that children with ill parents may find solace in a structured religious environment, potentially experiencing a more effective protective effect against depression than other populations in disadvantaged communities or maltreatment victims.

Given the significance of various protective factors in preventing depression, it may be worthwhile to explore an approach that considers the cumulative effect of these preventive factors, as illustrated by Zhang et al ⁶⁸. In their study, which involved a sample of 2,288 high-risk individuals, they demonstrated that children with 2-3 positive childhood experiences exhibited better outcomes compared to those with 0-1

positive experiences, regardless of the specific nature of those positive experiences. Previous research highlights this quantitative balance, indicating that a cumulative impact of positive childhood experiences can counteract risk factors, irrespective of the specific quality or type of positive experience, contributing to improved outcomes⁶⁹. Consequently, families and communities might shift their focus from providing singular, advantageous experiences to cultivating a diverse array of positive experiences that align with individual, family, and cultural contexts⁵⁷.

To our knowledge, this is the first review conducted with this preventive perspective in longitudinal studies in high-risk children and adolescents. However, we encountered limitations due to the prevailing illness-focused academic landscape, resulting in a scarcity of studies exploring protective factors and resilience, potentially skewing the available literature towards pathology-oriented research. The diverse methodologies employed for assessing depressive symptoms across the included studies, along with innovative statistical approaches, posed challenges in conducting a meta-analysis, which prevented a reliable quantitative comparison of effect sizes for distinct protective factors. Moreover, the heterogeneity that arose from diverse study methodologies, populations, and quality levels complicated the synthesis of results and constrained our ability to draw definitive conclusions. It's noteworthy that our search methodology lacked manual searches, potentially overlooking relevant manuscripts. Additionally, publication bias, favoring studies with positive or significant results, could influence the overall interpretation of evidence. Furthermore, although our study wasn't registered in PROSPERO, we have made our comprehensive study protocol available in the supplemental material to ensure transparency regarding our methodology.

In conclusion, the prevalence of depression and its impact on individuals' lives and functioning make it a significant public health concern. Early identification of potential protective factors is crucial, as effective interventions in high-risk children and adolescents can prevent adverse mental outcomes in adulthood. By addressing protective factors and providing appropriate support, we can strive to promote mental well-being and enhance the overall quality of life for individuals across the lifespan. Shifting our perspective to center on protective factors and embracing a mental health-oriented approach could prove pivotal in how we comprehend and effectively assist

high-risk individuals, fostering a more comprehensive and proactive approach to mental health care.

CONFLICT OF INTEREST

All authors report no competing interests.

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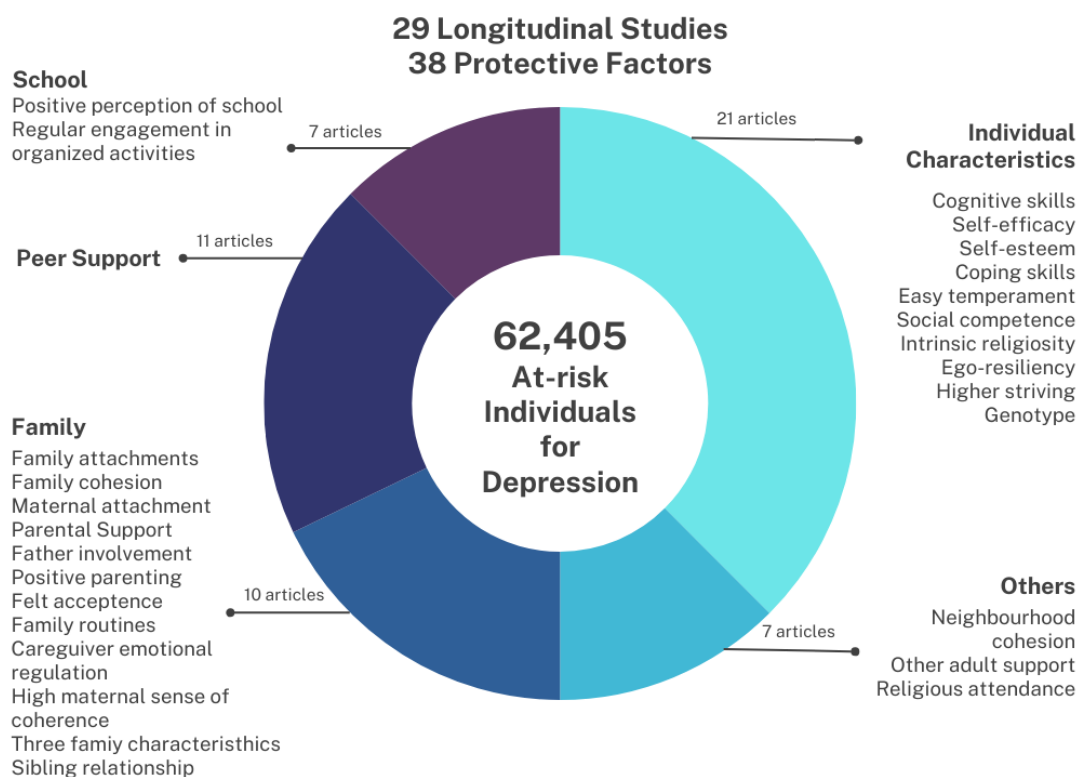
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FIGURE 1. VISUAL ABSTRACT



Source: Tietbohl-Santos et al, 2024. *Revista brasileira de psiquiatria*, 46, e20233363 (Sao Paulo, Brazil).

TABLE 1: INCLUSION AND EXCLUSION CRITERIA.

Inclusion Criteria	Exclusion Criteria
Longitudinal population studies.	Review articles, clinical trials, any therapeutic or public intervention trial, pre-Clinical trials, case-control studies or cross-sectional studies.
<p>Included:</p> <p>*high-risk for depression individuals aged 18 years or younger.</p> <p>*High-Risk criteria (at least one of the following):</p> <ol style="list-style-type: none"> 1) Low socioeconomic level 2) Positive parental psychiatric history 3) Maltreatment 	<p>Studies that did not specifically examine high-risk individuals for depression.</p> <p>OR</p> <p>Studies that did not examined children and adolescents (18-year-old or younger).</p>
Studies that assessed protective factors during childhood that reduced the incidence of depression.	Studies that did not investigate protective factors for depression.
Original studies published in any language.	

Table 1. Summary of Reviewed Inclusion and Exclusion Criteria for the Systematic Literature Search
 Source: Tietbohl-Santos et al, 2024. *Revista brasileira de psiquiatria*, 46, e20233363 (Sao Paulo, Brazil).

TABLE 2. DETAILED INFORMATION - EXTRACTION TABLE

Author (Year)	(% male), country	Mean age at baseline (years) ± SD (or range)*	Mean follow up time in Years	At-Risk criteria (Measure)	Relevant findings					*GRADE evidence (high, moderate, low, or very low)					
					Outcome / Depressive symptoms (measure)	Protective factor (measure)	Direction of affect	Additional information	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence
Agnafors (2017)	889 (52.8%), Sweden	Birth	12	Childhood Maltreatment (The Life Stress Score -LSS); Parent with Mental Health Problems (The Edinburgh Postnatal Depression Scale -EPDS)	Internalizing and externalizing problems (The Child Behavior Check List - CBCL)	A high maternal sense of coherence (The Sense of Coherence form - SOC)	Protective		internalizing B -0.05 (CI = -0.08 to -0.01, p = 0.005) externalizing B -0.05 (CI = -0.09 to -0.01, p = 0.005)	VL	VL	VL	VL	VL	High
						Easy temperament (form created based on the concept of the "difficult child")	Protective	Only protective to externalizing problems	internalizing NS externalizing B -0.14 (CI = -0.21 to -0.07, p = < 0.001)						
						Good social functioning (The Child Behavior Check List - CBCL)	Protective		internalizing B -0.07 (CI = -0.13 to -0.18, p = < 0.001) externalizing B -0.34 (CI = -0.52 to -0.16, p = < 0.001)						
						5-HTTLPR genotype	Protective		internalizing B -0.97 (CI = -1.66 to -0.30, p = 0.005) externalizing B -0.84 (CI = -1.61 to -0.07, p = < 0.033)						

Bayer (2015)	283 (53.4 %), Australia	1	3	Parent with Mental Health Problems (The Depression, Anxiety, Stress Scale - DASS); Psychosocial Risk (Health service screening questions assessed home violence, substance misuse and social isolation)	Internalizing and externalizing problems (The Child Behavior Check List - CBCL)	Potentially protective aspects of maternal parenting: Nurturing, appropriate developmental expectations, and low harsh discipline (Parent Behaviour Checklist).	Protective	Only low harsh discipline fostered resilient child outcomes.	Canonical R = 0.45; Chi-square F (12, 1) = 20.87, p = .05)	Mod	VL	VL	Mod	L	Mod
Cahill (2022)	14694 (52.3 %), UK	Birth	23	Childhood Maltreatment (parent questionnaire with 87 questions about the child's exposure to 15 ACEs between the ages of 11 and 16 years)	Depressive symptoms (Short mood and feelings questionnaire)	Higher IQ (Task Wechsler Intelligence Scale for Children I, II - Wechsler, 1992)	NS		B 1.47 (CI = -0.10 to 3.04, p = 0.066)	VL	VL	VL	VL	VL	High
						Easy temperament (Emotionality Activity Sociability scale)	Protective		B 0.28 (CI = 0.24 to 0.32, p = < 0.001)						
						Internal locus of control (Nowicki-Strickland Internal-External scale for preschool and primary children)	NS		B 0.25 (CI = -0.07 to 0.57, p = 0.127)						

					High mental flexibility (Stop Signal)	NS		B - 0.02 (CI = - 0.36 to 0.33, p= 0.928)						
					High self-esteem (Harter's Self Perception Profile for Children)	Protective		B 0.08 (CI = 0.01 to 0.14, p = 0.033)						
					High linguistic ability Reading Skills and Accuracy (Neale Analysis of Reading Ability),	Protective		B 0.21 (CI = 0.06 to 0.35, p = 0.008)						
					High cognitive skills (15 questions answered by the mother on cognitive skills)	Protective		B 2.75 (CI = 0.97 to 4.53, p = 0.004)						
					Attachment to grandparent (Mother asked whether child was particularly attached to grandparent),	NS		B - 0.04 (CI = - 0.33 to 0.26, p = 0.803)						
					Sibling relationship (7 questions answered by the mother)	Protective		B 0.05 (CI = 0.02 to 0.09, p = 0.007)						
					High school engagement / School attendance (Total number of days off	NS		NS						

						school the child had taken in the last year)									
						Positive perception of school (questions answered by the child aged 11 yrs 2 months and 14 years 1 month on how strongly they agreed with seven positively stated opinions of school)	Protective		B 0.13 (CI = 0.09 to 0.18, p = < 0.001)						
						Regular engagement in extracurricular activity (two questions answered by the mother)	Protective		B 0.54 (CI = 0.26 to 0.82, p = < 0.001)						
						Supportive friendships (Friendships questionnaire from the Cambridge Hormones and Moods Project)	NS		NS						
						Engagement with religion (two questions)	NS		NS						
Carbonell (2002)	102, (44.85 %), USA	5	21	Parent with Mental Health Problems and Psychosocial Risk (Family	Major Depressive Disorder (The Diagnostic Interview	Family Cohesion (The Family Adaptability and Cohesion	Protective		t = 1.96 (p = < 0.05)	Mod	L	Mod	L	VL	Mod

