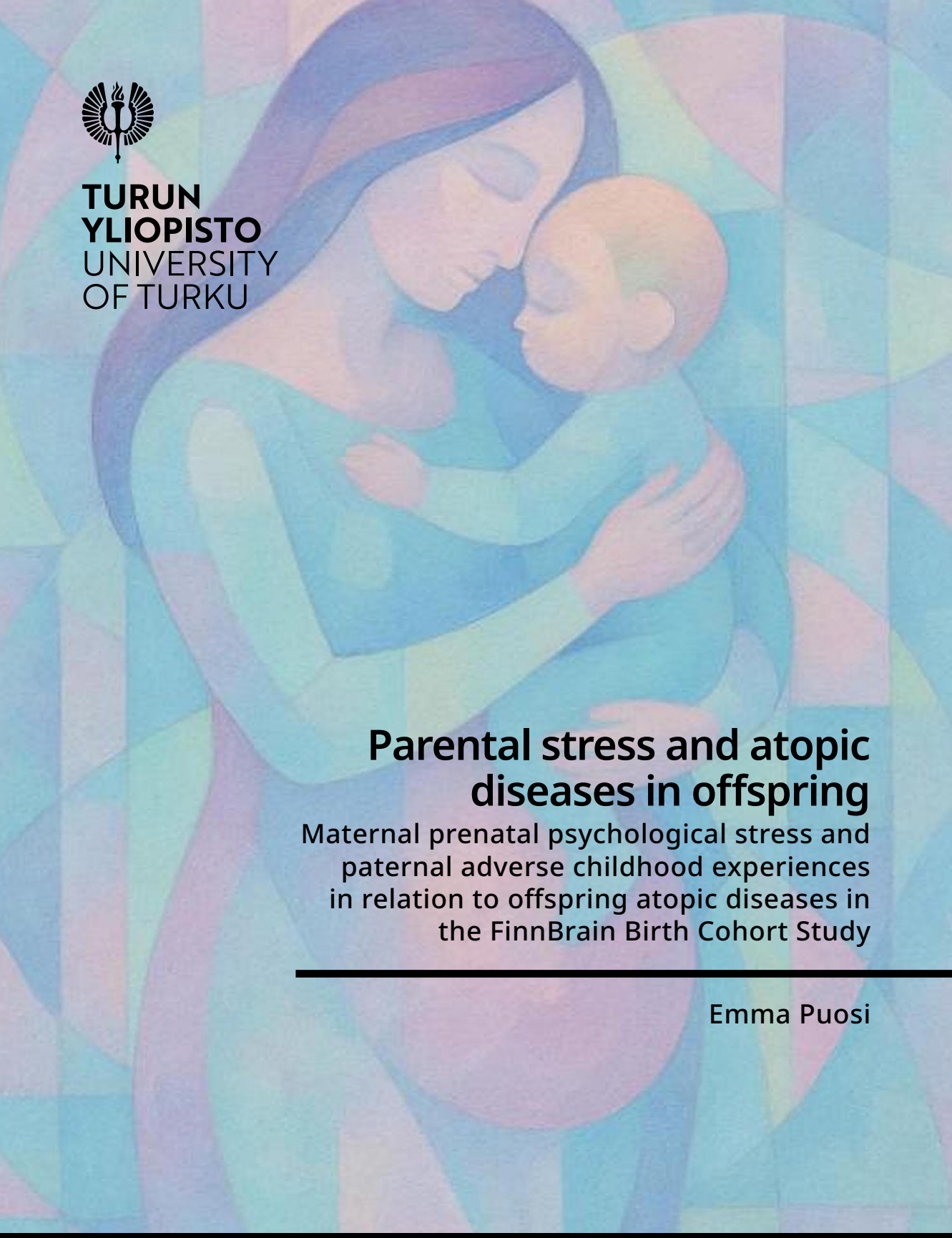

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Parental stress and atopic diseases in offspring

Maternal prenatal psychological stress and paternal adverse childhood experiences in relation to offspring atopic diseases in the FinnBrain Birth Cohort Study

Emma Puosi

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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University of Turku

Faculty of Medicine
Department of Clinical Medicine
Paediatrics
Doctoral Programme of Clinical Research

Supervised by

PhD, Minna Lukkarinen
University of Turku
Turku, Finland

Docent, Heikki Lukkarinen
University of Turku
Turku, Finland

Reviewed by

Professor, Catarina Almqvist Malmros
Karolinska Institutet
Solna, Sweden

Professor, Petri Kulmala
University of Oulu
Oulu, Finland

Opponent

Professor, Eero Kajantie
University of Oulu
Oulu, Finland

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To my family

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Clinical Medicine
Paediatrics
EMMA PUOSI: Parental stress and atopic diseases in offspring – Maternal prenatal psychological stress and paternal adverse childhood experiences in relation to offspring atopic diseases in the FinnBrain Birth Cohort Study
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ABSTRACT

