Psychoneuroimmunology in Children: The Interaction between Psychosocial Stress, the Immune System and the association with Psychopathology

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Abstract (Nederlands)

Introductie. Psychoneuroimmunologie onderzoekt de samenhang tussen processen binnen de psychologie, het immuunsysteem en neurowetenschappen. Meerdere wetenschappelijke studies hebben aangetoond dat het ervaren van psychosociale stress medische en psychische gezondheidsproblemen hebben veroorzaakt bij volwassenen. Minder duidelijk is of dezelfde psychische problemen optreden bij kinderen. In deze literatuurstudie wordt gekeken naar welke psychopathologische symptomen gevonden zijn door de invloed van psychosociale stress op het immuunsysteem van kinderen, welke wetenschappelijke onderzoeksmethoden zijn gebruikt, welke beperkingen van andere wetenschappelijke studies worden benoemd, welke leeftijdsgroepen zijn onderzocht en wat belangrijk is voor toekomstig onderzoek. **Methode.** Een systematische literatuurstudie is uitgevoerd, waarbij wetenschappelijke databases zijn gebruikt. Scopus, PubMed en PsycINFO zijn gebruikt om mogelijke studies te vinden. Door het gebruiken van de PRISMA methode zijn 12 wetenschappelijke studies gevonden en geanalyseerd. **Resultaten.** Symptomen van angst, depressie, vroege psychose en autisme hangen samen met de invloed van psychosociale stress op het immuunsysteem van kinderen. De meeste studies maakten gebruik van een cross-sectioneel design, andere studies maakten gebruik van een longitudinaal design. Mogelijke beperkingen volgens verschillende onderzoekers waren het gebruik van een cross-sectioneel onderzoek, het meten van psychosociale stress door het afnemen van veneuze bloedmonsters en het niet meenemen van andere bio-markers van het immuunsysteem voor het meten van mogelijke ontstekingen binnen het immuunsysteem. Adolescenten (12 tot 18 jaar) en schoolkinderen (4-12 jaar) zijn meer frequent bestudeerd dan zuigelingen (0-1 jaar). Er zijn geen studies gevonden van kinderen van 1-4 jaar. Aanbevelingen voor toekomstig onderzoek zijn het opzetten van longitudinaal onderzoek en het uitwerken van theoretische modellen binnen de psychoneuroimmunologie. **Discussie.** De belangrijkste uitkomsten van dit onderzoek zijn dat meer longitudinaal onderzoek nodig is, meerdere mogelijkheden nodig zijn om psychosociale stress te meten bij kinderen, meer kennis van de verschillende biomarkers binnen het immuunsysteem en het bijhouden van mogelijke veranderingen binnen verschillende leeftijdsgroepen van kinderen. De beperkingen van bestaande onderzoeken hangen voor een zeer groot deel samen, waardoor aanbevelingen voor toekomstig onderzoek worden gemaakt.

Keywords. Psychoneuroimmunologie, kinderen, mentale gezondheid

Abstract (English)

Introduction. Psychoneuroimmunology is the science that focuses on the interaction between psychology, the immune system and neurology. Several scientific studies have demonstrated that the experience of psychosocial stress caused medical and mental health problems in adult samples. Much less research has examined whether the same problems arise in children samples. This review evaluates what psychopathological symptoms were found due to the influence of psychosocial stress on the immune system of children, the sort of scientific designs that were used, which limitations are being mentioned by other researchers, the different age groups that were studied and what is important for future research. **Method.** A scoping review of the literature was performed. Articles were obtained via Scopus, PubMed and PsycINFO. By using the PRISMA method, 12 studies were found and thoroughly analysed. **Results.** Symptoms of anxiety, depression, early-onset psychosis and autism correlated with the influence of psychosocial stress on the immune system of children. Most studies have performed a cross-sectional design, while some studies performed a longitudinal study. Possible limitations of the current studies were using a cross-sectional study design, measuring psychosocial stress by taking solely venous blood samples, not including other biomarkers of the immune system for measuring inflammatory responses. Adolescents (12-18 years) and school-aged children (4-12 years) were studied more frequently than infants (0-1 year). No studies were found of children of 1-4 years. Recommendations for future research are setting up longitudinal study designs and work out theoretic models of psychoneuroimmunology. **Discussion.** The most important findings of this research are that more longitudinal research is needed, more possibilities to measure psychosocial stress in children, more knowledge of the different biomarkers in the immune system and keeping track of possible changes in different age groups of children. In addition, an overlap of the most common limitations of the included studies is discovered, what can be helpful for future researchers to expand our current knowledge of psychoneuroimmunology in children.

Keywords. Psychoneuroimmunology, children, mental health

Contents

1. Introduction

Over the last few decades, a large number of studies has showed that stress predisposes individuals to the development of mental disorders and medical diseases (e.g. Segerstrom & Miller, 2004; Cohen, Janicki-Deverts & Miller (2007); Miller, Chen & Cole, 2009). Factors such as chronic stress or acute stress can have a direct or indirect influence on the immune system and in the long term, to a variety of diseases (Cohen et al., 2007). The majority of early studies suggested that the experiences of stress had a major impact on the immune system and that this was the underlying cause of poor physical and mental health of individuals (e.g. Angell, 1985; Ali, Haribabu & Snyderman, 1997). Psychoneuroimmunology (PNI) focuses on the interaction between psychological processes, the immune system and the brain. An overwhelming quantity of literature in psychoneuroimmunology has been published, studying different biological and behavioral mechanisms. However, most of this research focused on adults and prenatal stress (e.g. Lobel et al., 2008; Gillespie, Cole & Christian, 2019). For example, they showed that stress associated with abuse, poverty or work-related stress on pregnant women, have enduring effects on their infants' physiology and psychopathology (Coussons-Read, 2012). Therefore, prenatal stress can increase risk for lasting disease or psychological disorders. However, there is much less research on the extent to which similar adverse effects of stress exist when this is experienced by children. Determining if inflammation in children is truly linked with adverse health risks related to psychopathology, might have considerable advantages for improving psychological health of children.

1.1: Psychoneuroimmunology

It is first essential to describe and explain some of the main concepts within psychoneuroimmunology that will be mentioned throughout this article. The concept of psychoneuroimmunology was first introduced by Ader in 1980, to show the importance of the connection, between the brain and the immune system (Ader, 1980). As an example, Ader and Cohen (1975) first showed interest in conditioned changes in immunologic reactivity. They discovered that substances released by cells of the immune systems influence brain activity and behavior. Disruptions in the communication between the immune system and the brain can produce inflammatory diseases, such as asthma, coeliac disease or rheumatoid arthritis

(Kiecolt-Glaser, McGuire, Robles & Glaser, 2002). In addition, dysregulations in the immune activity can affect the onset of several psychiatric disorders, such as schizophrenia (Dameshek, 1930). They started to speculate about the hypothesis if abnormalities in the immune system affect the development of major psychiatric disorders, such as schizophrenia or depression. Nowadays, inefficient immune activity has been incorporated into a variety of psychological disorders of the brain, that can affect behavior and mental processes. Psychoneuroimmunology helps to explain how mental processes inflect the immune system and how the immunological activity influences the function of the mind (Daruna, 2004).