				History Assessment Module)	Schedule IV - DIS IV)	Evaluation Scales III - FACES-III)									
						Social Support (Arizona Social Support Interview Schedule - ASSIS)	Protective		$\chi^2 = 3.60$ (p = < 0.05)						
						Positive Outlook of self (Total Self-Concept score on the Self-Appreciation subscale, the Rosenberg Self-Esteem Scale, and one item on the CDI "Things will work out for me okay.")	Protective		t = 4.33 (p = < 0.001)						
						Interpersonal Relations (The Piers-Harris popularity subscale)	Protective		t = -1.81 (p = < 0.05)						
Causadias (2012)	136 (55.14 %), USA	4	28	Psychosocial Risk (sociodemographic questionnaire)	Internalizing and externalizing problems (Adult Self-Report - ASR)	Ego-control - the capacity to regulate and express emotions and feelings (California Child Q-Set - CCQ)	Risk	Risk for externalizing problems.	internalizing NS externalizing β 0.29 (p = < 0.001)	L	VL	VL	L	L	High
						Ego-Resiliency - the capacity to adapt and be	Protective		internalizing β - 0.31 (p = < 0.001)						

						flexible in responding to situational demands (California Child Q-Set - CCQ)			externalizing β - 0.26 ($p = < 0.05$)						
Chester (2007)	242(N A%), USA	7-15	1	Psychosocial Risk (sociodemographic questionnaire)	Depressive symptoms (Child Depression Inventory - CDI)	Peer relationship quality (Best Friend Questionnaire - BFQ)	Protective		β -0.18 ($p < 0.001$)	Mod	L	VL	Mod	VL	Mod
						Positive parenting (“The Monitoring and Control Questionnaire” and “The short form of the Interaction Behavior Questionnaire”)	Protective		β -0.17 ($p < 0.01$)						
Cotter (2016)	5894, (49.1 %), USA	11-13	3	Psychosocial Risk (belonging to economically disadvantaged counties)	Internalizing and externalizing symptoms (Youth Self Report - YSR)	Future optimism (Future optimism scale)	NS		NS	L	L	L	L	L	High
						Parent Support (Parent Support scale)	Protective	Prevented internalizing symptom but did not affect externalizing symptoms.	internalizing β 0.975 ($p = < 0.01$) externalizing NS						
						Friend Support (measured with a five- item Likert scale)		Significantly buffered against externalizing behavior for females only.	internalizing NS externalizing β 1.025 ($p = < 0.01$)						

						Teacher support (Teacher Support scale)	NS		NS						
						Religious Orientation (Three-item religious orientation scale)	Protective	Significantly buffered against externalizing behavior for females only.	internalizing NS externalizing β 0.980 ($p = <0.01$)						
						School Satisfaction (School Satisfaction scale)	Protective	Prevented externalizing symptoms for females but did not affect internalizing symptoms.	internalizing NS externalizing β 0.950 ($p = <0.001$)						
						Ethnic Identity (Phinney's six-item Multigroup Ethnic Identity Measure - MEIM)	NS		NS						
Doom (2017)	13341 (50.9%), USA	15.9	14	Childhood Maltreatment (retrospective questionnaire about child maltreatment)	Depressive symptoms (Center for Epidemiologic Studies Depression Scale)	Striving (sum of six Likert style questions about belief in hard work, school engagement, optimism, and educational aspirations)	Protective	Higher striving was also associated with lower CVD risk, higher income and college degree attainment.	B -0.19 (CI = -0.22, -0.17, $p < 0.001$)	Mod	VL	VL	VL	Mod	High
Ezpeleta (2008)	72, (56%), Spain	9-13	3	Psychosocial Risk (schedule for risk factors - SRF)	Internalizing and externalizing symptoms (Diagnostic Interview for Children and	Children's social skills and self-esteem (questionnaire)	NS		NS	Mod	L	VL	L	Mod	Mod
						Good school achievement (questionnaire)	NS	NS							

					Adolescents, the MAGIC)	Low perception of marital discord (Family Psychiatric History Screen for Epidemiologic Studies)	Protective		OR = 0.83 (CI = 0.26–2.59, p = 0.044)						
						Family's characteristics (Family APGAR; parental monitoring scale; Parental Discipline Practices Scales; Child's Perception of Interparental Conflict Scale; Dyadic Adjustment Scale)	NS		NS						
Gaylord-Harden (2009)	393 (49%), USA	10-16		Psychosocial Risk (sociodemographic questionnaire)	Depressive symptoms (The Children's Depression Inventory - CDI)	Maternal attachment (Parent and Peer Attachment (IPPA)	Protective	Higher maternal attachment predicted higher active coping, which in turn predicted fewer depressive symptoms at Time 2	β -0.299 (p= <0.001)	L	L	L	VL	L	High
						Coping strategies (Children's	Protective	Greater use of active coping strategies	β -0.236 (p= <0.001)						

						Coping Strategies Checklist)		predicted fewer depressive symptoms for girls but not for boys.							
Hardaway (2016)	312 (50%), USA	14		Psychosocial Risk (sociodemographic questionnaire)	Internalizing problems and externalizing problems (Child Behavior Checklist and Youth Self Report)	Parental involvement (Parenting Style Index)	Protective		internalizing β -1.47 ($p < 0.01$) externalizing β 1.53 ($p < 0.01$)	VL	L	Mod	L	VL	Mod
						Kinship Support (Kinship Support Scale)	Protective		internalizing β -1.13 ($p < 0.05$) externalizing NS						
Harold (2014)	Sample 1: 100 (0%), Sample 2: 145 (0%), UK	Sample 1: 11.54 Sample 2: 11.70	Sample 1: 2 Sample 2: 2.25	Sample 1: Childhood maltreatment (living in foster care) Sample 2: Parent with Mental Health Problems (individuals with a history of recurrent unipolar depression recruited predominantly from general practices across South Wales)	Depressive symptoms (Center for Epidemiologic Studies Depression Scale - CESD)	Maternal caregiver involvement (time they spent with their caregiver)	Risk/Protective	Time with caregiver had a protective effect on initial symptoms on sample 1, but was related to increased symptoms over time on both samples.	Sample 1 (T1): β 0.28 ($p = 0.01$) Sample 1 (T2): NS Sample 1 (T3): NS Sample 2: NS	L	Mod	Mod	Mod	L	Mod
Helms (2015)		17.13	1	Psychosocial Risk (belonging	Depressive symptoms	Intrinsic religiosity (The	Protective		β 0.64 ($p < 0.001$)	L	VL	L	L	L	Mod

	313 (56%) , USA			to low-income high schools)	(Mood and feelings questionnaire)	Duke University Religion Index)									
						Religious attendance (7- point Likert question regarding frequency of attendance to service)	NS	Attendance was only protective when not controlling for intrinsic religiosity	NS						
Jain (2012)	911 (51%) , USA	11-16	7	Psychosocial Risk (My ETV scale)	Depressive symptoms (Youth Self Report and Young Adult Self Report scales)	Family support (Provision of Social Relations instrument)	Protective		$\beta - 0.24$ ($p = < 0.001$)	VL	VL	VL	L	VL	High
						Friend support (Provision of Social Relations instrument)	Protective		$\beta - 0.08$ ($p = < 0.05$)						
						Other adult support (Provision of Social Relations instrument)	Protective		$\beta - 0.10$ ($p = < 0.01$)						
						Positive peer influence (10 items from Deviance of Peers)	Protective		$\beta - 0.16$ ($p = < 0.001$)						
						Time spent in structured activities (calculated based on 2 items from the school questionnaire)	NS		NS						
						Neighborhood social cohesion (5 items from	NS		NS						

						the community survey)									
Kasen (2012)	126 (41.1 %), USA	>6	20	Parent with Mental Health Problems (based on Research Diagnostic Criteria -RDC)	Major Depressive Disorder (Diagnostic interviews DSM-III-R diagnoses)	Religious importance (Questionnaire)	NS		NS	L	VL	L	L	L	High
						Service attendance (Questionnaire)	Protective	Attendance was protective for any mood disorder in the offspring of depressed parents	OR = 0.94 (CI = 0.58–1.53, p = <0.05)						
Klasen (2015)	1643 (49.4 %), Germany	11-17	2	Parent with Mental Health Problems (Symptom-Check List 9-item Short-version - SCL-S9)	Depressive symptoms (Center for Epidemiologic Studies Depression Scale - CES-DC)	Social support (Social Support Survey)	Protective		β -0.104 (p = < 0.001)	VL	VL	VL	L	L	High
						Self-efficacy (General Self-efficacy Scale - GSE)	Protective		β -0.190 (p = < 0.001)						
						Family climate (German Family Climate scale - FCS)	Protective		β -0.065 (p = 0.012)						
Kliewer (2004)	70 (55%), USA	11-15	0.5	Psychosocial Risk (Children's Exposure to Community Violence)	Internalizing and externalizing problems (The Child Behavior Check List - CBCL)	Caregiver emotional regulation (Meta-emotion philosophy interview)	Protective		internalizing β -0.29 (p = <0.001) externalizing β -0.42 (p = <0.001)	Mod	L	L	Mod	Mod	L
						Felt acceptance (Acceptance/Rejection subscale from the Child Report of Parent Behavior Inventory)	Protective		internalizing β -0.58 (p = <0.001) externalizing β -0.55 (p = <0.001)						
						Child emotional regulation (Emotion	Protective		internalizing β -0.41 (p = <0.001)						

						Regulation Checklist			externalizing β -0.42 (p = <0.001)						
						Caregiver-Child Relationship Quality (Observed caregiver-child interaction)	Protective		internalizing β NS externalizing β -0.30 (p = <0.05)						
						Neighborhood Cohesion (Neighborhood Cohesion Scale)	Protective		internalizing β -0.39 (p = <0.01) externalizing β NS						
Kuper (2019)	3374 (49.8 %), USA	15	7	Childhood Maltreatment (Retrospective questionnaire)	Depressive symptoms (Center for Epidemiologic Studies Depression Scale - CES-DC)	Verbal intelligence (age-normed Add Health Picture Vocabulary Test - PVT)	Protective		β -0.019 (p = < 0.01)	VL	L	L	Mod	L	Mod
Kwak (2018)	790 (40.9 %), USA	12-16	3	Childhood Maltreatment (Caseworkers reported maltreatment)	Depressive symptoms (Children's Depression Inventory - CDI)	Family attachments (5 Likert-scale questions)	Protective		β -0.062 (p = < 0.01)	Mod	L	L	Mod	Mod	Mod
						Organized activity participation (Open-ended question from the Youth Self Report instrument)	Protective	Participation in academic organizations was the only type of activity that was related to lower depressive symptoms.	β -1.49 (p = < 0.05)						
Laucht (2002)	348 (48.8 %), Germany	0.25	8	Psychosocial Risk (Family adversity index)	Internalizing and externalizing problems (The number of	Healthy Mother-infant dyads (The videotaped interactions	Protective	Children of depressed mothers developed especially	Not available	High	Mod	Mod	High	High	L

					problem behaviours was summed up leading to a total problem score)	were rated with the Mannheim-Rating-System for Mother-Infant Interaction MRS-MII)		favourable (and did not differ from the control group in the number of externalizing problems), if their mothers had displayed more reactivity and used more babytalk during interaction with their infants.							
Markowitz (2015)	8570 (47.7%), USA	12-18	14	Childhood Maltreatment (Retrospective questionnaire)	Depressive symptoms (Center for Epidemiologic Studies Depression Scale)	School connection (Questionnaire about participants' subjective feelings of belongingness and support at school)	Protective		β -0.09 (p = < 0.01)	VL	VL	L	VL	Mod	Mod
Monti & Rudolph (2017)	165 (48.4%), USA	12.43	4	Parent with Mental Health Problems (Structured Clinical Interview for the DSM)	Major Depressive Disorder (Schedule for Affective Disorders and Schizophrenia for School-Age Children—	Responses to stress (Responses to Stress Questionnaire)	Protective	Adaptive responses to stress (high effortful engagement and low involuntary disengagement) buffered the effect of maternal	Effortful engagement β 0.25 (p = < 0.0) Effortful disengagement NS Involuntary engagement NS Involuntary disengagement β 0.25 (p = < 0.0)	Mod	L	L	L	Mod	Mod

					Epidemiologic Version 5)			depression on initial levels and trajectories of youth depression								
Oshri (2017)	1179 (42.1%), USA	12.75	3	Childhood Maltreatment (Maltreatment Classification System)	Depressive symptoms (Children's Depression Inventory – CDI)	Caregiver-child closeness (In-Home Questionnaire)	Protective		β -0.10 (p = < 0.01)	L	L	L	VL	L	High	
						Peer relationships (Sum of six self-reported items, assessing for social competency and satisfaction in peer friendships)	Protective		β -0.21 (p = < 0.01)							
						School engagement (Seven 4-item Likert-Scale type questions)	Protective		β -0.27 (p = < 0.01)							
						Positive community environment (Four 3-item Likert-Scale type questions)	Protective		β -0.04 (p = < 0.01)							
Pargas (2010)	816 (48%), USA	15	5	Parent with Mental Health Problems (Delusions-Symptoms States Inventory)	Internalizing and externalizing behavior problems and Youth Axis I diagnoses	Service provision (Caseworkers responded to a single, dichotomous item about	NS		NS	Mod	VL	L	L	Mod	L	

				of Bedford and Foulds -DSSI)	(Structured Clinical Interview for the DSM / The Young Adult Self-Report - YASR)	service provision)									
						Child IQ estimate (Wechsler Intelligence Scale for Children)	Protective			OR = 1.14 (CI = 1.04–1.26, p = 0.01)					
						Self-esteem (Self-Perception Profile for Adolescents)	Protective			OR = 1.39 (CI = 1.04–1.84, p = 0.02)					
						Perceived parent–child relationship quality (Children’s Report of Parental Behavior Inventory - CRPBI)	Protective	One factor—maternal warmth—was associated with continued high functioning (or resilience) regardless of maternal depression status.		OR = 1.01 (CI = 1.01–1.02, p = 0.02)					
Plass-Christl (2018)	325 (51.2 %), Germany	11-17	2	Parent with Mental Health Problems (Symptom-Check List 9-item Short-version - SCL-S-9)	Internalizing and externalizing problems (strengths and difficulties questionnaire -SDQ)	Child peer relationships and child social functioning (A semi- structured interview for adolescents was developed from earlier versions of chronic strain and functioning for adults and children of the UCLA Life	NS		NS	L	Mod	L	VL	Mod	Mod