Allergic diseases, including food allergies, atopic eczema, wheezing, asthma and allergic rhinitis, have a complex and multifactorial pathogenesis. The most important risk factor for atopic diseases in children is genetic predisposition, meaning that either or both parents may have any of these conditions. However, each disease has its unique risk factor profile. Research into early-life determinants of atopic diseases has grown considerably, with increasing focus on prenatal influences. The impact of parental psychological stress before and during pregnancy on atopic diseases in children has attracted increasing interest. Evidence to date suggests an association between parental prenatal stress and child adverse health outcomes, although the underlying mechanisms remain largely unknown.

This dissertation focused on two types of parental prenatal stress. First, it examined the impact of maternal psychological stress, symptoms of depression and anxiety during pregnancy, on the development of atopic diseases in children, including food allergies, atopic eczema, wheezing, asthma and sensitisation. Additionally, it explored the impact of paternal adverse childhood experiences on the development of the child's sensitisation and allergic rhinitis. The findings showed that maternal prenatal psychological stress, particularly in late pregnancy, was associated with increased odds of infant food allergy, toddler wheezing, as well as asthma and non-atopic asthma at 5 years, but also with decreased odds of sensitisation. Similarly, paternal adverse childhood experiences were associated with decreased odds of sensitisation and allergic rhinitis at 5 years of age.

The results of this dissertation suggest that maternal prenatal psychological well-being is associated with atopic diseases in children, corroborating previously reported findings. The observed link between paternal adverse childhood experiences and a reduced odds of child sensitisation and allergic rhinitis is novel and represents one of the first studies in this field. Further research, especially on potential causal relationships, is needed as this thesis cannot establish causality or provide mechanistic explanations.

KEYWORDS: adverse childhood experiences, allergic diseases, atopic diseases, atopy, child, IgE, psychological symptoms, sensitisation

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Lastentaudit
EMMA PUOSI: Vanhempien stressi ja lapsen atooppiset sairaudet – Äidin raskauden aikaisen psykologisen stressin ja isän lapsuuden aikaisten negatiivisten kokemusten yhteys lapsen atooppisiin sairauksiin FinnBrain syntymäkohorttitutkimuksessa
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TIIVISTELMÄ

Allergiset sairaudet, kuten ruoka-aineallergiat, atooppinen ekseema, hengityksen vinkuminen, astma ja allerginen nuha, ovat monimutkaisia ja monitekijäisiä sairauksia. Lapsen atooppisten sairauksien tärkein riskitekijä on geneettinen alttius. Kullakin atooppisella sairaudella on kuitenkin oma erityinen riskitekijäprofiilinsa. Raskauden aikainen olosuhteet, ja jopa tätä edeltävä aika, ovat nousseet keskeiseksi tutkimuskohteeksi lapsen kasvun ja kehityksen osalta. Tutkimukset viittaavat siihen, että vanhempien psykologinen stressi voi liittyä lapsen myöhempään terveyteen, vaikkakin mekanismit tämän taustalla ovat edelleen osin tuntemattomia.

Tämä väitöskirja keskittyi tutkimaan kahta erilaista vanhempien stressiä, jotka ajoittuivat aikaan ennen lapsen syntymää. Äidin raskaudenaikaisten masennus- ja ahdistusoireiden yhteyttä selvitettiin lapsen atooppisten sairauksien, kuten ruoka-aineallergioiden, atooppisen ekseeman, hengityksen vinkumisen, astman ja herkistymisen kehittymiseen. Lisäksi tutkittiin isän lapsuudenaikaisen kaltoin-kohtelun vaikutusta lapsen herkistymisen ja allergisen nuhan kehittymiseen.

Tulokset osoittivat, että äidin raskaudenaikainen psykologinen stressi, erityisesti loppuraskauden aikana, oli yhteydessä lisääntyneeseen todennäköisyyteen lapsen ruoka-aineallergioille imeväisiässä, hengityksen vinkumiselle taaperoiässä sekä astmalle ja ei-atooppiselle astmalle viisivuotiaana, mutta samalla pienemmälle herkistymisen todennäköisyydelle. Samoin isän lapsuudenaikaiset haitalliset kokemukset olivat yhteydessä vähäisempään lapsen herkistymiseen ja allergiseen nuhaan viisivuotiaana.