1.2: The Immune System of Children

To understand the interaction between the immune system, psychosocial stress and psychopathology in children, a short explanation of the development of the immune system of children is necessary. The immune system exists of different layers of tissue and its function is to protect the system from invading forms of damaged cells or infections (Howell & Shepherd, 2018). During childhood, the immune system is still in its developing phase. The quality of the immune system of the child is partially determined through hereditary influences and prenatal influences (Ygberg & Nilsson, 2011). However, neonatal and childhood influences also have significant influence on the development of the immune system (Satwani, Morris, van de Ven & Cairo, 2005). During the neonatal phase, the antibody response has a shorter duration of antibody persistence (Pihlgren et al., 2006). Meaning, compared to adults, their bodies have a more limited time of releasing antibodies during the infiltration of pathogens. Psychosocial stress during the neonatal phase can have enduring effects on the development of the immune system (Avitsur & Sheridan, 2009). Neonatal stress can disrupt the development of the immune system and reduces resistance to infectious challenges.

Recent studies show that psychosocial stress during childhood, such as childhood maltreatment, can have a significant, negative impact on the inflammatory response of the immune system (Bertone-Johnson et al., 2012; Pace et al., 2012). Meaning, children who experienced childhood maltreatment (psychosocial stress), early in life, are more vulnerable to unbalanced immune regulations (Coelho et al., 2014). These vulnerabilities in the immune system are risk factors for the manifestation of psychopathology later in life.

1.3: Psychosocial Stress and Children

A number of psychological factors and their impact on immunity have been studied, such as personality traits (Coe & Laudenslager, 2007) or the social support system (Uchino, Vaughn, Carlisle & Birmingham, 2012). However, studies of the effects of early, psychosocial stress on the immune system continue to show a long-term predisposition to inflammation (Danese, Pariante, Caspi, Taylor & Poulton, 2007). Psychosocial stress causes a variety of changes in the physiological state, such as changes in the blood pressure, blood electrolytes, the number of white blood cells or gastrointestinal tract ulcers. Studies in the early 1930s already showed that a large number of harmful stressors, caused endocrine effects and changes in the immune system (Viner, 1999). Examples of psychosocial stressors during childhood are parental divorce, (sexual) abuse and neglect that might have significant impact on the development of physical and mental health (Kagamimori, Nasermoaddeli & Wang, 2004). For instance, research showed immunological disruptions after being sexually abused during childhood (Ayaydin et al., 2016). The immunological disruptions were often accompanied by a significant decrease of activated T-cells of those children. Meaning, there were less cells present that are necessary for the activation of immune cells to fight potential, invading pathogens. This causes the immune system of the child to be less able to target different pathogens and enhance the immune responsiveness. Wismer-Fries, Shirtcliff and Pollak (2008) showed that children who are exposed to psychosocial stress early in life may increase the risk of maladaptive regulations of the hypothalamic-pituitary-adrenal (HPA) axis. Exposure to chronic stress leads to the production of the hormone cortisol, that is regulated through the HPA-axis (Shea, Walsh, MacMillan & Steiner, 2005). For instance, different types of unpleasant, parental care, such as neglect or abuse, may cause unhealthy quantities of cortisol, that can adversely affect the development of the HPA-axis (Gunnar & Donzella, 2002). Adequate physiological stress responses are characterized through a rapid increase and subsequently decrease of the hormone cortisol, that is essential for the management of stress. Abnormalities in the stress regulations of the HPA-axis may form a risk for the development of psychiatric disorders later in life (Maniam, Antoniadis & Morris, 2014). Research showed that exposure to psychosocial stress during childhood, caused reduced phagocytosis in children (Bartlett, Demetrikopoulos, Schleifer & Keller, 1997). Meaning, psychosocial stress might reduce the amount of white blood cells, that causes the cells to be more vulnerable to inflammatory responses and weakens the activity of the immune system.

These findings underline the importance of increasing our knowledge of the major effect psychosocial stressors have on our immune system. Knowing the effect of psychosocial stress on the immune system, can lead research into several future directions. For example, remediating the negative physical effects of early-life stressors before the onset of medical or psychopathological symptoms (Danese & Lewis, 2017). In addition, non-pharmalogical interventions, such as mindfulness, psychotherapy or physical exercise might work as a buffer for the influence of psychosocial stress on the immune system, early in life. For example, Lewitus and Schwartz (2008) showed the possibility of using the adaptive immune system to enhance resilience of psychosocial stress. In other words, the immune system gets to 'learn' to enhance its ability to cope with psychosocial stress by experiencing moderate stressors. They performed their study with significant results and showed there is a possibility to enhance the adaptive immune system, to increase its protection against the pathological consequences induced by psychosocial stress.

1.4: Psychopathology and Children

Several studies show associations between inflammation and psychiatric symptoms (O'Connor, Irwin & Wellisch 2009; Capuron & Miller, 2011). For example, Fillman et al., (2013) demonstrated evidence for the correlation between dysregulations in inflammation and psychosocial stress in symptoms of schizophrenia. In addition, Seong, Seasholtz and Burmeister (2002) showed a correlation between the susceptibility of the HPA-axis, inflammation and manifestation of symptoms of psychiatric disorders. However, existing research in the altered immune functions during childhood and the development of psychiatric symptoms is much more limited.

Several elements in the immune system are believed to influence the development of psychiatric symptoms, such as infections in the nervous system, autoimmune diseases and the influence of cytokines on the alteration of mental processes (Maier & Watkins, 1998). Changes in the immune system are visible during childhood and cause significant biological changes. Exposure to psychosocial stress during childhood can trigger changes within the immune system in children. Nanni, Uher and Danese (2012) showed adverse childhood experiences may cause symptoms of psychiatric disorders, long after the initial threat (infections during childhood) has passed, such as depression or posttraumatic stress disorder. Thus, there are two domains within the interaction of psychosocial stress, the immune system and symptoms of psychopathology during childhood. First, the onset of psychopathological symptoms during their childhood due to the influence of psychosocial stress on the immune

system. Second, the onset of psychopathological symptoms after their childhood, due to the impact of psychosocial stress on the immune system during their childhood. A description of psychiatric symptoms of adults, due to the impact of psychosocial stress on the immune system during childhood goes beyond the scope of this review. Various extensive reviews on this topic can be reviewed for more detailed information (Danese & Baldwin, 2017; Agnew-Blais & Danese, 2016; Lippard & Nemeroff, 2019).