						Stress Interview)									
						Self-efficacy (General Self-Efficacy Scale - GSE)	Protective		Internalizing β -0.12 (p = <0.001) Externalizing β -0.09 (p = <0.001)						
						Social competence (Five 3-item-likert-style questions developed in the Health Behavior in School-aged Children study)	Protective		Internalizing β -0.39 (p = <0.001) Externalizing β -0.13 (p = <0.01)						
Russotti (2023)	260 (0%), USA	15.29		Childhood Maltreatment (caseworker reports)	Depressive symptoms (The Beck Depression Inventory - BDI-II)	Parental and peer attachment (The inventory of parent and peer attachment - IPPA)	Protective	Maltreatment did not significantly predict depression for those with the Global High, Global Low, and Low Father profiles, possibly indicating protective effects conferred by diverse constellations of relationship quality.	Parental T1 Warmth β - 0.17 (p = <0.001) Parental T1 Control NS	L	VL	High	VL	L	High
Thakur (2022)	943 (49.7 %), USA	12	6	Childhood Maltreatment (Retrospective questionnaire)	Depressive and PTSD symptoms (Trauma	Family climate (German Family Climate scale - FCS)	Protective		Internalizing β NS Externalizing β -0.09 (p = <0.001)	Mod	Mod	VL	Mod	L	Mod

					Symptom Checklist for Children)	Social cohesion (Quality of Neighborhood, Residential Stability & Organizational and Religious Affiliation Questionnaire)	NS		NS						
Wang (2021)	3426 (52.5%), USA	0	15	Childhood Maltreatment (Parent-Child Conflict Tactic Scale)	Depressive and anxious symptoms (Center for Epidemiologic Studies Depression Scale)	Family routines (Family Routines Questionnaire)	Protective		$\beta -0.02$ (p = < 0.001)	L	L	L	VL	Mod	Mod
						Parental warmth (Home Observation for Measurement of the Environment /HOME Inventory parental warmth subscale)	Protective		$\beta -0.05$ (p = < 0.05)						
						Father involvement (Mothers reported four questions about father's involvement)	Protective		$\beta -0.07$ (p = < 0.001)						
						School connectedness (Panel Study of Income Dynamics scale - PSID-CDS-III)	Protective		$\beta -0.09$ (p = < 0.001)						
						Peer relationship	Protective		$\beta -0.13$ (p = < 0.001)						

						(Panel Study of Income Dynamics scale - PSID-CDS-III)										
Zhang (2021)	2288 (57.6%), China	8.15	6	Childhood Maltreatment (Parent Questionnaire)	Depressive symptoms (Strengths and Difficulties Questionnaire -SDQ and Moods and Feelings Questionnaire)	Collective efficacy (Collective Efficacy Scale)	Protective	Compared with those reporting 0 to 1 PCEs, adolescents reporting 2 to 3 PCEs had significant lower depressive symptoms and ODD, while those with 4 to 5 PCEs had more reduced depressive symptoms and ODD. Findings suggest that PCEs may mitigate the negative effect of chronic childhood maltreatment on psychopathology reported at age 14 in a dose-response manner.	β -0.09 (p = < 0.001)	VL	VL	L	VL	VL	High	
						High parental education (Socioeconomic questionnaire)	Protective		β -1.70 (p = < 0.001)							
						High perceived SES (Socioeconomic questionnaire)	NS		NS							
						High parental warmth (Self-Reported Parenting Attitudes and Behaviors Scale)	Protective		β -3.10 (p = < 0.001)							
						Two-parent family (Socioeconomic questionnaire)	Protective		β -2.07 (p = 0.003)							
						Peer support (indicator for high peer support was the number of good friends -three or more were considered high)	Protective		β -2.89 (p = < 0.001)							

Table 2. Compilation of Extracted Information from Reviewed Articles.

*GRADE, Grading of Recommendations Assessment, Development, and Evaluation; VL, very low; L, low; Mod, moderate; NA, not applicable; OR, odds ratio; NS, not significant

Source: Tietbohl-Santos et al, 2024. *Revista brasileira de psiquiatria*, 46, e20233363 (Sao Paulo, Brazil).

TABLE 3. COMPREHENSIVE DATA SUMMARY TABLE

INDIVIDUAL CHARACTERISTICS

Significant Protective Factors	Non-significant or Risk Factors
[4] Child IQ estimate (Internalizing and externalizing behavior problems and Youth Axis I diagnoses)/ High cognitive skills (Depressive Symptoms)/ High linguistic ability Reading Skills and Accuracy (depressive symptoms) / Verbal intelligence (Depressive symptoms)	[1] Higher IQ (Depressive Symptoms)
[3] Self-efficacy (Depressive symptoms 2x and Internalizing and externalizing problems)	
[3] High self-esteem 2x (Depressive Symptoms and Internalizing and externalizing behavior problems and Youth Axis I diagnoses)/ Positive Outlook of self (Major Depressive Disorder)	[1] Self-esteem (Internalizing and externalizing symptoms)
[2] Coping strategies (Depressive symptoms) / Responses to stress (Major Depressive Disorder - Adaptive responses to stress, high effortful engagement and low involuntary disengagement, buffered the effect of maternal depression)	[1] Internal locus of control (Depressive Symptoms)
[2] Easy temperament (externalizing problems and depressive symptoms)	[1] Easy temperament (internalizing problems)
[2] Good social functioning (Internalizing and externalizing problems) / social competence (Internalizing and externalizing problems)	[1] Children's social skills & self-esteem (Internalizing and externalizing symptoms)
[2] Intrinsic religiosity (Depressive symptoms) / Religious Orientation (Significantly buffered against externalizing behavior for females only)	[1] Religious importance (Major Depressive Disorder)
[1] Striving (Depressive Symptoms)	

[1] Ego-Resiliency (Internalizing and externalizing problems)

[1] Ego-control (Risk for externalizing problems)

[1] 5-HTTLPR genotype (Internalizing and externalizing problems)

[1] Ethnic Identity (Internalizing and externalizing symptoms)

[1] Future optimism (Internalizing and externalizing symptoms)

[1] High mental flexibility (Depressive Symptoms)

PARENTING AND FAMILY CHARACTERISTICS

Significant Protective Factors	Non-significant or Risk Factors
<p>[7] Parental involvement (Internalizing problems and externalizing problems) / Caregiver-child closeness (Depressive symptoms) / Parental attachment (Depressive symptoms) / Parental warmth x2 (Depressive symptoms and Depressive & anxious symptoms) / Family attachments (Depressive symptoms) / Perceived parent-child relationship quality (Internalizing and externalizing behavior problems and Youth Axis I diagnoses)</p>	<p>[1] Attachment to grandparent (Depressive Symptoms)</p>
<p>[3] Family Cohesion (Major Depressive Disorder) / Family climate x2 (Depressive symptoms and Depressive & PTSD symptoms)</p>	<p>[1] Family's characteristics (Internalizing and externalizing symptoms)</p>
<p>[3] Maternal attachment (Depressive symptoms) / Healthy Mother-infant dyads (Internalizing and externalizing problems) / Maternal caregiver involvement (Time with caregiver had a protective effect against Depressive symptoms initially on sample 1, but was related to increased symptoms over time on both samples)</p>	<p>[2] Protective aspects of maternal parenting: nurturing, appropriate developmental expectations. (Depressive Symptoms) / Maternal caregiver involvement (Time with caregiver had a protective effect against Depressive symptoms initially on sample 1, but was related to increased symptoms over time on both samples)</p>
<p>[2] Parent Support (Prevented internalizing symptom but did not affect</p>	

externalizing symptoms) / Family support
(Depressive symptoms)

[1] Father involvement (Depressive
and anxious symptoms)

[1] Positive parenting (Depressive
Symptoms)

[1] Felt acceptance (Internalizing
and externalizing problems)

[1] Family routines (Depressive and
anxious symptoms)

[1] Caregiver emotional regulation
(Internalizing and externalizing problems)

[1] Two-parent family (Depressive
symptoms)

[1] Low perception of marital
discord (Internalizing and externalizing
symptoms)

[1] high maternal sense of coherence
(Internalizing and externalizing
problems)

[1] High parental education
(Depressive symptoms)

[1] Sibling relationship (Depressive
Symptoms)

SCHOOL, COMMUNITY, AND RELATIONSHIPS OUTSIDE THE FAMILY

Significant Protective Factors	Non-significant or Risk Factors
<p>[11] Interpersonal Relations (Major Depressive Disorder) / Peer relationship quality (Depressive Symptoms) / Peer relationships x2 (Depressive symptoms and Depressive & anxious symptoms) / Child peer relationships (Internalizing and</p>	<p>[1] Supportive friendships (Depressive Symptoms)</p>

externalizing problems) / Peer attachment (Depressive symptoms) / Positive peer influence (Depressive symptoms) / Peer support (Depressive symptoms) / Friend Support x2 (one study found it to be protective against Depressive symptoms only for girls and another found it protective to both genders) / Kinship Support (Internalizing problems and externalizing problems)

[5] Positive perception of school (Depressive Symptoms) / School Satisfaction (Prevented externalizing symptoms for females but did not affect internalizing symptoms) / School connection (Depressive symptoms) / School engagement (Depressive symptoms) / School connectedness (Depressive and anxious symptoms)

[1] High school engagement & School attendance (Depressive Symptoms)

[3] Other adult support (Depressive symptoms) / Social Support 2x (Major Depressive Disorder and Depressive symptoms)

[1] Teacher support (Internalizing and externalizing symptoms)

[3] Neighborhood Cohesion (Internalizing and externalizing problems) / Positive community environment (Depressive symptoms) / Collective efficacy (Depressive symptoms)

[2] Neighborhood social cohesion (Depressive symptoms) / Social cohesion (Depressive and PTSD symptoms)

[2] Regular engagement in extracurricular activity (Depressive Symptoms) / Organized activity participation (Participation in academic organizations was the only type of activity that was related to lower depressive symptoms)

[1] Time spent in structured activities (Depressive symptoms)

[1] Religious Service attendance (Major Depressive Disorder)

[2] Religious attendance (Depressive symptoms) / Engagement with religion (Depressive Symptoms)

[1] High perceived SES (Depressive symptoms)

[1] Service provision (Internalizing and externalizing behavior problems and Youth Axis I diagnoses)

[1] Good school achievement
(Internalizing and externalizing symptoms)

Table 3. Summary of protective factors identified for depression in high-risk children and adolescents. The factors are arranged based on their frequency of appearance, denoted by the number of occurrences in brackets, and listed with the nomenclature as they appeared in the respective articles. To aid comprehension, the intensity of color-coding correlates with the frequency of each protective factor; more intense colors signify higher frequencies. The outcomes prevented by each protective factor are indicated in parentheses. Non-significant factors are listed beside their corresponding significant factors, facilitating a comparison between the frequencies of significant and related non-significant factors. Additionally, factors highlighted in red denote protective elements that, unexpectedly, elevate the risk of depression.

Source: Tietbohl-Santos et al, 2024. *Revista brasileira de psiquiatria*, 46, e20233363 (Sao Paulo, Brazil).

SUPPLEMENTAL MATERIAL

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SUPPL_TABLE 1. PRISMA 2020 CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4

METHODS

Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4 Table 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication	5

bias, selective reporting within studies).