Tämän väitöskirjan tulokset viittaavat siihen, että äidin raskaudenaikaisella psyykkisellä hyvinvoinnilla voi olla merkittävä vaikutus lapsen atooppisten sairauksien kehittymiseen, mikä tukee aiemmin raportoituja tutkimustuloksia. Havainto siitä, että isän lapsuudenaikaiset haitalliset kokemukset yhdistyivät lapsen vähäisempään herkistymiseen ja allergiseen nuhaan, on uusi ja yksi ensimmäisistä tutkimuksista tällä alalla. Lisätutkimusta tarvitaan erityisesti mahdollisten syy-seuraussuhteiden selvittämiseksi eikä tämä väitöskirja pysty tarjoamaan selitystä havaitulle yhteydelle.

AVAINSANAT: allergiset sairaudet, atooppiset sairaudet, atopia, herkistyminen, IgE, lapsi, lapsuusajan haitalliset kokemukset, psyykkinen oireilu

Table of Contents

Abbreviations

ACEs	Adverse Childhood Experiences
aOR	Adjusted Odds Ratio
BDI	Beck Depression Inventory-II
BSI	Brief Symptom Inventory
CCEI	Crown-Crisp Experimental Index
CI	Confidence interval
CRISYS-R	Crisis in Family Systems-Revised Survey
DoHaD	Developmental Origins of Health and Disease
EPDS	Edinburgh Postnatal Depression Scale
Gwks	Gestational weeks
HR	Hazard ratio
HPA (axis)	Hypothalamic-Pituitary-Adrenal axis
Ig	Immunoglobulin
IL	Interleukin
IQR	Interquartile range
ISAAC	International Study of Asthma and Allergy in Childhood
MR	Mother-reported
NLE	Negative life events
ncRNA	non-coding RNA
OR	Odds ratio
PNMS	Prenatal maternal psychological stress
PRAQ	Pregnancy Related Anxiety Questionnaire
PSS	Perceived Stress Scale
RR	Risk ratio
SCL-90	Symptom Checklist 90
STAI	State-Trait Anxiety Inventory
TADS	Trauma and Distress Scale
Th	T-helper
11β-HSD2	11*β*-hydroxysteroid dehydrogenase type-2

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Lukkarinen M, Puosi E, Kataja EL, Korhonen L, Lukkarinen H, Karlsson L, Karlsson H. Maternal psychological distress during gestation is associated with infant food allergy. *Paediatric Allergy And Immunology*, 2021; 32(4): 787-792.

II Puosi E, Korhonen L, Karlsson L, Kataja EL, Lukkarinen, H, Karlsson H, Lukkarinen M. Maternal prenatal psychological distress associates with offspring early-life wheezing - FinnBrain Birth Cohort. *Paediatric Allergy And Immunology* 2022; 33(1): e13706.

III Puosi E, Karlsson H, Lukkarinen H, Karlsson L, Lukkarinen M. Paternal adverse childhood experiences are associated with a low risk of atopy in the offspring. *Acta Paediatrica*. 2024;00:1–14.

IV Puosi, E, Lukkarinen H, Perasto L, Karlsson H, Karlsson L, Lukkarinen M. Maternal prenatal distress is associated with non-atopic asthma in offspring. Submitted.

1 Introduction

Atopic diseases, including food allergy, atopic eczema, wheezing, asthma and allergic rhinitis, are a heterogeneous group of diseases. While they share some similarities and often co-exist, they form a complex and diverse spectrum of conditions (Ferreira et al., 2017; Martinez & Vercelli, 2013). They carry a significant global socioeconomic burden with a rising incidence (Dierick et al., 2020).

The pathophysiology of atopic diseases is characterised by dysregulation of the immune system, resulting in aberrant responses followed by the typical symptoms of each individual disease (Wang et al., 2023). Central to the deviant immune responses are T-helper 2 (Th2) cell dominance, immunoglobulin E mediated hypersensitivity and the release of inflammatory mediators (Wang et al., 2023). In allergic reactions, symptoms are triggered upon contact with an allergen, a substance that a normal immune system would recognise as harmless. Allergens can also provoke and exacerbate atopic eczema and asthma. Some children who are at risk of later developing asthma experience wheezing during viral respiratory infections in early childhood. While many of these children outgrow this tendency, it is a major risk factor for later developing asthma (Kusel et al., 2007).

Atopic diseases carry a significant genetic predisposition with several other risk factors depending on the specific disease (Civelek et al., 2011; Miller et al., 2021; Peters et al., 2021; Ravn et al., 2020). These risk factors include exposure to tobacco smoke (Pfirrman et al., 2024; Vork et al., 2007), dietary factors in infancy and early childhood (Koukou et al., 2023; Sicherer & Sampson, 2014) and the extent of exposure to micro-organisms (Pfirrman et al., 2024). Increasing attention has been directed toward the prenatal period as a critical window during which environmental exposures may influence immune development and disease susceptibility, as well as the potential intergenerational transmission of health risks.