1.5: Existing Research and Future Directions

A growing body of research has confirmed that psychosocial stress during childhood is associated with poor mental and physical health (e.g. Dong, Dube, Felitti, Giles & Anda, 2003; Deater-Deckard et al., 2009). However, there are some limitations of the existing literature, that are mentioned by several studies (Nassau, Tien & Fritz, 2008; Tagge et al., 2013). A previously performed review of the literature demonstrated a number of methodological shortcomings, such as the presence of confounding variables, having small samples and no follow-up research (Nassau et al., 2008). In addition, most studies have been primarily cross-sectional, which makes it harder to view any changes over time. Cross-sectional designs do analyse variables such as psychosocial stress, inflammatory responses and psychopathological symptoms, but provides no knowledge of the inherence to causality over time (Caruana, Roman, Hernández-Sánchez & Solli, 2015). Longitudinal studies utilize continuous measurements to follow individuals over lengthened periods of time – mostly years (Broom, Hand & Tovey, 2009). In general, cross-sectional designs can be considered to function as an indication for possible associations between variables and can be used as a starting point before setting up longitudinal study designs, that are more time-consuming. For example, Mills, Scott, Wray, Cohen-Woods and Baune (2013) performed a review on depressed adolescents and the association with inflammation and depression. This review found several studies that indicated evidence for the association between the previously mentioned variables, but warrant to interpret these findings with caution, because of the cross-sectional study design.

Knowing what sort of study designs were used by previously performed studies in the field of psychoneuroimmunology in children, gives a valuable view of what directions future research should follow. In addition, studies in adult samples demonstrate evidence for future directions to improve mental health, such as prevention strategies or innovative treatments on immunity (Miller & Cohen, 2001). An extensive evaluation of several psychological interventions, such as relaxation, stress management and hypnosis showed a relatively

positive effect on different elements of the immune system However, this meta-analysis was performed on mostly adults and mentions that very little research is performed in studies of children. Naussau et al., (2008) performed a review of the integration of psychoneuroimmunology into medical illness interventions, specifically for children. Although these authors concluded psychological interventions can increase immune functions of children, only a small amount of studies were found. According to Nausseau et al., (2008), an important challenge in this particular field of research, is associated with ethical considerations, such as exposing children with medical diseases to unnecessary stressors. For example, measuring biomarkers of the immune system is largely done by taking blood samples, that requires additional needle sticks, that might alter the experience of additional stress. Giving a clear description of what directions future research should follow in extant literature gives valuable knowledge to future researchers in this area.

1.6: Summary and Research Question

Considering the enumeration above, in which it is clear a connection exists between the influence of psychosocial stress and its impact on the immune system, and the onset of psychiatric symptoms in children, it is highly important to find out the current findings, limitations and what directions future research should follow. Knowledge on the association between psychosocial stress and the immune system, might give future research stronger foundation in developing targeted interventions in preventing and treatment of psychopathological symptoms. Therefore, a scoping review will be performed, to provide answers of what is already known, the gaps in knowledge and directions to future research subjects (Colquhoun et al., 2014).

To make a clear distinction, childhood will be divided into four different subgroups, to clarify the differences of between the influence of psychoneuroimmunology on different age groups. An important advantage of making this distinction, is to view whether some age groups have been more investigated up till now than others. The distinction is also made, because the experience of psychosocial stress of the first three age groups might be based on the view of the experiences of their parents. The last age group, which is the group of adolescents, will rely on the experiences of the child. The first one will focus on ‘infants’, which are the years of 0 till 1. The second one focuses on ‘pre-schoolers’, which are the years of 1 till 4. The third one will focus on ‘school-aged-children’, which are the years of 4 till 12. The fourth and final group will focus on ‘adolescents’, which are the years of 12 till 18.

Several sub-questions were formulated to divide the main research question into different themes.

1) What psychopathological symptoms are found during childhood, due to the influence of psychosocial stress on the immune system of children?
2) What scientific designs have been used to research psychoneuroimmunology in children?
3) What are the most common limitations reported by other researchers in the field of psychoneuroimmunology in children?
4) What age groups have been studied in the field of psychoneuroimmunology in children?
5) What kind of future research topics are mentioned by other researchers in the field of psychoneuroimmunology in children?

2: Method

2.1: Search Strategy and Selection-Criteria

Electronic searches of Scopus, PubMed and PsycINFO were used. First, Scopus was included for covering a wide range of scientific articles. Second, PubMed was included, since it contains articles referring to the biomedical domain (neurology, immunology and the nervous system). Third, PsycINFO was included, since it constitutes a database covering the psychological domain, so therefore it will contain articles of psychosocial stress and psychopathology. Next, search strings were established. To make sure to search for articles related to psychoneuroimmunology, several synonyms were used, which are often used in the psychological and medical world of psychoneuroimmunology. The search strings used for the different databases are the following:

(Psychoneuroimmunology **OR** ‘’Immune System’’ **OR** ‘’PNI’’ **OR** ‘’Psychoendoneuroimmunology’’ **OR** ‘’PENI’’ **OR** ‘’Psychoneuroendocrinoimmunology’’ **OR** ‘’PNEI’’) **AND** (stress*) **AND** (child*)

(Psychoneuroimmunology **OR** ‘’Immune System’’ **OR** ‘’PNI’’ **OR** ‘’Psychoendoneuroimmunology’’ **OR** ‘’PENI’’ **OR** ‘’Psychoneuroendocrinoimmunology’’ **OR** ‘’PNEI’’) **AND** (stress*) **AND** (child*) **AND** (mental health)

The articles have been selected based on several inclusion and exclusion criteria, established in March, 2020. The process of selection is illustrated below in the flow chart (Figure 1), following the guidelines of the PRISMA documentation method (Moher, Liberati, Tetzlaff & Altman, 2009). Articles identified by the search terms were screened by the snowball method, to view possible, additional studies. The inclusion criteria were (1) published in English or Dutch, (2) studies based on psychoneuroimmunology and inflammatory responses, (3) data was taken from participants of 0-18 years and (4) published in peer-reviewed journals. Studies were excluded if their emphasis lied specifically on medical diseases; if the experience of psychosocial stress was not clearly described; if data was based on adults or animals and if data was based on prenatal stress. In addition, reviews, editorials or multiple publications of the same data were excluded.