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5-6 Suppl_Table3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-9 Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Suppl_Table4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-13

FUNDING

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14
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Suppl_Table S1. Table describing the itens suggested in the Prisma Guidelines.

Source: Tietbohl-Santos et al, 2024. *Revista brasileira de psiquiatria*, 46, e20233363 (Sao Paulo, Brazil).

SUPPL_TABLE S2. QUESTIONS BASED ON THE RESEARCH TRIANGLE INSTITUTE ITEM BANK AND DOMAINS OF BIAS

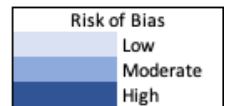
Domains of bias	Questions
Selection	Q1. Are critical inclusion/exclusion criteria clearly stated (does not require the reader to infer)?
Selection, Confounding	Q2. Are the inclusion/exclusion criteria for the at-risk individuals measured using valid and reliable measures?
Selection, Confounding	Q3. Was the sample size sufficiently large to detect a clinically significant difference of 5% or more between groups in at least one primary outcome measure?
Selection, Confounding	Q4. Are the important outcomes prespecified by the researchers?
Attrition, Detection	Q5. Did researchers isolate the impact from a concurrent intervention or an unintended exposure that might bias results, e.g., through multivariate analysis, stratification, or subgroup analysis?
Attrition, Detection	Q6. Are outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Reporting	Q7. Are any important primary outcomes missing from the results?
Overall	Q8. Are the statistical methods used to assess the primary benefit outcomes appropriate to the data?
Confounding	Q9. Are the interpretation of the results believable taking study limitations into consideration?

Suppl_Table S2. Questions used to review articles according to the Research Triangle Institute Item Bank.

Source: Tietbohl-Santos et al, 2024. *Revista brasileira de psiquiatria*, 46, e20233363 (Sao Paulo, Brazil).

**SUPPL_TABLE S3. RISK-OF-BIAS ASSESSMENT OF THE INCLUDED STUDIES
BASED ON THE RESEARCH TRIANGLE INSTITUTE ITEM BANK, BY HEAT
MAP**

Author	Year	Score									Quality Score		
		Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Score	risk of bias-score	Overall risk of bias
Agnafors	2016	0	0.5	0	0	0.5	0	0	0	0	1	11.11	Low
Bayer	2015	0	0.5	0	0	0	0	0	0	0.5	1	11.11	Low
Cahill	2022	0	0	0	0	0	0	0	0	0	0	0.00	Low
Carbonell	2002	0	0.5	0	0.5	1	0	0	0	0.5	2.5	27.78	Low
Causadias	2013	0	0.5	0	0	0	0	0	0	0	0.5	5.56	Low
Chester	2007	0.5	0	0	0.5	0	0	0	0	0	1	11.11	Low
Cotter	2015	0.5	0	0	0.5	0	0	0	0	0	1	11.11	Low
DOOM	2017	0.5	0	0	0.5	0	0	0	0	0	1	11.11	Low
Ezpeleta	2008	0.5	0.5	1	0	0	0.5	0	0	0	2.5	27.78	Low
Gaylord-Harden	2009	0.5	0	0	0.5	0	0	0	0	0	1	11.11	Low
Hardaway	2016	0.5	0	0	0.5	0	0	0	0	0	1	11.11	Low
Harold	2014	0	0.5	0	0	0.5	0	0	0	0.5	1.5	16.67	Low
Helms	2015	0.5	0	0	0.5	0	0	0	0	0	1	11.11	Low
Jain	2012	0.5	0	1	0	0	0	0	0	0.5	2	22.22	Low
Kasen	2011	0	0	0	0	0	0	0	0	0.5	0.5	5.56	Low
Klasen	2014	0	0	1	0	0	0	0	1	0.5	2	22.22	Low
Kliewer	2004	0.5	0	0.5	0	0	0	0	0	0	1	11.11	Low
Kuper	2019	0	0	0	0.5	0	1	0	0	0.5	2	22.22	Low
kwak	2018	0.5	0	0	0.5	0	0	0	0	0	1	11.11	Low
Laucht	2002	0.5	0	0	0.5	1	1	0	1	0.5	4	44.44	Moderate
Markowitz	2016	0.5	0.5	1	0.5	0	1	0	0	0.5	4	44.44	Moderate
MONTI and RUDOLPH	2017	0.5	0	0	0	0	0	0	0	0	0.5	5.56	Low
Oshri	2017	0.5	0.5	0	0.5	1	0	0	0	0.5	3	33.33	Low
Pargas	2010	0	0	0	0	0	0	0	0	0	0	0.00	Low
Plass-Christl	2017	0	0	0	0.5	0	0	0	0	0	0.5	5.56	Low
Russotti	2023	0	0	0.5	0	0	0	0	0	0	0.5	5.56	Low
Thakur	2020	0.5	1	0	0.5	0	0	0	0	0.5	2.5	27.78	Low
Wang	2021	0	0	0	0.5	0	0	0	0	0.5	1	11.11	Low
Zhang	2021	0.5	0	0	0.5	0	0	0	0	0.5	1.5	16.67	Low



Suppl_Table S3. Risk of bias assessment results.

Source: Tietbohl-Santos et al, 2024. *Revista brasileira de psiquiatria*, 46, e20233363 (Sao Paulo, Brazil).

**SUPPL_TABLE S4. EVIDENCE MAP ACCORDING TO GRADE CRITERIA
(GRADING OF RECOMMENDATIONS, ASSESSMENT, DEVELOPMENT, AND
EVALUATION)**

	Protective Factors	Articles	GRADE (certainty of evidence)
Individual Characteristics	Easy temperament	Agnafors, 2017; Cahill,2022;	High
	High self-esteem / High global self-worth/ Positive outlook on self	Cahill,2022; Carbonell, 2002; Pargas, 2010;	Moderate
	High cognitive skills / Higher IQ	Cahill,2022; Pargas, 2010; Kuper, 2019	Moderate
	Reading comprehension	Cahill,2022	High
	Ego-resiliency	Causadias, 2012;	High
	Higher striving	Doom, 2017;	High
	Social competence	Plass-Christl, 2018; Agnafors, 2016;	Moderate
	Self-efficacy	Plass-Christl, 2018; Klasen, 2014;	Moderate
	Adaptive responses to stress / Child emotional regulation	Monti and Rudolph, 2017; Kliewer, 2004;	Moderate
	Genetic characteristic (5-HTTLPR genotype)	Agnafors, 2017;	High
Parental Characteristics & Family-related Factors	Parental support	Cotter, 2016; Jain, 2012;	High
	Low marital discord	Ezpeleta, 2008;	Moderate
	Two-parent family	Zhang, 2021;	High
	High parental warmth	Zhang, 2021; Pargas, 2010; Wang, 2021;	Moderate
	High parental education	Zhang, 2021;	High
	Parental involvement	Hardaway, 2016; Harold, 2014; Wang, 2021;	Moderate
	Family attachments / Higher maternal attachment / caregiver closeness	Kuper, 2019; Gaylord-Harden, 2009; Oshri, 2017; Russotti, 2023;	Moderate
	Positive parenting (monitoring and warmth)	Chester, 2007;	Moderate
	Caregiver–Child Relationship Quality / healthy Mother-infant dyads	Laucht, 2002; Kliewer, 2004;	Low
	Low harsh discipline	Bayer, 2015;	Moderate
	Caregiver emotional regulation	Kliewer, 2004;	Low
	Maternal sense of coherence	Agnafors, 2016;	High
	Felt acceptance	Kliewer, 2004;	Low
	Positive sibling relationship	Cahill,2022;	High
	Family climate	Plass-Christl, 2017; Klasen, 2014;	Moderate
Family routines	Thakur, 2020; Wang 2021;	Moderate	
family Cohesion	Carbonell, 2002;	Moderate	
School Factors	School characteristics	Cotter, 2015; Cahill, 2022;	High
	School satisfaction / Positive opinion of school	Cotter, 2015; Cahill,2022	High
	School connection (a student’s sense of belongingness in and support from school)	Markowitz, 2015; Wang, 2021;	Moderate
	Regular participation in extracurricular activities / Participated in academic clubs	Cahill,2022; Kwak, 2018;	Moderate
	School engagement (enjoyment, interest, productivity, and relationships)	Oshri, 2017;	High
Peer-related Factor	Kinship support / Peer support / High quality peer relationships / Social support	Hardaway, 2016; Zhang, 2021; Wang, 2021; Jain, 2012; Chester, 2007; Klasen, 2014; Oshri, 2017; Carbonell, 2002; Russoti, 2023;	High
Other Factors	Religiosity / Religious orientation	Kasen, 2011, Cotter, 2015; Helms, 2015	Moderate
	Religious Service attendance	Kasen, 2011;	High
	Neighborhood characteristics	Cotter, 2016; Wang, 2021; Oshri, 2017;	High
	Neighborhood social cohesion	Kliewer, 2008;	Low
	Social support provided by environment	Klasen 2014;	High
	received social support (social services)	Oshri, 2017;	High

Suppl_Table S4. Map of evidence according to the GRADE criteria.

Source: Tietbohl-Santos et al, 2024. *Revista brasileira de psiquiatria*, 46, e20233363 (Sao Paulo, Brazil).

STUDY PROTOCOL

Protocol for Protective factors against depression in high-risk children and adolescents: a systematic review of longitudinal studies

First Author: Bárbara Tietbohl-Santos, MD

Co-Authors: Augusto Ossamu Shintani, MSc; Bruno Braga Montezano, BSc; Paola Biazin; Giovanna Maioli Signori; Rafaela Pulice; Giancarlo Franceschi Dalla Vecchia; Júlio César Bebbler; Lucas Noronha; Ives Cavalcante Passos, MD, PhD .

Review question:

What are the protective factors that reduce the incidence of depression in high-risk populations of children and adolescents?

1. INCLUSION

- Longitudinal population studies;
- Studies that included populations at risk of developing any mental disorder (population according to high-risk criteria: childhood adverse experiences, poverty and having parents with a mental disorder)
- We will include studies that assessed protective factors during childhood that reduced the incidence of any mental health disorders or their symptoms at adolescence or adulthood.
- We will include original studies published in any language (ver Confúcio UFRGS).

2. EXCLUSION CRITERIA

- Review articles
- Clinical trials
- Any therapeutic or public intervention trial
- Pre-Clinical trials

- Cross-sectional

3. OUTCOMES

- The reduction of diagnosis of mental health disorders and/or their symptoms in this specific population.

4. SEARCH STRATEGY

Studies were identified through searching electronic databases and reference lists. With the preliminary filter:

("Personality Disorder" OR "Avoidant Personality Disorder" OR "Avoidant Personality Disorders" OR "Personality Disorder, Avoidant" OR "Personality Disorders, Avoidant" OR "Inadequate Personality" OR "Personality, Inadequate" OR "Narcissistic Personality Disorder" OR "Personality Disorder, Narcissistic" OR "As If Personality" OR "Personality, As If" OR "Impulse-Ridden Personality" OR "Impulse Ridden Personality" OR "Personality, Impulse-Ridden" OR "Disorder, Borderline Personality" OR "Borderline Personality Disorders" OR "Disorders, Borderline Personality" OR "Personality Disorders, Borderline" OR "Personality Disorder, Borderline" OR "Attention Deficit Disorders with Hyperactivity" OR "ADHD" OR "Attention Deficit Hyperactivity Disorder" OR "Hyperkinetic Syndrome" OR "Syndromes, Hyperkinetic" OR "Attention Deficit-Hyperactivity Disorder" OR "Attention Deficit-Hyperactivity Disorders" OR "Deficit-Hyperactivity Disorder, Attention" OR "Deficit-Hyperactivity Disorders, Attention" OR "Disorder, Attention Deficit-Hyperactivity" OR "Disorders, Attention Deficit-Hyperactivity" OR "ADDH" OR "Attention Deficit Hyperactivity Disorders" OR "Attention Deficit Disorder" OR "Attention Deficit Disorders" OR "Deficit Disorder, Attention" OR "Deficit Disorders, Attention" OR "Disorder, Attention Deficit" OR "Disorders, Attention Deficit" OR "Brain Dysfunction, Minimal" OR "Dysfunction, Minimal Brain" OR "Minimal Brain Dysfunction" OR "Schizophrenia" OR "Schizophrenias" OR "Schizophrenic Disorders" OR "Disorder, Schizophrenic" OR "Disorders, Schizophrenic" OR "Schizophrenic Disorder" OR "Dementia Praecox" OR "Bipolar Disorder" OR "Bipolar Disorders" OR "Disorder, Bipolar" OR "Affective Psychosis, Bipolar" OR "Bipolar Affective Psychosis" OR "Psychoses, Bipolar Affective" OR "Psychosis, Bipolar Affective" OR "Manic-Depressive Psychosis" OR "Manic Depressive Psychosis" OR