Maternal psychological stress during pregnancy has emerged as one such factor (Andersson, Hansen, et al., 2016; Flanigan et al., 2018), possibly acting via dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, epigenetic modifications, and changes in cytokine profiles (Garcia-Flores et al., 2020; Howland et al., 2016; Irwin et al., 2021). Although accumulating evidence links prenatal maternal psychological stress (PNMS) to adverse health outcomes in offspring,

studies focusing specifically on atopic diseases remain limited, and the findings are not yet conclusive. Furthermore, studies often vary in the definitions and timing of both stress exposure and atopic outcomes, which complicates the interpretation of results and underscores the need for further research.

Additionally, another factor that has garnered interest in relation to offspring outcomes is parental adverse childhood experiences (ACEs), including neglect and abuse. Although associations between parental ACEs and offspring developmental or behavioural outcomes have been reported (Dennis et al., 2019; Folger et al., 2018; Lacey et al., 2020; Lê-Scherban et al., 2018), evidence linking paternal ACEs specifically to offspring immunological or atopic outcomes is scarce. The mechanisms explaining the findings of parental ACEs are yet to be understood (Bath et al., 2016; Curry, 2019; Demaestri et al., 2020; Ellis & Honeycutt, 2021; Gapp et al., 2014; Garcia-Flores et al., 2020; Zazara et al., 2018). Examining paternal ACEs and their association with offspring atopic diseases offers a way to control for increased maternal prenatal psychological stress resulting from ACEs.

Taken together, these gaps in the literature suggest that more research is needed to elucidate how both maternal PNMS and paternal ACEs may contribute to the risk of atopic diseases in offspring. This thesis aimed to address these knowledge gaps by examining the association of two distinct forms of parental stress with the early development of atopic diseases. The first part of the thesis explores the association between maternal prenatal psychological stress, assessed as symptoms of depression or anxiety, and the development of food allergy at the age of 6 months, atopic eczema and wheezing at 24 months, and sensitisation and asthma at 5.5 years of age. The second part investigates whether paternal ACEs are associated with sensitisation and allergic rhinitis in the child at 5.5 years of age. Although these are separate exposures of parental stress, together they explore the influence of stress both prior to conception and during pregnancy. The following chapter reviews the current literature on risk factors for atopic disease and the potential impact of prenatal stress and intergenerational stress exposure, thereby providing context for the study's aims.

2 Review of the Literature

2.1 Pathogenesis, risk factors and epidemiology of atopic diseases

Atopic diseases, including food allergies, atopic eczema, wheezing, asthma, allergic rhinitis and sensitisation, are some of the most prevalent chronic conditions affecting children worldwide. The prevalence and incidence of these conditions vary significantly between developed and developing countries, influenced by environmental exposures, socioeconomic status and access to healthcare. Atopic diseases often involve an abnormal immune response to environmental allergens. The atopic triad—asthma, atopic eczema and allergic rhinitis—often coexists in affected individuals due to shared immune dysregulation and hypersensitivity.

In developed countries, paediatric atopic diseases have reached epidemic proportions. For instance, the prevalence of atopic eczema among children in western countries is up to 20% (Odhiambo et al., 2009). Asthma prevalence in children varies significantly, ranging from 5% to 30% in developed nations, with notable geographical differences due to genetic and environmental influences (Asher et al., 2021; Berz et al., 2007; Johnson et al., 2021). Allergic rhinitis affects up to 10–15% of children (Henriksen et al., 2015; Schmitz et al., 2012; Singh et al., 2016). Food allergies are also on the rise, with estimates suggesting that up to 10% of children in developed countries have one or more of these (Prescott & Allen, 2011; Sicherer & Sampson, 2018). The surge in the incidence of atopic diseases has been particularly pronounced for asthma in recent decades but appears to have plateaued over the past 10 years (Akinbami et al., 2016).

Paediatric atopic diseases have a profound impact on an individual's quality of life and carry a significant economic burden. Children with atopic diseases often experience significant physical discomfort, sleep disturbances and psychological distress that can also negatively impact school performance (Kouzegaran et al., 2018; Xu et al., 2019). Paediatric atopic diseases also place a heavy financial strain on families and healthcare systems. In developed countries, direct costs related to treatments, hospitalisations and medications are particularly high (Drucker et al., 2017; Meltzer & Bukstein, 2011; Zhang & Zheng, 2022). Indirect costs, such as lost productivity of parents due to caregiving responsibilities and missed workdays, add

to this burden. Limited access to healthcare and medications in developing countries often worsens disease outcomes, leading to exacerbations of the diseases that further strain healthcare systems (Mortimer et al., 2022; Mosam & Todd, 2023).