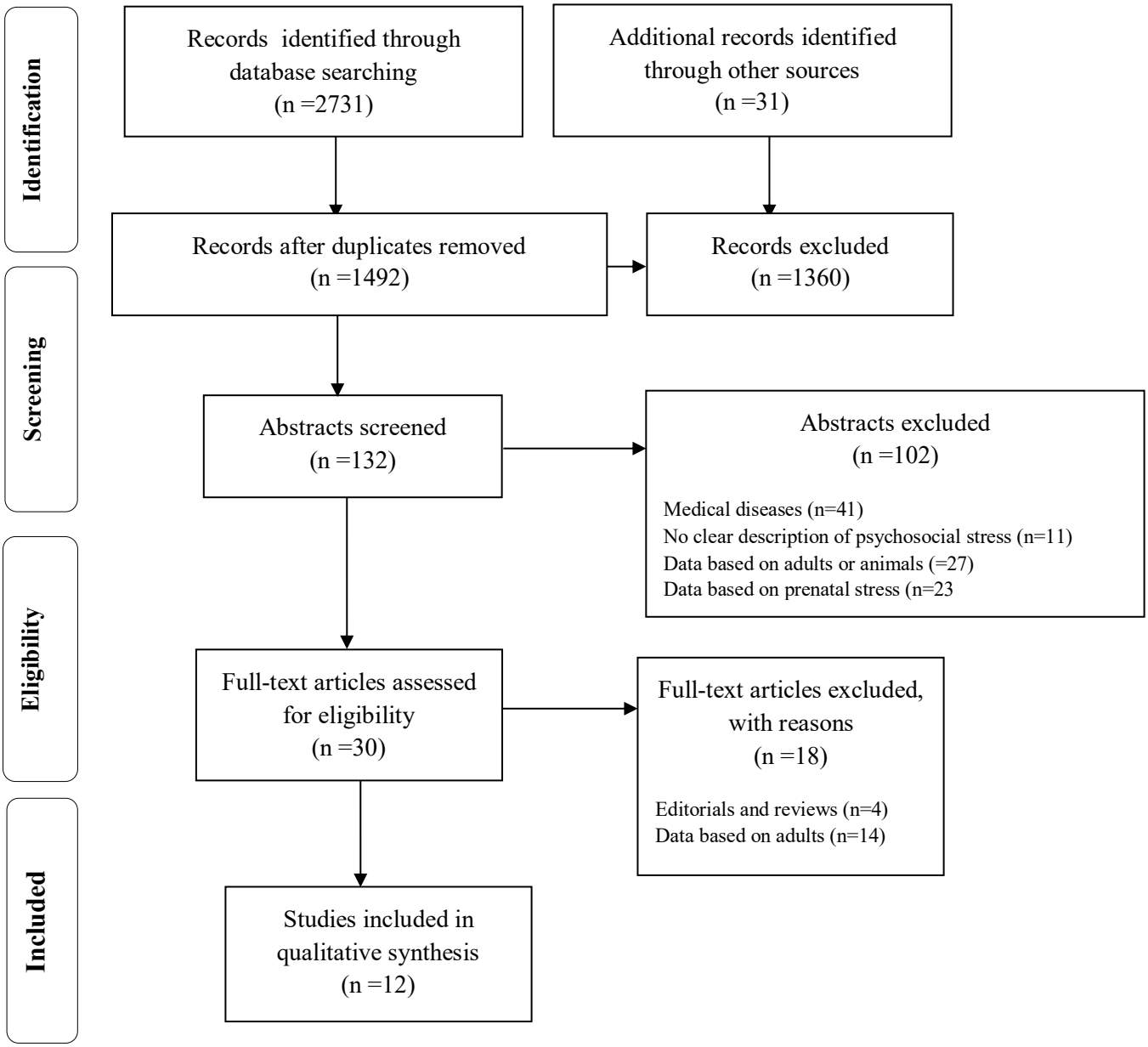

Figure 1. Workflow of the process of screening and exclusion of articles.

2.2: Procedure and Analysis

Ultimately, 12 articles were included in this review. After using the PRISMA method (Moher et al., 2009), 30 full-text articles were assessed for eligibility and 19 articles were excluded for reasons such as; no associations with symptoms of psychopathology and unclear descriptions of inflammatory responses due to psychosocial stressors. The 12 articles that have been included in this review were analysed following the five research questions. The first research question was about what psychopathological symptoms were found during childhood, due to the influence of psychosocial stress in their immune system. The results sections were screened for different psychopathological symptoms and added into Table 1. 'Not specified' was used if the article did mention that symptoms of psychopathology were found due to inflammatory responses, but did not further describe what sort of psychopathology was found. The second research question was about what sort of study designs were used to research psychoneuroimmunology in children. To answer this question, the method sections of the different articles were analysed to view what sort of scientific design the authors used for their study. The third research question aimed at what limitations were mentioned by other studies of psychoneuroimmunology in children. The different articles were screened for possible limitations, by fully analysing their discussion and conclusion sections. The fourth research question was about the different age groups in childhood. To answer this question, the method sections were analysed, to find out the age group of the participants. Finally, the fifth research question was about which topics were considered of relevance in future research. To answer this question, the selected articles were fully read, to screen for mentioned topics for future research.

3. Results

3.1: Descriptive Values

The five different research questions will be reported by the identified descriptive values. In addition, a table will be demonstrated that shows an overview of the 12 included articles (see Table 1).

3.1.1: Psychopathological Symptoms and Psychoneuroimmunology in Children

The 12 articles showed substantial differences in the mentioned psychopathological symptoms associated with the experience of psychosocial stress and inflammatory responses during childhood. Wedervang-Ressel et al., (2019) showed in their study that adolescents with early onset psychosis had elevated plasma levels of IL-18 and IL-18/IL-18BP ratios by the contribution of stress symptoms. The inflammatory cytokine IL-18 is suggested to be responsible for transferring stress signals into inflammatory responses. Cortisol levels and IL-18 cytokines were measured by taking venous blood samples and compared to a sample of healthy controls. They found evidence suggesting inflammatory responses are activated in patients with early-onset psychosis, with cytokine IL-18 elevated, compared to healthy controls. Meaning, the authors showed a potential link between early-onset psychosis, psychosocial stress and IL-18 in adolescents.

Several studies showed correlations between the experience of psychosocial stress, inflammatory responses and symptoms of anxiety disorders in children. Ulmer-Yaniv, Djalovski, Yirmiya, Halevi, Zagoory-Sharon and Feldman (2018) performed a longitudinal study of children in which they followed their participants in their early childhood (M = 2.76 years), middle childhood (M = 7.68 years) and late childhood (M = 9.3 years). They hypothesized about children exposed to war trauma, insensitive parenting behaviour and social engagement of the child led to a higher buffering effect of the immune system and a direct link with increased anxiety symptoms. Salivary immunoglobulin A (s-IgA) was used as a biomarker of the immune system and serves as a first line of defence against pathogens invaders in the immune system. Children exposed to war showed higher s-IgA levels, but the results of the study showed that when mothers were more sensitive as a parent, children showed lower levels of s-IgA and a decrease in anxiety symptoms than children without sensitive parenting. Meaning, the immune responses are partially shaped by the more or less sensitive parenting style performed by mothers. In addition, Yirmiya, Djalovski, Motsan, Zagoory-Sharon and Feldman (2018) showed an association between s-IgA, higher cortisol levels (CT) and anxiety symptoms of adolescents. They showed increased s-IgA due to the influence of psychosocial stress. Again, they showed a critical role of the mother's parenting behaviour in shaping resilience against the experience of psychosocial stress.

Ferguson et al., (2016) examined the correlation between stress-responsive cytokines, increases in cortisol and symptoms of autism-spectrum disorder in the age-group of 6-18 years. They showed a potential interplay between the immune system, the experience of

psychosocial stress and symptoms of autism-spectrum disorder. Greater lower gastrointestinal symptoms were associated with CT (cortisol levels) and stress-related endocrine responses exposure to psychosocial stress. This correlation was higher for children with symptoms of autism disorder.