“Psychosis, Manic-Depressive” OR “Psychosis, Manic Depressive” OR “Bipolar Mood Disorder” OR “Bipolar Mood Disorders” OR “Disorder, Bipolar Mood” OR “Mood Disorder, Bipolar” OR “Psychoses, Manic-Depressive” OR “Psychoses, Manic Depressive” OR “Depression, Bipolar” OR “Bipolar Depression” OR “Manic Depression” OR “Depression, Manic” OR “Depressions, Manic” OR “Manic Disorder” OR “Disorder, Manic” OR “Manic Disorders” OR "mental health" OR “Generalized Anxiety Disorder” OR “Panic Disorder” OR “Social Anxiety Disorder” OR “Obsessive Compulsive Disorder” OR “Obsessive-Compulsive Disorder” OR “Depressions” OR “Depressive Symptoms” OR “Depressive Symptom” OR “Symptom, Depressive” OR “Symptoms, Depressive” OR “Emotional Depression” OR “Depression, Emotional” OR “Depressions, Emotional” OR “Emotional Depressions” OR “Hypervigilance” OR “Nervousness” OR “Social Anxiety” OR “Anxiety Disorder” OR “Disorder, Anxiety” OR “Disorders, Anxiety” OR “Neuroses, Anxiety” OR “Anxiety Neuroses” OR “Anxiety States, Neurotic” OR “Anxiety State, Neurotic” OR “Neurotic Anxiety State” OR “Neurotic Anxiety States” OR “State, Neurotic Anxiety” OR “States, Neurotic Anxiety” OR “Psychological Distress” OR “Stress” OR "mental disorder" OR "mental illness" OR "mental disorders" OR "mental illnesses")

AND (“cohort” OR “longitudinal”)

AND ("ultra high risk" OR "ultra-high risk" OR "high risk" OR "high-risk" OR "at risk" OR “clinical high-risk” OR "sub-threshold states" OR “attenuated symptoms” OR “episodic symptoms” OR “functional decline” OR “attenuated syndrome”)

AND (“Factor, Protective” OR “Factors, Protective” AND “Protective Factor” OR "protective factors" OR "prevention" OR "resilience" OR “Psychological Resilience” OR “Resiliency, Psychological” OR “Psychological Resiliency” OR “adaptive response” OR “adaptive responses”)

NOT ("systematic review" OR "review" OR "meta analysis" OR “Clinical Trial” OR “Randomized Controlled Trial” OR “placebo” OR “therapeutic intervention trial” OR “intervention trial”)

NOT (“mice” OR “rat” OR “animal”)

NOT (“inmates” OR “inmate” OR “prison” OR “prisoners” OR “prisoner” OR “probationers” OR “criminals”)

NOT (“soldiers” OR “soldier” OR “deployment” OR “Combat Exposure” OR “Army Enlisted”)

NOT (“malignant neoplasm” OR “cancer” OR “elderly” OR “HIV” OR “AIDS”)

PubMed/MEDLINE

Search Date: 15/12/22

Retrieved references: 485

Embase

Search Date: 15/12/22

Retrieved References: 466

Emcare

Search Date: 15/12/22

Retrieved References: 217

APA

Search Date: 15/12/22

Retrieved References: 178

Total references: 1346

5. DUPLICATES

Retrieved References (without duplicates): 620

Removed Duplicates: 726

6. STUDY DESIGN

- This systematic review will comply to the PRISMA guidelines;
- The primary (i.e., title/abstract) screening will be independently performed by two teams of investigators (two in each team);

- The PDFs (i.e., full-texts) of potentially eligible articles will be retrieved;
- The secondary screening will be independently performed by two teams of investigators (two in each team);
- Disagreements will be resolved through consensus.

7. DATA EXTRACTION

- Extracted variables: Author, publication year, sample size, age, gender distribution, follow-up time, socioeconomic variables, type of study population, the geographic location, sample size per group, types of risk factors (e.g., low socioeconomic level, parental psychiatric history, or maltreatment), tools utilized to measure risk and protective factors, authors' key conclusions, and the outcome studied in each article and their corresponding measurement tools.

- Where a study was reported in more than one article, data were extracted from the most recent report.

8. ANALYSIS

- Strategy for data synthesis: We will provide a synthesis of the findings from the included studies, structured around the protective factors identified, target population characteristics, type of outcome (as there are many ways to assess the incidence of depressive symptomatology in children and adolescents). If it is possible, we will pool the results using a random-effects meta-analysis, with risk ratios for binary outcomes (SMD for continuous variables), and calculate 95% confidence intervals (standard deviation in case of continuous variable) and P values for each outcome. We will compare the high-risk individuals exposed to the protective factor to those not exposed to the risk/protective factor. We will also provide summaries of each study by calculating risk ratios for dichotomous outcomes and standardized mean difference (SMD) for continuous variables.

- Heterogeneity: We will use the Q statistic to test the existence of heterogeneity and I-squared to assess the proportion of total variability due to heterogeneity. An I-squared value of about 25% could be regarded as low, about 50% as medium, and about 75% as high. We will use t-squared to estimate the total amount of heterogeneity. We will explore sources of heterogeneity in studies using meta-regression analysis.

- Software: We will use R package "metafor" to run the analyses.
- Subgroup meta-analysis: We will perform a subgroups analysis with populations with specificities such as racial minorities, continent, and gender.
- Risk of bias: Egger's linear regression test will be used to assess publication bias. This is a test for asymmetry of the funnel plot, and it will be done whenever three or more studies are included. For this specific test a p value of less than 0.1 shows significant asymmetry and therefore publication bias. If Egger's linear regression test reveal a potential publication bias, we will use Duval and Tweedie's trim and fill method to test the data. We also will use the so-called leave-one-out function for doing sensitivity analyses. This method consists of the removal of one study at a time from the data set to run the meta-analysis without it. This analysis tests if the effect size of the meta-analysis is driven by one study. The method should not be regarded as a way of yielding a more valid estimate of the overall effect or outcome, but as a way of examining the sensitivity of the results to one particular selection mechanism. Finally, we will describe the characteristics and quality of the included studies in a table.

9. QUALITY ASSESSMENTS

- Quality assessment: The methodological quality of included studies will be determined through the Research Triangle Institute scale (RTI item bank).
- Evidence quality assessment: We will use the GRADE criteria (Grading of Recommendations, Assessment, Development, and Evaluations) to evaluate the evidence quality (classified as high, moderate, low, or very low) for each found association.

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6.2. ARTICLE 2

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Trends in Psychiatry and Psychotherapy

<https://trends.org.br/article/doi/10.47626/2237-6089-2024-0804>



ORIGINAL ARTICLE

Exploring protective factors in a high-risk subsample: the pivotal role of paternal support in preventing depression in a cohort of young adults

[Barbara Tietbohl-Santos](#), [Bruno Braga Montezano](#), [Taiane de Azevedo Cardoso](#), [Tháise Campos Mondin](#), [Fernanda Pedrotti Moreira](#), [Luciano Dias de Mattos Souza](#), [Ricardo Azevedo da Silva](#), [Flavio Kapczinski](#), [Karen Jansen](#), [Ives Cavalcante Passos](#)

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Trends Psychiatry Psychother, Ahead of Print, 2024



Downloads: 1

Views: 143

Abstract

Background

Major depressive disorder (MDD) is a global concern due to its widespread prevalence and morbidity. Identifying protective factors in high-risk individuals, including those with a familial predisposition, maltreatment history, and socio-economic vulnerabilities, is crucial.

Methods

We assessed a high-risk subsample within a young adult population cohort (n = 791; mean age = 31.94 [SD = 2.18]) across three waves. Using multiple regression models to analyse higher education, feeling supported, spirituality, psychotherapy access, higher socioeconomic status, involvement in activities, cohabitation, and family unity in Waves 1 and 2, and their association with MDD resilience at Wave 3

TITLE PAGE**Exploring protective factors in a high-risk subsample: the pivotal role of paternal support in preventing depression in a cohort of young adults**

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Abstract word count: 250 words

ABSTRACT

Background: Major depressive disorder (MDD) is a global concern due to its widespread prevalence and morbidity. Identifying protective factors in high-risk individuals, including those with a familial predisposition, maltreatment history, and socio-economic vulnerabilities, is crucial.

Methods: We assessed a high-risk subsample within a young adult population cohort (n = 791; mean age = 31.94 [SD = 2.18]) across three waves. Using multiple regression models to analyse higher education, feeling supported, spirituality, psychotherapy access, higher socioeconomic status, involvement in activities, cohabitation, and family unity in Waves 1 and 2, and their association with MDD resilience at Wave 3

Results: In the high-risk group, MDD incidence was 13.7% (n=24). Paternal support had a protective effect on MDD incidence (OR = 0.366; 95% CI [0.137 to 0.955], p = 0.040) and suicidal attempt risk (OR = 0.380; 95% CI [0.150 to 0.956], p = 0.038). Higher resilience scores were also protective (OR = 0.975; 95% CI [0.953 to 0.997], p = 0.030), correlating with reduced BDI (r = 0.0484; B = -0.2202; 95% CI [-0.3572 to -0.0738]; p = 0.003) and MADRS scores (r = 0.0485; B = -0.2204; 95% CI [-0.3574 to -0.0741]; p = 0.003).

Conclusions: Our paper emphasizes reorienting the MDD approach, focusing on positive prevention strategies. It highlights fathers' crucial role in family-based interventions and promoting resilience in high-risk populations.

Funding: CAPES - Finance Code 001 and financial support from CNPq, with ICP and KJ as CNPq research fellows.

Keywords: protective factors, major depressive disorder, at-risk population, cohort, social support, paternal support, resilience.

1. INTRODUCTION

Major Depressive Disorder (MDD) has consistently occupied a notable position among the leading ten contributors to disability-adjusted life-years (DALYs) across diverse age brackets, retaining this status for individuals aged 10–49, as documented in the latest report by The Global Burden of Diseases.¹ Furthermore, the presence of depression and anxiety in early life poses a significant threat to one's future physical and mental well-being, educational achievements, financial stability, and interpersonal relationships.² Given the far-reaching consequences of depressive episodes and the alarmingly high prevalence of this disorder, it becomes imperative to gain a deeper understanding of the individuals who are most susceptible to its development and the factors that either contribute to or mitigate its occurrence.

Parental mental health problems increase the chance of an individual to experience a depressive episode by 42%³ and are a well-established risk factor for child psychopathology.⁴ Substantial research indicates that the offspring of depressed mothers are at increased risk for psychological and social maladjustment⁵ and that children of depressed parents are more likely to experience depression, phobias, panic disorders, substance misuse and problematic gaming during adolescence.^{6,7} It is worth noting that both genetic factors and the family environment make substantial and significant contributions to the familiarity of depression⁸ and other mental disorders⁹.

Protective factors can be viewed as positive traits and influences that can facilitate healthy development. Their significance lies not necessarily in the promotion of normal development in any environment, but they play a crucial role when there is an interplay with risk factors.¹⁰ The most frequently discussed environmental factors encompass individual characteristics and various categories of supportive relationships, including parents, neighborhood, peers, and school.¹¹ In addition, Askeland et al. (2020) associate individual factors such as goal orientation, self-confidence, social competence, social support, and family cohesion with a reduction in depressive symptoms.¹² In contrast, Solmi et al. (2021) highlight the lack of convincing support for either risk or protective factors for Major Depressive Disorder (MDD).¹³ Despite being extensively examined in cross-sectional research, these studies frequently lack the essential longitudinal dimension required for a comprehensive assessment of their impact on MDD prevention in high-risk individuals¹⁴.

Addressing this research gap, our study strives to enrich existing knowledge by providing a nuanced understanding of the effectiveness of various protective factors in preventing depressive symptoms among high-risk individuals. The primary objective is to

leverage prior knowledge about protective factors and assess their preventive impact on depressive symptoms within this specific subsample of a population cohort comprising high-risk young adults.