Atopic diseases share some similarities in their pathogenesis, which primarily involves dysregulation of the immune system. Atopic diseases are driven by a predominant Th2-skewed immune response, characterised by increased production of IL-4, IL-5, IL-9 and IL-13. These cytokines facilitate IgE class switching, eosinophil recruitment and chronic inflammation. In addition, Th17 cells and regulatory T cells are crucial in maintaining the balance of immune responses, and dysregulation of their interplay is commonly observed in atopic diseases (Gorska, 2025; Noval Rivas & Chatila, 2016; Sugaya, 2020). The Th2-skewed immune response underlies the pathogenesis of atopic diseases, driving inflammation, tissue damage and the resulting symptoms and clinical manifestation of these conditions. The various factors contributing to the development of atopic allergic diseases are illustrated in Figure 1.

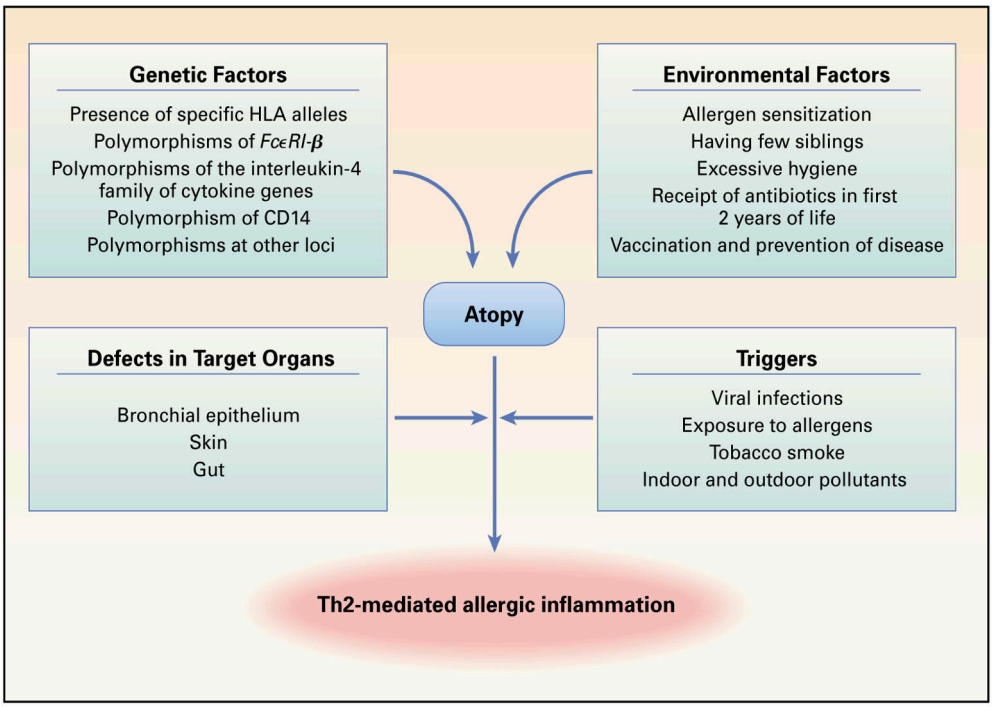

Figure 1. Various factors drive the development of atopic allergic diseases. These include genetic predisposition, environmental factors, diverse triggers and specific features of target organs, such as increased permeability to antigens. Reprinted with permission from Kay et al (2001).

Not all phenotypes of atopic disease, however, share this Th2-dominant background and are characterised as non-atopic (Calvani et al., 2020; Flohr et al., 2004; Miller et al., 2021). While atopic diseases share common pathogenic mechanisms, each condition has distinct characteristics, which are discussed in subsequent sections. Paediatric atopic diseases arise from a complex interaction of genetic, environmental and prenatal influences. A strong family history increases risk, particularly due to genetic polymorphisms affecting immune regulation, skin integrity and IgE signalling (He et al., 2003; March et al., 2013). Filaggrin is one of the most well-established risk genes; mutations in this gene weaken the skin barrier, increasing permeability and allergen penetration. This allows for early sensitisation to allergens and could enhance the progression of atopic march (Drislane & Irvine, 2020). Filaggrin mutations are the strongest genetic risk factor for atopic eczema, with up to half of patients with severe atopic eczema carrying this loss-of-function mutation (Palmer et al., 2006). These mutations also increase the risk of food allergies by two- to threefold and promote the outbreak of allergic rhinitis, asthma and sensitisation (Weidinger et al., 2008).