Gariup et al., (2015) aimed to find possible biomarkers of inflammatory responses in a sample of children with psychopathological symptoms. Children and adolescents' of 8-17 years were examined. The authors showed a correlation between the experience of psychosocial stress during infancy and adolescence, inflammatory responses (cytokines) and psychopathological symptoms, such as depression, dysthymia and other psychiatric symptoms. Children and adolescents' acute psychopathology was associated with several biomarkers of the immune system, with the experience of psychosocial stress as the presumed causal factor. In addition, Giletta et al., (2017) examined the experience of psychosocial stress and the influence on inflammatory responses in adolescents who are at risk for developing mental health problems. They specifically tested adolescent girls, who were frequently exposed to peer victimization. The participants were exposed to *in vivo* psychosocial stressors and saliva samples were collected before and after the experience of psychosocial stress through blood samples. The saliva samples were used to measure the inflammatory responses, by measuring three different cytokines. The authors showed that adolescents who were frequently exposed to peer victimization showed greater levels of inflammatory responses and more depressive symptoms, when compared to healthy controls.

In sum, several psychopathological symptoms were linked with inflammatory responses due to the experience of psychosocial stress in children. Symptoms such as early-onset psychosis, symptoms of anxiety, autism spectrum disorder and symptoms of mood disorder were found in different studies. Different types of biomarkers in the immune system were used to measure the inflammatory responses of children.

3.1.2: Scientific Designs in Psychoneuroimmunology in Children

In 53.8% of the articles included, a cross-sectional study-design was performed. For example, Pearlstein, Staudenmaier, West, Geragthy and Cosgrove (2020) performed a cross-sectional study in assessing the biomarkers of the immune system and their responses to psychosocial stress as a predictor the outcome of the effects of Cognitive-Behavioural-Therapy (CBT) for adolescents with mood disorders. In addition, Cunha et al., (2018) performed a cross-sectional study of children between 6-12 years and investigated the

association between peripheral biomarkers and child psychopathology. The authors found several patterns of association between cytokines, chemokines, cytokine receptors and oxidative stress markers and several clusters of psychiatric symptoms.

In 46.2% of the articles included, a longitudinal study design was performed. Ma, Serbin & Stack (2018) performed a longitudinal study examining the association between anxiety symptoms, inflammatory responses and the experience of psychosocial stress in children. The association between anxiety symptoms and lower levels of sIgA has been reported, with a long-term report over several years. Between the ages of 9-12, the children's anxiety symptoms, levels of sIgA and psychosocial stress were measured. In addition, anxiety symptoms, total levels of sIgA and psychosocial stress were reported in three data waves. By performing a longitudinal study, underlying associations between symptoms of anxiety, sIgA levels in a life-span of more years were demonstrated. Another example of a longitudinal study was performed by O'Connor et al., (2017) by examining a possible relationship between biomarkers of the immune system, cortisol markers and the temperament of infants (0-1 years). The infants were examined at 6 months and 17 months. In behavioral development, associations between immune biomarkers and symptoms of parent-reported temperament were found. In addition, significant associations between immunological biomarkers and the intensity of temperament at 6 months and 17 months were found.

3.1.3: Limitations in the Studies of Psychoneuroimmunology in Children

As mentioned previously, mostly cross-sectional studies were performed. The performed cross-sectional studies included in this review all mention not being able to demonstrate causality between the experience of psychosocial stress, inflammatory responses and psychopathology in children. As an example, Wedervang-Ressel et al., (2019) mention their cross-sectional study did not allow exploration of cause and effect. Early-Onset Psychosis (EOP) patients are known for having dysregulations in their hormonal profiles, which is also cortisol. Therefore, the authors state it is unclear to what extent the measured cortisol can be interpreted as a measurement of psychosocial stress. In addition, Cunha et al., (2018) performed a cross-sectional study in school-aged children (6-13 years), in which inflammatory biomarkers, psychosocial stress and psychopathological symptoms were studied. Although the study demonstrated evidence for a correlation between these biomarkers and psychopathology, the authors warn to interpret the results with caution, because changes in stress-induced inflammatory responses might vary over time. Meaning,

the experience of psychosocial stress might be different when measured at different periods of age, which can change the inflammatory responses in the immune system.

Several studies mentioned they were limited in measuring the inflammatory responses, due to the experience of psychosocial stress. Meaning, most of the studies only used 1-3 different biomarkers of the immune system and state that more biomarkers should have been used to view a possible link between the immune system and psychopathological symptoms in children. As an example, de Bruine, Giletta, Denissen, Sijtsema & Oldehinkel (2019) mentioned it is important to examine other markers of inflammation, because in their study they used only one marker of low-grade systematic inflammation, hsCRP (a high sensitive C-reactive protein). In addition, Yirmiya et al., (2018) highlighted the fact that they only used s-IgA as a component of inflammatory responses and future studies should assess additional inflammatory parameters.

The lack of stress markers other than cortisol is also mentioned by several studies. For example, de Bruine et al., (2019) include the lack of other stress markers as one of their limitations. Furthermore, the experience of psychosocial stress can be influenced by other possible moderators, because not every adolescents reacts in the same way and extent to peer experiences. In addition, Wedervang-Ressel et al., (2019) mention it is unclear to what extent levels of cortisol can be interpreted as a function of psychosocial stressors. In addition to the measurement of cortisol, the authors state that other measurements of psychosocial stress are needed to further establish the potential link between inflammatory responses, psychosocial stress and psychopathology in children. However, no other, possible measurements of psychosocial stress are mentioned.

O'Connor et al., (2017) mention that the sample size in their study of immune markers, psychosocial stressors and psychopathology in infants was modest. This caused the authors to have limited ability to examine more complex interactions and are more at risk of reliability issues or bias. In addition, Ma et al., (2018) mention their sample size was too small in terms of ethnically and culturally diverse participants, which makes it more difficult to interpret the results in a general matter.

In sum, by analysing all the different articles, several studies indicate their results should carefully be interpreted, because of the mentioned limitations above. According to the different authors, causality could not be inferred in all studies, because of their cross-sectional study designs. In addition, measuring only one or two parts of the immune system might have led to the exclusion of other important parts of the immune system associated with

psychopathology in children. The lack of stress markers other than cortisol and small sample sizes were also mentioned as limitations by most of the articles included

3.1.4: Different Age Groups

As described previously, four different age groups in childhood were established. Several studies studied more than one age group. In total, three studies focused on infants (18.8%), no studies focused on pre-schoolers (0%), six studies focused on school-aged children (37.5%) and seven studies focused on adolescents (43.8%).

3.1.5: Future Research Directions

In line with the limitations of the included studies, several studies mention future research should explore the implications of the immunological and stress response profiles of children. As an example, O'Connor et al., (2017) indicate that the integration of interventions focused on behaviour in psychoneuroimmunology in children focused might have a positive effect on the mental health of children. In addition, Ulmer-Yaniv et al., (2018) state that further research is needed to test stress-buffering systems in children to construct resilience in specific interventions for children while they are growing up.