2. Methods

2.1. Study design

This paper is a longitudinal study derived from a subsample from a population cohort. The first wave (T1) of data collection spanned from 2007 to 2009. The second wave (T2) occurred approximately five years later, spanning from 2012 to 2014, and the third wave (T3) was conducted from 2018 to 2020, roughly a decade after the T1. All young adults who were part of the initial phase were invited to return for a follow-up assessment. Participants were informed about the research objectives and provided informed consent. The study received approval from the Research Ethics Committee of the Universidade Católica de Pelotas under protocol number 2008/118. Further information about the study's design has been previously published elsewhere.¹⁵

2.2. Participants

In the initial wave, a total of 1560 participants, aged between 18 to 24 years, residing in urban Pelotas, Brazil, were included. The rate of participation in the third follow-up assessments was 50.7%, with a total of 791 individuals ($n = 791$). At T3, the average age of participants was 31.94 years ($SD = 2.18$). Those respondents who were identified as having a psychiatric disorder were referred to appropriate healthcare services as required.

2.3. Data Sources/ Measurements

Socio-demographic Characteristics

Participants completed a comprehensive questionnaire that covered various socio-demographic and economic questions at T1. These variables encompassed sex, skin color, age, marital status, years of education, occupational status, access to psychotherapy, and spirituality factors, including participation in a religious group, attending religious services, and having a religion. In addition to these questions, participants were asked family-related questions regarding the structure of their family, such as cohabitation and the number of individuals

within the family. Furthermore, individuals reported their economic classification based on the criteria established by the Brazilian Association of Research Companies - ABEP.¹⁶

Social support

Perceived social support pertains to the subjective perception of the care and assistance one receives from social relationships. This perception encompasses emotional support (e.g., expressions of empathy), instrumental support (e.g., assistance with household tasks), and informational support (e.g., financial advice) that can be provided by various sources, such as friends or family.¹⁷ In our study, the assessment of the subjective feeling of support involved a series of dichotomous questions collected at T1. These questions covered whether the participant felt supported in general and specifically whether they felt supported by particular individuals within their family, including parents, siblings, partners, and their own children, if applicable.

Resilience

The measurement of resilience as a trait was conducted using the Resilience Scale for Adults (RSA) at T2.¹⁸ The RSA consists of 33 items and employs a 7-point Likert scale. This scale is designed to evaluate protective factors associated with personal attributes and support systems that have been demonstrated to promote adaptation in the face of psychosocial adversities.

Childhood Trauma Questionnaire

This retrospective, self-reported, standardized instrument is specifically designed for assessing childhood trauma, standing as one of the most widely employed measures for this construct¹⁹. The CTQ comprehensively examines five categories of maltreatment experiences—specifically, emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect—employing a Likert-scale approach to assess the severity of each incident. It is noteworthy that the instrument has undergone validation for use in Brazilian Portuguese.²⁰ The questionnaire was also used to collect information about the participants' sense of family unity during childhood.

High-Risk for MDD

The high-risk criterion was determined by assessing the participants' family psychiatric history at T1. They were asked whether someone in their family had ever been diagnosed with a psychiatric disorder. In cases of a positive response, participants were then asked a series of questions related to each specific family member. To meet the high-risk criteria, at least one immediate family member needed to have a prior diagnosis of a mental health disorder.

Main Outcome

The assessment of MDD was carried out using the Mini International Neuropsychiatric Interview – PLUS (MINI – PLUS) ²¹ by trained psychologists at each time point. In cases where there was uncertainty regarding the diagnosis of MDD, subjects underwent a reassessment using the semi-structured clinical interview for DSM Structured Clinical Interview ²² to confirm the diagnosis.

Secondary Outcomes

Furthermore, the MINI – PLUS collected at T3 was utilized to gather clinical history information regarding depression severity, including the age of onset of first depressive disorder, history of psychiatric in-patient care, history of lifetime suicide attempts, and current suicide ideation. The severity of depressive symptoms was also evaluated at T3 using both the Montgomery-Asberg Depression Rating Scale ²³ and the Beck Depression Inventory ²⁴.

2.4. Variables

To assess demographic variables, we employed multinomial qualitative variables for sex, skin color, age, marital status, and occupational status, along with economic classification based on the ABEP strata. Some variables were dichotomous, such as access to psychotherapy, participation in a religious group, attendance at religious services, having a religion, cohabitation with the individuals' father and mother, perceived social support from those in the individuals' social circle, as well as certain depression-related variables like previous psychiatric in-patient treatment, previous suicidal attempts, and current suicidal ideation. Additionally, we generated quantitative variables to measure years of education, age of the first depressive episode, resilience scores, and depression severity scores.

Creating a high-risk variable involved establishing a dichotomous measure for a positive immediate family history, after excluding individuals already diagnosed with MDD at baseline. Moreover, in relation to our main outcome, the absence of MDD at T3, we established a dichotomous variable concerning the diagnosis of MDD according to the MINI – PLUS.

2.5. Statistical Methods

All statistical analyses were conducted using R programming language (version 4.3.1), with packages "tidyverse", "MASS", "dplyr", and "epiDisplay". No imputation or adjustment for missing data was performed, the analysis being carried out exclusively on the observed cases. Significance in all statistical tests was established at $p < 0.05$. The analysis was conducted in accordance with the following steps:

Group Selection

Initially, participants were identified based on the high-risk criterion. This subsample was subsequently scrutinized with respect to our primary outcome—specifically, the absence of MDD at T1 and the presence of the diagnosis at T3. Following this, the cohort was stratified into four sub-groups: "incident," "recurrent," "recovered," and "resilient." Our focus then shifted to comparing a subset of high-risk individuals who manifested incident cases of MDD with those exhibiting resilience.

Descriptive Statistics and Bivariate Analysis

The descriptive data were presented, detailing mean and standard deviation, along with absolute and relative frequency. Subsequently, we examined the incidence of MDD within the high-risk group and the entire sample. Following this, normality assessments were conducted for continuous variables using the Shapiro-Wilk test. The socio-demographic and economic characteristics of both groups underwent analysis through the t-test, Chi-square, and Mann-Whitney U test, as appropriate. The same methods were applied to assess the multiple proposed protective characteristics. Additionally, a bivariate analysis explored group differences regarding suicide attempts, current suicide risk, in-patient psychiatric treatment, and age of the first depressive episode. Variables with a significance level of $p < 0.200$ in this analysis were included in the subsequent multivariate analysis.

Multivariate Analysis

Logistic regressions were utilized to explore the connection between protective factors and resilience, examining group distinctions in relation to these factors and employing resilience to MDD (inverted incidence of MDD variable) as the dependent variable. Subsequently, logistic regressions were performed incorporating the previously identified significant protective factors, now exploring various outcomes such as suicide attempts, current suicide risk, in-patient psychiatric treatment, and the age of the first depressive episode as dependent variables. This aimed to determine whether the protective factors identified for resilience to MDD had implications for these crucial indicators of depression severity. Additionally, linear regressions were executed to delve into the association between significant protective factors and the severity of depression scores (MADRS and BDI). Then, additional post-hoc bivariate analyses were conducted investigating differences between groups with higher and lower frequencies of the identified protective factors and how these factors influenced various secondary measures of depression severity.

3. Results

3.1. Participants

At T3, complete data on depression incidence were available for 780 individuals. Subsequently, we excluded recurrent (n=23) and recovered individuals (n=66), focusing our analysis on the resilient (n=627) and incident (n=64) cases. These participants were then categorized based on our risk criteria into high-risk (n=175) and normal-risk groups (n=417). Observations with missing data on the risk criterion were omitted, resulting in a final participant count of 669 individuals. Among these, a significant difference in sex distribution between the groups was noted ($p=0.001$), with females constituting 70.3% of the high-risk group (n=123) and 55.9% of the normal-risk group (n=233). No other significant differences were observed in sociodemographic variables, as detailed in Supplementary Table 1. At T3, the normal-risk group exhibited a 7.67% incidence of new MDD cases (n=32). In contrast, the high-risk subgroup displayed an MDD incidence of 13.7% (n=24), signifying a 78.5% higher incidence of depression compared to their normal-risk counterparts ($p=0.032$).

Within the high-risk group (n= 175), no significant differences were observed in socio-demographic and economic characteristics between high-risk participants with and without a new diagnosis of MDD, as depicted in Table 1.

3.2. Descriptive Data

The primary significant protective factors against the incidence of MDD within the high-risk group included having a supportive father and exhibiting higher resilience scores. The subsequent data pertains to our initial comparisons between the incident group and the resilient high-risk group, followed by post-hoc analysis investigating differences between groups with higher and lower frequencies of the identified protective factors.

Comparisons between incident and resilient high-risk groups.

Participants in the resilient group were more likely to report having a supportive father (n=104; 74.3%) compared to the incident group (n=10; 43.5%; p-value = 0.006). Interestingly, the same pattern did not emerge for maternal support, as a majority of our sample reported feeling supported by their mothers. Additionally, resilient individuals reported higher resilience scores (140; [127-151]) compared to the incident group (127; [110-139]; p=0.009). The resilient group appeared to have lower exposure to trauma, reflected in lower CTQ scores (11.5; [6-20]), in contrast to the incident group (18.5; [9.5-30]; p=0.032). Resilient individuals also had a lower frequency of suicidal attempts (n=12; 7.9%) compared to incident individuals (n=11; [45.8%]; p < 0.001). The groups did not significantly differ regarding suicidal ideation at T3, parental marital status, cohabitation with the father, parental mental health diagnosis, and other socio-economic variables. Additional details are provided in Table 1. Differences between groups with a significance level of p<0.200, were incorporated into the subsequent multivariate analysis. These encompassed socio-economic level, skin color, paternal support, resilience scores, and CTQ scores.

Comparisons between high risk individuals according to presence vs absence of paternal support.

Individuals who reported having a supportive father displayed lower depression severity scores (MADRS= 0 [0-6]; BDI= 6.5 [1-16]) compared to those reporting an absent father (MADRS= 4 [2-16]; p= 0.0002 and BDI=13 [8-26]; p= 0.001). The presence of a supportive father was also correlated with lower rates of psychiatric in-treatment (p= 0.0422). Interestingly, the groups did not exhibit differences in resilience scores, the presence of paternal psychiatric diagnosis, or CTQ scores. Furthermore, no distinctions were observed in socioeconomic characteristics, as indicated in Table 2.

Comparisons between high risk individuals with higher and lower resilience scores

Participants were stratified based on the 25% (Q1= \leq 124) and 75% percentile (Q4= \geq 149) of their RSA scores for comparative analysis. Those who scored higher were older at baseline (mean = 20.92; SD= 1.82) than those who scored lower (mean= 20.13; SD= 2.00; $p=$ 0.03832). Individuals with higher resilience scores also exhibited lower depression severity scores (MADRS= 2 [0-6]; BDI= 5 [2-11]) than those who had lower resilience scores (MADRS= 5 [1.5-14.5]; $p=$ 0.0001 and BDI= 12 [4.75-27.2]; $p=$ 0.002). Additionally, individuals with higher resilience scores had a lower frequency of suicidal attempts ($n=$ 4; 7.8%) compared to those with lower scores ($n=$ 11; 25%; $p=$ 0.045). It is noteworthy that the groups did not differ concerning their history of past trauma. Additional information about group characteristics regarding resilience scores can be found in Table 3.

3.3. Outcome Data

Supportive Father

The presence of a supportive father at T1 reduced in 63% the likelihood of developing depression at T3 (Odds Ratio = 0.366 ; 95% CI [0.137 to 0.955], $p=$ 0.040). Also, having a supportive father reduced the risk of suicidal attempt in T3 in 62% (Odds Ratio = 0.380 ; 95% CI [0.150 to 0.956], $p=$ 0.038)

Resilience Scores

Higher resilience scores were associated with a minor, albeit significant, effect on MDD prevention in high-risk individuals. (Odds Ratio = 0.975; 95% CI [0.953 to 0.997], $p=$ 0.030). Furthermore, there was also a small but significant correlation between the resilience scores and depression severity in T3, according to both the BDI scores ($r=$ 0.0484; $B=$ -0.2202 ; 95% CI [-0.3572 to -0.0738]; $p=$ 0.003), and the MADRS scores ($r=$ 0.0485; $B=$ -0.2204 ; 95% CI [-0.3574 to -0.0741]; $p=$ 0.003).

Other Protective Factors

Several other potential protective factors, including having a religion, participating in a religious group, attending religious services, having access to psychotherapy, higher socioeconomic status, involvement in educational or professional activities, cohabitation with mother or father, a sense of family unity during childhood, and feeling supported by siblings,

mother, and/or spouse, were not found to be statistically significant for MDD prevention, as indicated in Supplementary Table 2.