The concept of the atopic march describes the sequential progression of allergic diseases, where infants with atopic eczema are at increased risk of developing food allergies, followed by asthma and allergic rhinitis in later childhood (Spergel, 2010). Epidemiological evidence has supported the sequential development of atopic diseases in many cases, yet not all individuals with early atopic eczema progress to allergic rhinitis or asthma, suggesting heterogeneity in disease pathways and risk factors. A study by Belgrave et al. (2014), which analysed data from two birth cohorts using Bayesian machine learning methods, demonstrated various developmental profiles of atopic disease, with only around 7% of the children following the classical atopic march trajectory (Belgrave et al. 2014). However, the presence of one atopic disease is a significant risk factor for the onset of others. For example, childhood atopic eczema significantly increases the likelihood of later diagnosis of asthma, food allergy or allergic rhinitis (Kim et al., 2024). Some studies even suggest that the atopic march could be stalled in some cases (Papadopoulos et al., 2022).

The incidence and prevalence of atopic diseases have increased in recent decades, leading to research on potential prevention strategies. Interventional studies aim to prevent further development of atopic diseases and establish stronger evidence for the atopic march (Hill & Spergel, 2018). These prevention strategies for paediatric atopic diseases focus on modifying environmental and lifestyle factors, particularly during early life. Environmental exposures, including air pollution, tobacco smoke, allergens and dietary changes, play a crucial role in the development and exacerbation of atopic diseases (Dunlop et al., 2016; Vork et al., 2007; Xing et al., 2023; Ziou et al., 2023). Reduced exposure to microbial diversity and changes in

the microbiome have been linked to an increased risk of asthma (Indrio et al., 2017; Karvonen et al., 2014; Sudo, 2012). According to the hygiene hypothesis, modern lifestyle changes, particularly reduced microbial exposure due to improved hygiene and urbanisation, may have altered immune system development, contributing to the rise in allergic and autoimmune diseases (Figure 2). While observational studies support this hypothesis, a causal link has yet to be established due to the complexity of the underlying interactions.

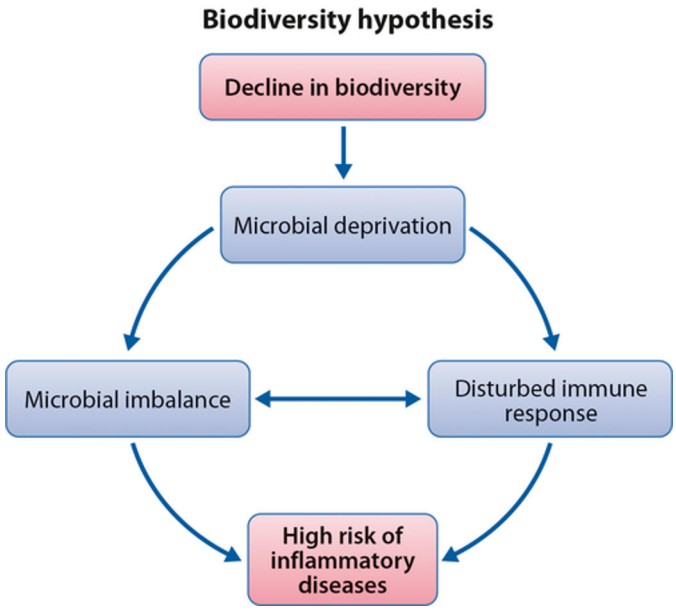

Figure 2. Illustration of the hypothesis of biodiversity and microbial exposure. Reprinted with permission from Haahtela et al. (2019).

Preventative strategies for atopic diseases are scarce, with varying effectiveness. Early introduction of allergenic food, such as eggs and peanuts, along with high dietary diversity in infancy, has shown significant potential in reducing the risk of food allergies, asthma and atopic eczema (Calvani et al., 2020; Lv et al., 2024). Dietary factors during pregnancy and early childhood have also been linked to altered risks of asthma, allergic rhinitis and atopic eczema, with most studies indicating that a diverse, healthy diet is associatied with a lower incidence of atopic diseases (Baïz et al., 2019; Lee-Sarwar & Litonjua, 2018; Trikamjee et al., 2021). However, evidence regarding vitamin D supplementation, prebiotics and probiotics remains inconclusive, highlighting the need for further research. Environmental interventions, including reducing exposure to tobacco smoke and air pollutants, have demonstrated benefits in minimising respiratory and atopic conditions (Pfirrman et

al., 2024; Wegienka et al., 2014). Breastfeeding has been extensively studied for its potential protective effects against the development of atopic diseases. The evidence proposes that breastfeeding, particularly in the first 4 to 6 months, is beneficial in reducing the risk of atopic eczema and wheezing in early childhood in genetically susceptible children (Libuda et al., 2023). However, there is no clear-cut evidence that breastfeeding yields long term benefits in reducing the incidence of atopic diseases (Schoos, 2024).