Several studies mention the importance of further research in a broader range of psychoneuroimmunology, to build psychoneuroimmunology developmental models. Gariup et al., (2015) indicate if more research in this particular field is done, psychoneuroimmunology developmental models can be created, so interventions can be targeted in the right way, to further develop treatment and prevention strategies in children. In addition, further research on the underlying pathways and interactions between inflammatory responses and stressors might give further insight into the cause and development of psychopathological symptoms in children.

Table 1.

Characteristics of the Included Articles

Study	Objectives	Method	Inflammatory Response	Psychopathological Outcome	Limitations/Future Research	Age Group
1.Wedervang-Ressel et al., (2019)	To examine increased interleukin 18-activity in adolescents with early-onset psychosis.	Cross-Sectional	Inflammatory cytokine interleukin (IL)-18.	Early-Onset Psychosis	Need for longitudinal studies and better measurements of psychosocial stress Need for studies of other parts of the immune system.	12-18 years (adolescents)

2. de Bruine et al., (2019)	To examine the role of peer preference in predicting lower systematic inflammation in adolescence.	Cross-Sectional	Systematic inflammation (hsCRP).	Not Specified.	Need for studies markers of inflammation, more measurements of inflammation to view changes over time.	12-18 years (adolescents)
3. Ulmer-Yaniv et al., (2018)	To examine immune and affiliative biomarkers and sensitive parenting mediating the effects of chronic early trauma on child anxiety.	Longitudinal	Salivary Immunoglobulin A (s-IgA) and Oxytocin (OT).	Child Anxiety Disorder	No measurements of IgA and OT in early childhood. Further research needed to test other biomarkers of the immune system.	10 years (school-aged children)
4. Yirmiya et al., (2018)	The interaction between stress and immune biomarkers with parenting behavior to shape anxiety symptoms in trauma-exposed youth.	Longitudinal	s-IgA and cortisol (CT).	Anxiety Symptoms	Lack of stress markers other than cortisol, additional biomarkers of the immune system. Further research needed of the dynamic development s-IgA.	11 years (school-aged children)
5. Ferguson et al., (2016)	Associations between cytokines, endocrine stress response and gastrointestinal symptoms in autism spectrum disorders.	Cross-Sectional	Cortisol, endocrine markers, TNF-a and IL-6.	Autism spectrum disorder	A broader range of cytokines. Exploration of the implications of the immunological and stress response profiles of individuals with regressive ASD.	6-18 years (school-aged children and adolescents)
6. Gariup et al., (2015)	The innate immunity as biomarkers in acute child and adolescent psychopathology.	Longitudinal	Cytokine distribution (five cytokines).	Depression, dysthymia, OCD, anxiety	No clarification of temporal dynamics. The association between biomarkers and symptoms. other objective and biological measures should be added in the future.	8-17 years (school-aged children and adolescents
7 . Cunha et al., (2016)	Inflammation, neurotrophic and oxidative stress and childhood psychopathology.	Cross-Sectional	Cytokines	Not Specified	Because it is cross-sectional, no inferences can be made about causality. A follow-up of this cohort could demonstrate data about the predictive role of biomarkers.	6-12 years (school-aged children)
8. Giletta et al., (2017)	Peer victimizing predicts heightened inflammatory reactivity to social stress in cognitively vulnerable adolescents.	Cross-Sectional	Tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6).	Symptoms of Depression	Further research is needed to investigate whether positive, social relationships can work as a buffer against inflammatory responses. Longitudinal studies are needed to examine changes in stress-induced inflammatory responses over time.	12-18 years (adolescents)
9. Ma et al., (2018)	Children's anxiety symptoms and salivary immunoglobulin	Longitudinal	Salivary immunoglobulin A (sIgA)	Symptoms of Anxiety	Future studies should replicate the current findings using larger samples comprised of ethnically and culturally diverse participants. The lack of other possible biomarkers of inflammatory responses limits the interpretation of	9-12 years (school-aged children) and 12-18 years (adolescents)

					the interaction in psychoneuroimmunology.	
10. Pearlstein, Staudenmaier, West, Geragthy & Cosgrove, 2020	Immune response to stress induction as a predictor of cognitive-behavioural therapy outcome in adolescent mood disorders.	Cross-Sectional	Immuno-stimulatory IFNγ, IL-6, GMCF, IL-12P70 and TNF-α and immuno-regulatory cytokines IL-1β, IL-10, IL-8, and IL-2.	Symptoms of Depression	Future research with resources to recruit larger samples. There may be clinical utility of incorporating psychobiological response to stress induction into treatment planning and outcome evaluation, given intra-individual differences in CBT-driven changes in psychobiological stress response.	12-18 years (adolescents)
11. Spangler & Schieche (1994)	Bio-behavioral organization in one-year-olds and the quality of mother-infant attachment and immunological and adrenocortical regulation.	Cross-Sectional	Salivary immunoglobulin A (sIgA).	Symptoms of Anxiety	Future research should recruit larger samples, more possible markers of inflammatory responses and longitudinal for causal effects.	0-2 years (infants)
12. O'Connor et al., (2017)	Immune and neuroendocrine correlates of temperament in infancy.	Longitudinal	Innate immune cytokines.	Temperament and fear behaviour	Limited measures of inflammatory responses, a modest sample size and ethnically diverse samples.	0-2 years (infants)

4. Discussion

4.1: Overview of the Current Literature

The purpose of this study is to gain a better understanding of psychoneuroimmunology in children, demonstrate the gaps in the existing knowledge and indicate different paths of future research. The results of this research demonstrate some supporting evidence that an association exists between the experience of psychosocial stress, the immune system and symptoms of psychopathology in children. It was furthermore of interest to find out what sort of psychopathological symptoms were found, what sort of study designs were used, what limitations were mentioned frequently by other researchers and what topics were considered of relevance in future research. The five key findings of this research will be discussed in the following sections.

4.1.1: Psychopathological symptoms

Multiple psychopathological symptoms, such as early-onset psychosis, anxiety, depression and autism are found due to the influence of psychosocial stress on the immune system of children. Meaning, studies within the field of psychoneuroimmunology, do demonstrate some supporting evidence for the association between psychosocial stress, the immune system and psychopathological symptoms in children. However, in a time-frame of three decades, only 12 studies were found, which indicates there is still little research available in this field of psychoneuroimmunology in children. These results are consistent with the review of O'Connor et al., (2014), that claims little research of exposure to psychosocial stress, alterations in the immune system and increased susceptibility to psychopathological symptoms is done in children. One possible explanation is that it can be difficult to recruit children into clinical research, because of the ethical difficulties related to exposing children to unnecessary stressors or taking venous blood samples of children. As mentioned before, Nassau et al., (2008) indicate that taking blood samples of children can be seen as an ethical challenge, by causing possible extra stress. Another possible explanation is that the field of psychoneuroimmunology in children started to grow only a few years ago, with its initial focus on animal and adult studies (Ader & Cohen, 1993). Applying findings of animal studies into human studies has grown rapidly over the past decade (Graham, Christian & Kiecolt-Glaser, 2006). However, integrating results of adult studies into the research of children has multiple challenges. For example, the immune system of children is still developing and therefore cannot be simply compared to the same biomarkers of the immune system of adults. Thus, more research is needed in what sort of immune biomarkers are susceptible to the effects of psychosocial stress in children. As mentioned before, Avitsur and Sheridan (2009) showed that the experience of psychosocial stress can have a negative impact on the development of the immune system of children. This negative impact causes the immune system to be less able to target the infiltration of pathogens. Therefore, integrating results of adult studies into the studies of children is challenging and needs more preliminary research of the specific biomarkers of the immune system of children and its coherence with the developing immune system of those children.