4. DISCUSSION

This study delved into the influence of potential protective factors on the incidence of MDD within a subsample of a young adult cohort. Paternal support emerged as a critical factor, preventing MDD in high-risk individuals. This finding resonates with a recent meta-analysis that explored the dynamic nature of social support across the lifespan, underscoring the significance of parental support for adolescents, which evolves over time to encompass peer and spouse support.²⁵ Furthermore, it aligns with the broader literature on social support, where cohort studies, meta-analyses and systematic reviews have consistently demonstrated its protective impacts against depressive symptoms, post-traumatic stress disorder (PTSD), and suicidal ideation in young adults.²⁵⁻²⁹ To our knowledge, this study is among the first to demonstrate how paternal support plays a significant protective role in averting the development of MDD in high-risk individuals in a large cohort of young adults.

Furthermore, it was revealed that having a supportive father not only decreases the severity of depressive symptoms, but also reduces the risk of suicide attempts. These findings resonate with other studies that have highlighted the protective effect of paternal support in the context of adolescent suicidality.³⁰ Intriguingly, individuals who perceived support from their fathers did not demonstrate significant differences in resilience or trauma scores compared to those without such support in our study. Remarkably, even when controlling the analysis for these variables, father support exhibited protective effects against MDD. This evidence implies that a supportive father may wield greater significance in MDD prevention than individual characteristics, such as high resilience, even when considering past traumatic events. This phenomenon might be attributed to high-risk individuals, such as those with a positive family psychiatric history, potentially having lower intrinsic characteristics that contribute to better mental health outcomes, such as self-esteem³¹ and IQ³². Consequently, they may rely more on their environment to receive positive influences to prevent depression.

It's noteworthy that, contrary to expectations, while paternal support emerged as a significant factor for MDD prevention, maternal support did not. This contradicts previous findings highlighting the paramount influence of maternal support in averting MDD in children and adolescents.³³ Given that a substantial majority (86.5%) of our overall sample reported feeling supported by their mothers, we hypothesize that the combined influence of positive

maternal and paternal figures may be necessary to prevent MDD, as evidenced in previous studies.^{34,35} Indeed, it appears that the interaction of maternal and paternal parenting needs consideration when predicting youth symptoms.³⁶ Nevertheless, our study underscores the impactful role of a supportive father when maternal support is already in place.

Moreover, our study contributes to the body of literature by showing a small significant association between RSA scores and the prevention of MDD diagnosis, along with an inverse correlation between RSA scores and depressive symptoms scores. Extensive research has demonstrated that resilience plays a mediating role in the association between trauma and mood disorders^{37,38}, between victimization and suicidality³⁹, and it is linked to overall better treatment outcomes for anxiety⁴⁰, PTSD²⁶, and even clinical illnesses.⁴¹ In fact, a recent meta-analysis demonstrated that individuals with mood disorders exhibit lower resilience compared to those without mood disorders⁴². It is conceivable that more extensive studies with larger sample sizes may be requisite to comprehensively explore the nuanced aspects of resilience in relation to other MDD-related outcomes, such as the age of the first depressive episode and the number of mood episodes, which did not attain significance in our analysis.

Our group's recent systematic review has highlighted several protective factors in high-risk cohorts, some of which couldn't be confirmed in the present study.¹¹ Although other types of support, such as support from siblings, friends, and partners have been observed in multiple prior cross-sectional studies⁴³⁻⁴⁵, they did not exhibit a significant protective effect in our study. Moreover, variables such as spirituality, access to psychiatric treatment/psychotherapy, engagement in educational activities, family composition, and family cohesion have previously demonstrated a protective effect on mental health outcomes⁴⁶⁻⁵⁰. However, these factors did not exhibit a significant association with MDD prevention in our study. The complexities of these relationships and how they interact to shape resilience in high-risk circumstances warrant further investigation. Future studies are needed to better comprehend the intricate interplay of these factors.

While this study makes a valuable contribution to the literature, as there are few cohort studies that were able to assess how protective factors affect the incidence of MDD in high-risk individuals, it does have some limitations that should be considered. Firstly, the way the question was framed regarding support may introduce bias, as individuals can have a broad and subjective understanding of support. In addition, we did not analyze support in its various facets, such as emotional support or financial support. Additionally, the limited number of incident cases of MDD in high-risk individuals may have influenced the findings. The scarcity

of male participants in the incident depressed group, with only three males, could introduce gender bias. Finally, the study did not inquire about the participants' subjective feelings of support at T3, which means there is no evidence that the levels of perceived support remained consistent over time. These limitations should be taken into account when interpreting the results.

This young adult cohort study offers valuable insights into how a range of protective factors can influence the incidence of MDD in high-risk individuals. These findings have the potential to foster changes in the approach of psychological interventions within this population. Rather than solely focusing on mitigating negative factors, the emphasis may shift towards actively promoting positive elements.⁵¹ Additionally, the study highlights the crucial role of engaging fathers and the significance of employing family-based strategies to enhance mental well-being in high-risk populations.

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6. CONFLICT OF INTEREST

All authors report no competing interests.

7. REFERENCES

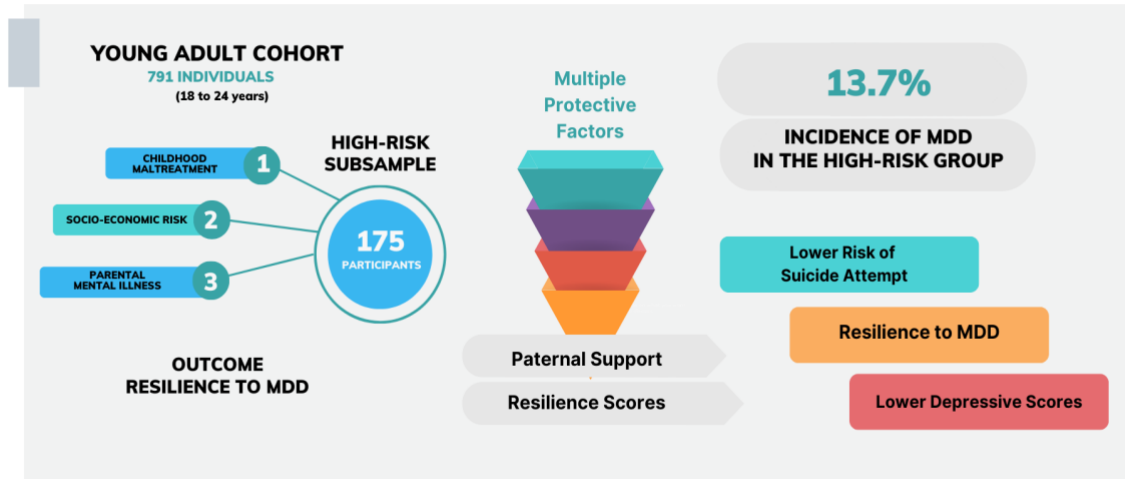
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FIGURE 1.



Source: Tietbohl-Santos et al. (2024). *Trends in psychiatry and psychotherapy*.

TABLE 1. CHARACTERISTICS OF THE RESILIENT VS INCIDENT FOR DEPRESSION GROUPS IN THE HIGH-RISK SUBSAMPLE.

Characteristics	Resilient Depression High-Risk Group (n= 151)	Incident depression High-Risk Group (n= 24)	p-value
Gender^a			0.0808
Male	49 (32.5%)	3 (12.5%)	
Female	102 (67.5%)	21 (87.5%)	
Age^b	20.6 (1.92)	20.1 (2.05)	0.9532
Skin Color^a			0.162
Not-White	44 (29.1%)	11 (45.8%)	
White	107 (70.9%)	13 (54.2%)	
Economic Classification^a			0.0555
High	84 (56.4%)	8 (33.3%)	
Intermediate	61 (40.9%)	16 (66.7%)	
Low	4 (2.7%)	0 (0%)	
Education^a			0.261
Incomplete High School or lower	59 (39.1%)	15 (65.2%)	
High school	69 (45.7%)	6 (26.1%)	
Secondary	23 (15.2%)	2 (8.7%)	
Education Lives With Father^a			0.289
Yes	65 (43%)	7 (29%)	
No	86 (57%)	17 (71%)	
Divorced Parents^a			0.293

Yes	96 (32.4%)	11 (46%)	
No	170 (67.6%)	13 (54%)	
Paternal Support^a			0.00613
Yes	104 (74.3%)	10 (43.5%)	
No	36 (25.7%)	13 (56.5%)	
Maternal Support^a			0.283
Yes	135 (92.5%)	20 (83.3)	
No	11 (7.5%)	4 (16.6)	
Resilience Score (RSA)^c	140 (127-151)	127 (110 -139)	0.009698
CTQ scores^c	11.5 (6-20)	18.5 (9.5-30)	0.03253
Suicide attempt^a			0.00000177
yes	12 (7.9%)	11 (45.8%)	
no	139 (92.1%)	13 (54.2%)	
Suicide ideation^a			0.0552
yes	10 (6.6%)	5 (20.8%)	
no	141 (93.4%)	19 (79.2%)	
Paternal Diagnosis^a			0.757
Yes	33 (21.9%)	4 (16.7%)	
No	118 (78.1%)	20 (83.3%)	
Maternal Diagnosis^a			0.639
Yes	83 (55%)	15 (62.5%)	
No	68 (45%)	9 (37.5%)	

Table 1. Characteristics of the Resilient vs Incident for depression groups in the high-risk subsample. RSA = Resilience Scale for Adults; CTQ = Childhood Trauma Questionnaire; a - Absolute and relative (%) frequencies, p-value according to Chi-square test; b - Mean (standard deviation), p-value according to t-test; c - Median (25th/75th quartiles), p-value according to Mann-Whitney U test.

Source: Tietbohl-Santos et al. (2024). *Trends in psychiatry and psychotherapy*.

TABLE 2. CHARACTERISTICS OF HIGH-RISK INDIVIDUALS ACCORDING TO PRESENCE VS ABSENCE OF PATERNAL SUPPORT.

Characteristics	Presence of Paternal Support (n=114)	Absence of Paternal Support (n=49)	p-value
Gender^a			0.171
Male	37 (78.7%)	10 (21.3%)	
Female	77 (66.3%)	39 (33.6%)	
Depressive Symptoms (MADRS score)^c	0 (0-6)	4 (2-16)	0.0002
Depressive Symptoms (BDI score)^c	6.5 (1-16)	13 (8-26)	0.00197
Resilience Scores (RSA)^c	138 (125-149)	134 (119- 146)	0.4266
Age of first depressive episode^a	20.0 (5.35)	17.7 (4.92)	0.0642
Suicide attempt (lifetime)^b			0.0520
Yes	11 (9.6%)	11 (22.4%)	
No	103 (90.4%)	38 (77.6%)	
Suicidal ideation (current)^b			0.162
Yes	107 (93.8%)	3 (85.7%)	
No	7 (6.2%)	46 (93.9%)	
Psychiatric in-patient treatment^b			0.0422

Yes	0 (0%)	3 (6.1%)	
No	114 (100%)	46 (93.9%)	
Paternal Psychiatric Diagnosis^b			0.858
Yes	24 (21%)	9 (18.4%)	
No	90 (79%)	40 (81.6%)	
CTQ^c	11 (6-20)	15 (8-27)	0.037

Table 2. Characteristics of high risk individuals according to presence vs absence of paternal support. MADRS = Montgomery-Asberg Depression Rating Scale; BDI= Beck Depression Inventory; RSA = Resilience Scale for Adults; CTQ = Childhood Trauma Questionnaire; a - Mean (standard deviation), p-value according to t-test; b - Absolute and relative (%) frequencies, p-value according to Chi-square test; c - Median (25th/75th quartiles), p-value according to Mann-Whitney U test.

Source: Tietbohl-Santos et al. (2024). *Trends in psychiatry and psychotherapy*.