2.1.1 Food allergy

Food allergy is a disease in which the immune system abnormally reacts to proteins found in specific foods, resulting in a spectrum of reactions ranging from mild gastrointestinal distress to life-threatening anaphylaxis (Longo et al., 2013). Affecting both children and adults, food allergies are complex disorders, with the incidence peaking in infancy and childhood depending on the specific allergen (Peters et al., 2021). The prevalence of food allergy varies globally, but around 4–11% of children are affected in Western countries, depending on age (Gupta et al., 2018; Peters et al., 2021; Soriano et al.,2024). Allergies to eggs and cow's milk tend to resolve with age, whereas peanut and tree nut allergies are more persistent and more likely to persist into adulthood (Peters et al., 2017).

Food allergies are commonly classified based on the immune mechanisms involved. The main types are IgE-mediated, non-IgE-mediated and mixed-type food allergies. In IgE-mediated food allergies, symptoms develop rapidly and can range from mild urticaria and gastrointestinal symptoms to severe anaphylaxis. Non-IgE-mediated allergies, on the other hand, involve delayed hypersensitivity reactions, where symptoms appear hours or even days after food ingestion and often present in gastro-intestinal tract symptoms. Mixed-type allergies involve both IgE and non-IgE immune mechanisms (Sicherer & Sampson, 2018). Allergens causing IgE-mediated food allergies often include tree nuts, peanuts, eggs and shellfish, whereas non-IgE-mediated food allergy is triggered commonly by cow's milk, wheat and soy (Anvari et al., 2019; Nowak-Węgrzyn et al., 2015)

Diagnosis of food allergy involves a combination of clinical history, laboratory tests and controlled food challenges. Skin prick testing and serum-specific IgE measurements are commonly used to confirm IgE-mediated food allergies, although these tests are not definitive and may yield false positives with IgE sensitisation but without clinical food allergy (Foong et al., 2021). In cases of non-IgE-mediated allergies, elimination diets and oral food challenges are often used to confirm diagnosis.

The pathogenesis of food allergy involves both genetic and environmental factors. Genetically, individuals with a family history of atopic diseases are at higher

risk of developing food allergies. Dietary habits, including the timing of allergen introduction and duration of breastfeeding, also play a role. Early introduction of allergenic foods may promote tolerance, whereas delayed introduction could increase the risk of allergy development (de Silva et al., 2020). The most significant risk factor for later development of food allergy is atopic eczema, highlighting their shared underlying background in the shift towards Th2-type immune responses (Tsakok et al., 2016).

Immunologically, food allergies involve complex interactions between different immune cells and mediators. IgE-mediated food allergies are triggered when specific food proteins bind to IgE antibodies on the surface of mast cells and basophils, leading to degranulation and release of mediators such as histamine, leukotrienes and cytokines, resulting in immediate symptoms. In contrast, non-IgE-mediated food allergies involve T-cell-mediated immune responses that typically display as delayed symptom onset (Calvani et al., 2020).

Atopic eczema, also known as atopic dermatitis, is a chronic, inflammatory skin condition characterised by intense itching, erythema and recurrent flare-ups. It is one of the most common inflammatory diseases globally, affecting up to 20% of children (Odhiambo et al., 2009). It often begins in infancy or early childhood, with prevalence decreasing to around 10% by adulthood (Hua & Silverberg, 2018). As well as with other atopic diseases, atopic eczema encompasses a group of diseases with varying disease trajectories. It is commonly associated with other allergic conditions, including asthma and allergic rhinitis, but other subtypes of atopic eczema have been identified, highlighting the importance of better understanding the heterogeneous background and outcomes of the disease (Roduit et al., 2017). The hallmark features of atopic eczema include disrupted skin barrier function and heightened sensitivity to environmental allergens, leading to characteristic symptoms and a heightened susceptibility to skin infections. There is no single diagnostic criterion for atopic eczema, but the clinical signs include eczematous lesions, pruritus and a relapsing or chronic disease course. The distribution of affected skin areas typically varies with age (Langan et al., 2020).

The pathogenesis of atopic eczema is multifactorial, involving genetic, environmental, immunological and skin barrier factors. Atopic eczema is associated with a hyper-responsive immune system, particularly with an overactivation of Th2 cells. This results in elevated levels of IgE antibodies and increased production of pro-inflammatory cytokines, leading to chronic skin inflammation and itching. Not all atopic eczema, however, is truly atopic; non-atopic atopic eczema lacks clear IgE-mediated allergic sensitisation and is an important phenotype (Flohr et al., 2004, Tokura & Hayano, 2022). In non-atopic atopic eczema, the inflammatory process is activated independently of IgE-mediated pathways and exhibits stronger Th1 and Th17 responses without significant eosinophilia. Microbial colonisation and

imbalances in the microbiome play an important role in the development and exacerbation of the disease (Langan et al., 2020).