4.1.2: Scientific Study Designs

Second, it is of interest what sort of scientific study designs were used to provide more knowledge on the different methodological ways studies were performed. On the one hand,

cross-sectional designs were used to view whether a correlation exists between psychosocial stress, inflammation and the onset of psychopathological symptoms in children. Although cross-sectional designs do provide evidence for a correlation between psychosocial stress, the immune system and psychopathological symptoms, they do not demonstrate exploration of changes over time or possible fluctuations in the severity of psychosocial stress, inflammatory responses and symptoms of psychopathology. Meaning, cross-sectional designs are performed at a single point of time to view whether a correlation exists, but do not give a clear view of whether the experience of enduring psychosocial stress has an enduring effect on the immune system of children. In other words, cross-sectional study designs do not provide us clues of the effect of psychosocial stress on the immune system of children over lengthened periods of time. Most of the studies that were found had a cross-sectional study design. Clarifying whether psychosocial stress, inflammatory responses and the onset of psychopathological symptoms in children are causally involved requires additional research.

On the other hand, almost half of the found studies do mention a longitudinal study design was used, to show possible changes over time or temporarily associations. O'Connor et al., (2017) performed a longitudinal design to demonstrate clues of causality in the experience of psychosocial stress, immune activation and infant fear and temperament. However, although O'Connor et al., (2017) measured several biomarkers of the immune system and the hormone cortisol, the authors used only two separate data waves, at 6 months and 17 months old. Meaning, despite the longitudinal design, this study design does not allow to view structural changes over time, based on only two measurements of time. This also applies to the other longitudinal designs, that show the biomarkers of the immune system, psychosocial stress and psychopathological symptoms were only measured in two or three separate periods of time.

One way of increasing our knowledge about the association between psychosocial stress, inflammatory responses and psychopathology in children is by setting up a longitudinal study design, to permit observations of the amount of psychosocial stress, what type of inflammatory responses are viewed and the onset of psychopathological symptoms during childhood. Instead of measuring those variables only two or three times, a lengthened period of time can be established, with multiple measurements of the associated variables. There are several advantages over the previously mentioned study designs, such as that the view of changes over time is more visible. Meaning, as mentioned before, the immune system of children is still in its developing phase during childhood. Monitoring visible changes in their

immune system by enhancing the number of measurements over time, can provide more insight of the temporal relationships between inflammatory responses, psychosocial stress and the onset of psychopathology in children. In addition, by expanding the period of time and frequency of measurements, it might be possible to view certain fluctuations of the amount of inflammatory responses in relationship to the amount of psychosocial stress in children. For example, Brennan et al., (2019) recently performed a longitudinal study to investigate associations between prenatal stressors, inflammatory responses and the onset of medical diseases in infants. The authors planned to assess infants at multiple times during an established period of 2-years, by measuring the amount of the experience of stress during that period, samples to evaluate inflammatory responses and physical health. Valuable insights were discovered related to visible changes of inflammatory responses at different periods of time and fluctuations of the inflammatory responses and physical health, induced by certain stressors. This example emphasizes the value of examining the effects of psychosocial stress on the immune system of children over longer periods of time.

However, solely longitudinal study designs do not imply causality. Improving our knowledge of a possible causal relationship between the experience of psychosocial stress, inflammatory responses and the onset of psychopathological symptoms during childhood might face several challenges. First, setting up a longitudinal study design, as described previously, comes with substantial costs in finance and time. Second, although longitudinal designs do make it possible to view changes over time, it is still challenging to inference causality. For example, social components and habits, such as personal dietary, or the influence of genetics can have a significant influence on the immune system (Ellul, Mariotti-Ferrandiz, Leboyer & Klatzmann, 2018). Third, in line with the previously described ethical challenges, such as having to take blood samples to measure the amount of psychosocial stress and immune analyses, we have to ask ourselves what is achievable in demonstrating causal linkages in this domain. One way of demonstrating possible causal linkages between psychosocial stress, inflammation and psychopathological symptoms is by using randomized clinical studies. For example, testing certain psychological, stress reducing interventions to establish the causal relationship between psychosocial stress on processes of the immune system. Testing whether psychosocial stress (as an independent variable) can influence the immune system (as a dependent variable) might be of substantial aid in establishing causality.

4.1.3: Limitations

First, as mentioned before, studies with a cross-sectional design mention their research design as a potential limitation, because no statements can be made about causality. Despite the cross-sectional designs, the studies do provide some supporting evidence that psychosocial stress may be linked to inflammatory responses and psychopathological symptoms. These possible associations can serve as a starting point for future researchers, in setting up their potential longitudinal designs to provide more knowledge of changes over time or certain fluctuations of the previously mentioned variables. For example, Wedervang-Ressel et al., (2019) were the first to indicate that the inflammatory cytokine interleukin (IL)-18 is sensitive to psychosocial stress and is associated with early-onset psychosis in adolescents. However, no follow-up research data is available, because their conclusion is based on observations of a single point in time. Follow-up research makes it possible to view potential changes over time in the amount of inflammatory cytokines and the severity of early-onset psychosis or temporarily changes might be discovered.

Second, psychosocial stress was mostly measured by taking blood samples of the plasma cortisol. Although most authors state that the way the experience of psychosocial stress was measured can be seen as a potential limitation, the measurement of psychosocial stress, is in a way, always subjective. Meaning, measuring psychosocial stress might always be a challenge in scientific research and future researchers can ask themselves what methods to measure psychosocial stress are achievable. In a world of substantial growth of technological possibilities may lie potential in increasing the amount of measurements of psychosocial stress. One way to increase our ways of measuring psychosocial stress is to include wearables as a method to measure the amount of psychosocial stress on a daily basis. Combining technological devices within scientific research, might hold considerable advantages over measuring psychosocial stress by only taking blood samples of cortisol plasma. For example, Setz et al., (2010) performed a study of participants using a electrodermal activity wearable that was able to measure psychosocial stress, apart from mild cognitive load which can also cause stress in individuals. A full description of using wearables to measure psychosocial stressors goes beyond the scope of this review. However, using wearables as part of potential methods of measuring psychosocial stress might held significant potential for future researchers.