TABLE 3. CHARACTERISTICS ACCORDING TO RESILIENCE LEVELS (HIGH VS LOW)

Characteristics	High Resilience (n=51)	Low Resilience (n=44)	p-value
Sex^b			0.0517
Male	21 (41.2%)	9 (20.4%)	
Female	30 (58.8%)	35 (79.6%)	
Age at Baseline^a	20.92 (1.82)	20.13 (2.00)	0.03832
Father Support^b			0.215
Present	34 (77.3%)	27 (62.8%)	
Absent	10 (22.7%)	16 (37.2%)	
Depressive Symptoms (MADRS score)^c	2 (0-6)	5 (1.5 - 14.5)	0.001223
Depressive Symptoms (BDI score)^c	5 (2-11)	12 (4.75 - 27.2)	0.00265
Age of first depressive episode^a	20.84 (6.22)	19.55 (5.35)	0.3184
Suicide attempt (lifetime)^b			0.0450
Yes	4 (7.8%)	11 (25%)	
No	47 (92.2%)	33 (75%)	
Suicidal ideation (current)^b			0.0545
Yes	2 (3.9%)	8 (18.2%)	
No	49 (96.1%)	36 (81.8%)	
Psychiatric in-patient treatment^b			1
Yes	1 (1.9%)	1 (2.3%)	
No	50 (98.1%)	45 (97.7%)	
Paternal Psychiatric Diagnosis^b			0.172
Yes	10 (19.6%)	15 (34%)	
No	41 (80.4%)	29 (66%)	
Maternal Psychiatric Diagnosis^b			1
Yes	28(54.9%)	24 (54.5%)	
No	23 (45.1%)	20 (45.5%)	
CTQ^c	12 (5 - 23.5)	18 (9.75 - 30)	0.05397

Supplementary Table 3. Characteristics according to Resilience Levels (High vs Low). Individuals grouped according to first and fourth percentiles of the distribution of RSA scores [Q1=< 124; Q4=>149]; MADRS = Montgomery-Asberg Depression Rating Scale; BDI= Beck Depression Inventory; RSA = Resilience Scale for

Adults; CTQ = Childhood Trauma Questionnaire; a - Mean (standard deviation), p-value according to t-test; b - Absolute and relative (%) frequencies, p-value according to Chi-square test; c - Median (25th/75th quartiles), p-value according to Mann-Whitney U test.

Source: Tietbohl-Santos et al. (2024). *Trends in psychiatry and psychotherapy*.

SUPPLEMENTARY MATERIAL

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<i>Supplementary table 1. Characteristics according to level of risk (Total Sample at T3)</i>	<i>1</i>
<i>Supplementary table 2. Statistical analysis of other potential protective factors.</i>	<i>2</i>

SUPPLEMENTARY TABLE 1. CHARACTERISTICS ACCORDING TO LEVEL OF RISK (TOTAL SAMPLE AT T3)

Characteristics	Normal-Risk Group (n= 417)	High-Risk Group (n= 175)	p-value
Sex^b			0.00149
Male	184 (44.1%)	52 (29.7%)	
Female	233 (55.9%)	123 (70.3%)	
Age at T3	31.94 (2.21)	31.89 (2.07)	0.9532
Skin Color			0.506
Not-White	118 (68.2%)	55 (31.8%)	
White	299 (71.4%)	120 (28.6%)	

Supplementary table 1. Characteristics of the whole sample at T3; a - Mean (standard deviation), p-value according to t-test; b - Absolute and relative (%) frequencies, p-value according to Chi-square test; c- Median (25th/75th quartiles), p-value according to Mann-Whitney U test;

Source: Tietbohl-Santos et al. (2024). *Trends in psychiatry and psychotherapy*.

SUPPLEMENTARY TABLE 2. STATISTICAL ANALYSIS OF OTHER POTENTIAL PROTECTIVE FACTORS.

Protective Factor	OR	95% CI	p-value
Maternal Support	0.560	0.158 to 2.341	0.389
Sibling Support	0.537	0.217 to 1.387	0.184
Friend Support	0.690	0.281 to 1.768	0.423
Spouse Support	2.445	0.765 to 9.634	0.157
Access to Psychotherapy	3.790	4.858 e-02 to 1.950	0.276
Having a Religious Belief	1.091	0.946 to 1.235	0.186

Belonging to a Religious Group	1.382	0.357 to 4.489	0.607
Frequently Attending to Religious Gatherings	0.840	0.544 to 1.270	0.416
Secondary Education	0.510	0.227 to 1.047	0.081
Parents Cohabiting (not separated)	0.734	0.308 to 1.779	0.485
CTQ scores	1.020	0.985 to 1.056	0.251

Supplementary Table 4. Statistical analysis of other potential protective factors (controlled for gender, ethnicity, and socio-economic level, resilience scores, and CTQ scores). Factors proven to be not statistically significant.

Source: Tietbohl-Santos et al. (2024). *Trends in psychiatry and psychotherapy*.

7. FINAL CONSIDERATIONS

The aim of this thesis was to delve into concepts associated with promoting healthy development and averting disorder trajectories in individuals at-risk for MDD. Thus, we focused on two main fronts: firstly, conducting a comprehensive literature review to identify significant factors in longitudinal studies with this population. Then examining these identified factors within an at-risk subsample of a cohort of young adults. This research has produced two studies, one already published at the Brazilian Journal of Psychiatry and another one submitted in the Journal Trends of Psychiatry.

In the initial study, we explored the landscape of protective elements influencing the onset of depression in individuals facing early adverse experiences through longitudinal studies. Our thorough literature review identified 38 protective factors correlated with a reduced incidence of depressive outcomes. These factors encompassed positive individual characteristics, family dynamics, peer relationships, school-related aspects, neighborhood characteristics, and intrinsic religiosity. An intriguing discovery emerged, while certain protective factors linked to individual characteristics such as IQ, temperament, or genotype were inherently non-modifiable, the majority of our findings emphasized the effectiveness of modifiable factors. Importantly, compelling evidence supports the protective effects of self-efficacy as a trait, and the implementation of healthy coping strategies has shown positive effects on the overall well-being of at-risk children and adolescents.

Moreover, papers assessing individual characteristics tended to yield more non-significant findings compared to other protective factors identified in our comprehensive literature review. This observation suggests that, in the context of at-risk individuals, the influence of personal traits on preventing depressive outcomes may be less pronounced. It is plausible that this population exhibits a greater diversity in individual characteristics, contributing to the variability in study results. Additionally, this trend aligns with the notion that individuals at risk may rely more on their environment for support, emphasizing the potential impact of external factors over intrinsic traits in mitigating the risk of depressive outcomes.

This aligns with another crucial finding from our initial study, emphasizing the pivotal role that a supportive family plays in preventing depressive outcomes. The evidence points to the notion that a more structured and cohesive family environment is particularly protective. Parents who actively foster a healthy parental attachment and engage with their children, exhibiting improved emotional regulation, appear to contribute to a lower incidence of

depression in their offspring. This emphasizes the importance of interventions focused on fostering robust parent-child relationships as pivotal elements in depression prevention. These interventions should prioritize enhancing attachment, promoting positive parenting techniques, and developing emotional regulation skills in parents. Additionally, effective treatment for parents requiring mental health support is paramount to ensure parents are in condition to care and bond to their young, preventing depression in the next generation.

Other pivotal factors highlighted in our review were the presence of positive peers and a perception of support from individuals outside the family. Notably, feeling supported by peers emerged as one of the most frequently observed and significant protective factors in our studies. Furthermore, numerous investigations showed the significant impact of a positive perception of school on preventing depression, whereas school attendance and participation in structured activities did not consistently yield significant findings across all studies. Thus, targeting interventions within school settings to foster improved peer relationships holds the potential for additional benefits, concurrently elevating both the school environment and peer support. This dual enhancement may exert an additional preventive effect against depression in children and adolescents.

Our second study illuminated the paramount importance of paternal support among at-risk individuals. Notably, paternal support emerged as a robust factor, significantly reducing the risk of developing MDD by nearly 65% and decreasing the risk of suicidal attempts by 62%. This finding underscores the crucial role fathers play in the well-being of at-risk populations. In tandem with our initial study, which unveiled the significance of various aspects of a supportive family in multiple papers, our second study also suggests that having both parents may be vital. The prevalence of supportive mothers in our subsample prompts us to extrapolate this observation, emphasizing the essential role of father support, even when mothers are present, within at-risk populations. Our study notably distinguishes itself as the first to explicitly highlight the indispensable contribution of fathers in the context of mothers' presence. Additionally, we contribute to the literature by demonstrating the efficacy of the resilience scale in measuring resilience longitudinally. Individuals with higher resilience scores in the second wave exhibited more favorable outcomes compared to those with lower resilience scores, further highlighting the utility of the resilience scale in assessing mental well-being.

In conclusion, the most significant contribution of this thesis lies in presenting a comprehensive demonstration of essential factors for averting depressive symptoms in at-risk individuals across longitudinal studies. These findings provide us with novel focal points for

effective interventions to assist this population. Addressing the family environment, with a particular emphasis on fathers, and expanding the accessibility of mental health treatments for parents is of utmost importance. Additionally, investing in school programs aimed at enhancing self-efficacy, fostering healthy coping mechanisms, and cultivating positive relationships between students to promote a favorable school experience holds paramount significance for at-risk individuals.

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9. APPENDIX

Following are the other works (articles and book chapters) conducted during the course of the PhD program.

SUBMITTED ARTICLES:

1. Becoming A Physician: A Qualitative Analysis Of Medical Students' Perspectives On Their Academic Environment, Well-Being And Mental Health. Tamires Martins Bastos, Carolina Stopinski Padoan, Vanina Lima Monteiro, Márcia Mocellin Raymundo, Cristina Plentz Pessi, **Bárbara Tietbohl Martins Quadros Santos**, Patrícia Fabrício Lago, Lucas França Garcia, Ana Margareth Siqueira Bassols, Pricilla Braga Laskoski, Simone Hauck. International Journal of Person Centered Medicine. Vol. 9 No. 2 (2019). <https://doi.org/10.5750/ijpcm.v9i2.968>
2. Psychotherapy Approaches for People with Disabilities: Literature Review. Charlie Trelles Severo, **Bárbara Tietbohl Martins Quadros Dos Santos**, Andréa Asti Severo, Marilú Mourão Pereira, Lucas Mendes De Oliveira, Gabriela Massaro Carneiro Monteiro, Tamires Bastos, Pricilla Braga Laskoski, Simone Hauck. Rev. Bras. Ed. Esp., Bauru, v.27, e0151, p.427-444, Jan.-Dez., 2021. 10.1590/1980-54702021v27e0151
3. Validation of the Brazilian Portuguese version of the Copenhagen Burnout Inventory (CBI) in healthcare professionals. Carolina M. Moser, **Bárbara Tietbohl-Santos**, Daniel Luccas Arenas, Aurora Xavier, Felipe Ornell, Rogerio Boff Borges, Simone Hauck. medRxiv2020.09.21.20198408; <https://doi.org/10.1101/2020.09.21.20198408>
4. Association between different types of childhood trauma and parental bonding with antisocial traits in adulthood: A systematic review. Schorr, Manuela Teixeira ; **Tietbohl-Santos, Bárbara** ; De Oliveira, Lucas Mendes ; Terra, Luciana ; De Borba Telles, Lisieux Elaine ; Hauck, Simone. CHILD ABUSE & NEGLECT, v. 107, p. 104621, 2020.

5. Arrais TR, Cavalli GD, **Dos Santos BT**, Pereira GB, Migliavaca CB, Grossman GB, Biolo A. MIBG cardiac imaging compared to ejection fraction in evaluation of cardiotoxicity: a systematic review. *J Nucl Cardiol*. 2021 Jul 6. doi: 10.1007/s12350-021-02610-0. Epub ahead of print. PMID: 34228328.

BOOK CHAPTERS

1. SANTOS, B. T. M. Q. ; ANTONELLI-SALGADO, T. ; ROZA, T. H. ; PASSOS, I. C. . Precision psychiatry in bipolar disorder. In: Rodrigo Machado-Vieira; Jair Soares. (Org.). *Biomarkers in Bipolar Disorders*. 1ed.: Academic Press - Elsevier, 2021, v. , p. 1-.
2. ANTONELLI-SALGADO, T. ; ROZA, T. H. ; SANTOS, B. T. M. Q. ; PASSOS, I. C. . Machine learning na psiquiatria. In: Alfredo Cataldo Neto; Gabriel José Chittó Gauer; Nina Rosa Furtado; Vanessa Sgnaolin. (Org.). *Psiquiatria para estudantes de Medicina*. 3ed.Porto Alegre: ediPUCRS, 2021, v. , p. 1-718. 1.
3. Tietbohl-Santos B, McIntyre, A. WA B. Chapter 20: Biomarkers of Neuroprogression. In: *Bipolar Disorder: An Evidence-Based Clinical Guide*. 1st ed. Elsevier; in production.