Third, using only one or several different biomarkers of the immune system as measurements of inflammatory response, is mentioned as a potential limitation by several studies. Ma et al., (2018) strongly advice future researchers to involve other biomarkers of the immune system and their interplay with psychosocial stress to further define the relationship between psychoneuroimmunology in children. It became clear that different biomarkers of the immune system were used to measure inflammatory responses in children, with no discovery of a certain pattern in the included articles in this review. Meaning, future research should have more attention for the argumentation of including the measurements of different biomarkers and the exclusion of other biomarkers. Building a stronger foundation of why certain biomarkers are being measured to view inflammatory responses might held considerable insights into the crucial role of the immune system in developing psychopathological symptoms. In addition, several studies mention future research should include a broader range of cytokines (e.g. Ferguson et al., 2016; de Bruine et al., 2017; Ma et al., 2018), but do not further explain on solid reasons why they did not include those cytokines in the first place. However, what aspects of the immune system should be explored remains a challenging question. O'Connor, Moynihan and Caserta (2014) explain there is still no consensus that some biomarkers of the immune system are more sensitive to psychosocial stress than others. Future research should therefore first clarify which biomarkers of the immune systems are targeted by the influence of psychosocial stress, before going forward into setting up behavioral interventions or pharmacological interventions in children.

4.1.4: Age Groups

Most of the included articles focused on the age groups of adolescents (12-18 years) and school-aged children (4-12 years). No studies were found of pre-schoolers (1-4 years) and only two studies focused on infants (0-2 year). There may be several explanations for this substantial difference in quantity. First, as described previously, researchers face the ethical challenge of for example, taking venous blood samples of children, that can form a possible barrier for parents to take part in clinical studies, especially for relatively young children. In addition to the ethical challenges researchers might face, researchers encounter several methodological challenges in working with young children. Designing research studies that involve working with young children, might cause researchers to encounter difficulties in gaining co-operation of different 'gatekeepers', such as teachers and parents (Fargas-Malet, McSherry, Larkin & Robinson, 2010). In addition to the co-operation of different gatekeepers,

another difficulty in working with young children is the way data is being collected. Cameron (2006) indicates that the researcher should always be aware of the communication style of young children, non-verbal signals of being uncomfortable and researchers should be able to adapt their methodological ways of collecting data fits the young ages of children. A complete description of the ethical and methodological challenges researchers might face in working with young children goes beyond the scope of this review. Various reviews can be reviewed for more detailed information (Kirk, 2007; Clark, 2011).

4.1.5: Future Directions

Most of the included studies strongly imply to use their research outcomes for building certain interventions or treatments in decreasing the experience of psychosocial stress or the effect of inflammatory responses (e.g. Ferguson et al., 2016; Yirmiya et al., 2018). However, research of psychoneuroimmunology in children and the association with psychopathological symptoms is limited in the existing literature. As described previously, a number of limitations of the performed studies are mentioned. It seems a certain pattern of overlapping limitations exists, which makes it more difficult to make solid statements of the interplay between psychosocial stress, the immune system and psychopathological symptoms in children. One study performed by Pearlstein et al., (2020) showed a correlation between the effect of cognitive behavioural therapy on the decrease of inflammatory responses, due to psychosocial stress in children. Meaning, the study offers evidence that immune responsivity to the induction of psychosocial stress serves as a possible intervention for psychopathology in children. However, it seems that increasing the existing number of studies performed in the relationship between psychosocial stress, the immune system and psychopathological symptoms is needed first. Building upon knowledge provided by previously performed studies, gives future researchers a more solid foundation to increase the amount of evidence for associations between psychosocial stress, the immune system and psychopathology in children.

4.2: Limitations of this Review

Although the present results clearly support the association between psychosocial stress, the immune system and psychopathological symptoms in children, it is appropriate to recognize several potential limitations of this review. First, the procedure of selecting articles to include in this review was done only by one author. The process of screening and selecting

relevant studies for use in a review is more reliable when a second reviewer is used to be more certain all relevant studies are included in the review.

Second, the applied search-strategy that excluded a certain amount of articles might have led to missing out on potential usable articles in this review. For example, expanding the search terms that were used, might have led to the discovery of more potential articles that could have been included in this review. However, using the PRISMA method (Moher et al., 2009) as a guideline for this review increased the quality, by adding a transparency of the research process, that shows other researchers a clear idea of the followed steps in this review.

Third, only three databases have been used to search for relevant studies in the domain of psychoneuroimmunology in children. Increasing the amount of databases might have made it possible to find more relevant studies in this domain. For example, the use of Web of Science or Google Scholar might have led to the discovery of more potential articles. However, the three databases used for this systematic review are known for including a worldwide range of scientific articles. In addition to the more general database (Scopus), a more biomedical-related database was included to further increase the chance of including relevant articles in this domain (PubMed) and further focus on the psychological domain, that involved the use of PsycINFO.

Fourth, instead of conducting only a systematic literature review, a meta-analysis could have been added, because of the type of results, to decrease the chance of bias at the different stages of the review and provide a more critical evaluation of comparable studies. A meta-analysis would have been possible, considering the type of research questions in this systematic review, that could also be answered in a more statistical manner. However, meta-analysis are focused on a summary of data and ignore the fact that results may be different from study to study (Bailar, 1997).

4.3: Conclusion

A more developmental approach in understanding the association between the influence of psychosocial stress on the immune system and the onset of psychopathological symptoms throughout the years of childhood is needed. Longitudinal study designs, with large enough sample sizes, more measurements of psychosocial stress, a broader range of biomarkers of the immune system and keeping track of possible changes during different periods of age in childhood are needed to further establish the interaction in this domain. However, it is clear an association between psychosocial stress, inflammatory responses of the immune system and the onset of psychopathological symptoms during childhood exists.

The present research shows that in the field of psychoneuroimmunology in children, the first steps of showing associations with mental health are demonstrated. However, the most important contribution of this review may be that the included studies showed an overlap of the most common limitations of the performed studies. In terms of future research, it would be useful to extend the current findings by examining the possibilities of increasing our current knowledge of the association of psychoneuroimmunology in children, by trying to decrease the chance of the mentioned limitations of the previously performed studies. In other words, this review showed, what steps in future research are needed to further establish the importance of integrating psychoneuroimmunology in children. If, as the present study suggests, more studies with a longitudinal study design, more knowledge of the specific immunological biomarkers that are sensitive to psychosocial stress is needed, future research can use that information as a starting point in setting up their specific research designs.

Another important finding besides what limitations reported by other researchers and what directions future researchers can follow lies in the fact that this review showed there are no studies of children of pre-schoolers (1-4 years) and only two studies focused on infants (0-2 years). If the idea exists of integrating prevention strategies and possible interventions to decrease the chance of developing psychopathological symptoms during childhood, a substantial opportunity lies in the fact that these age groups are still much less examined. Increasing our current knowledge of targeting the chance of inflammation at a young age can have a huge impact in the mental health domain.

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(References that are marked with an asterisk* are the studies that are included in this review)

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