The most significant risk factor for atopic eczema is a family history of atopic diseases, as the condition has strong hereditability. Children with a history of atopic disease are more prone to developing atopic eczema (Ravn et al., 2020). Other risk factors include mutations in the gene coding for the skin barrier protein filaggrin, exposure to outdoor and indoor pollutants, dietary factors, exposure to tobacco smoke and factors that disrupt the skin barrier (Flohr et al., 2014; Kantor & Silverberg, 2016; Langan et al., 2020).

The most common treatments for atopic eczema include moisturisers and topical corticosteroids, with topical calcineurin inhibitors used in some cases. Some systemic treatments for severe cases are also available.

2.1.2 Wheezing and asthma

Wheezing in children is a common respiratory symptom characterised by a high-pitched whistling sound during breathing, usually during a viral respiratory infection. It is caused by obstruction in the airways and can vary in severity. In Finland, the first wheezing episode in children under 12 months of age is referred to as bronchiolitis (Smyth & Openshaw, 2006), while wheezing associated with viral respiratory infections in children aged 12–36 months is termed constrictive bronchiolitis.

For some children, wheezing is an isolated event, but recurrent wheezing episodes are a significant risk factor for subsequent asthma development (Xing et al., 2023) Around 60% of children who wheeze during their second year of life outgrow of the tendency by 3 years of age (Taussig et al., 2003). The risk of developing subsequent asthma in children who wheeze is strongly influenced by the timing of wheezing episodes. Children can be classified into transient, persistent and late-onset wheezers. The prevalence of at least one wheezing episode during the first year of life is as high as 45%, while the prevalence of recurrent wheezing is 21% in European countries (Mallol et al., 2010).

Some persistent and late-onset wheezers develop asthma, and one of the diagnostic criteria used to classify recurrent wheezers as asthmatic is the Asthma Predictive Index, developed by Castro-Rodriguez et al. in 2000. According to the index, children with three or more wheezing episodes within a year and having at least one additional major risk factor (parental history of asthma, physician-diagnosed atopic eczema, sensitisation to aeroallergens) or two minor risk factors (IgE-mediated food allergy, wheezing episodes apart from viral respiratory infections, blood eosinophilia) are diagnosed with asthma. Diagnosing childhood asthma is not always straightforward. Diagnostic criteria are strongly dependent on

the child's age and differ between counties, with no single, clear definition of asthma (Van Wonderen et al., 2010). The diagnosis is based on clinical evaluation, symptom history and lung function tests. Hallmark symptoms include recurrent wheezing, shortness of breath, coughing and chest tightness, often triggered by allergens, infections or exercise. Objective confirmation involves tests that demonstrate airway obstruction, typically spirometry or peak expiratory flow measurements, which is reversible following bronchodilator administration. In addition, exhaled nitric oxide can be used to detect airway inflammation.

Asthma is a heterogeneous condition comprising different endotypes, each with unique disease manifestations, pathogenesis and, to some extent, different risk factors. Research into how to more precisely define, diagnose and optimise treatment strategies tailored to each endotype is still ongoing. Although there are significant differences in the immunology between endotypes, in a broad setting asthma is a chronic respiratory disease characterised by hyperreactivity and inflammation of the small airways, resulting in symptoms of cough, breathing difficulty, wheezing and shortness of breath. It is the most common lung disease in children and the second most common in adults after chronic pulmonary disease. The symptoms can be triggered by allergens, cold, exercise and respiratory infections. Asthma management has significantly improved over the past decades, particularly with the introduction of targeted therapies for difficult-to-treat and severe asthma. The cornerstone of treatment, however, is still inhaled corticosteroids for long-term disease control and inhaled beta agonists for symptom relief (Porsbjerg et al., 2023).

The definition of asthma has evolved over decades of research into its pathogenesis and the characteristics of its different subtypes. However, current definitions still do not fully capture the complexity of the asthma subgroups or the overlap of different phenotypes (Conrad, Cabana, et al., 2020; Kuruvilla et al., 2019). One, albeit oversimplified, approach is to divide asthma into atopic and non-atopic phenotypes. More recently, type 2-high and type 2-low asthma have been identified based on differences in the innate lymphoid type 2 cells, which contribute to eosinophilic airway inflammation, a key factor in the inflammatory cascade. (Porsbjerg et al., 2023). Yet another way of phenotyping asthma is based on age of disease onset into early-onset and late-onset. Late-onset asthma is typically diagnosed when symptoms begin at around 12 years of age or later (Turrin et al., 2022). In recent years, advances in asthma endotyping have been made with very large datasets that integrate clinical, environmental and biological characteristics, resulting in detailed but more complex phenotypes (Figure 3). The goal of precise and comprehensive classification is to improve early diagnosis and perhaps support a more personalised treatment approach, ultimately optimising medical care for each individual.

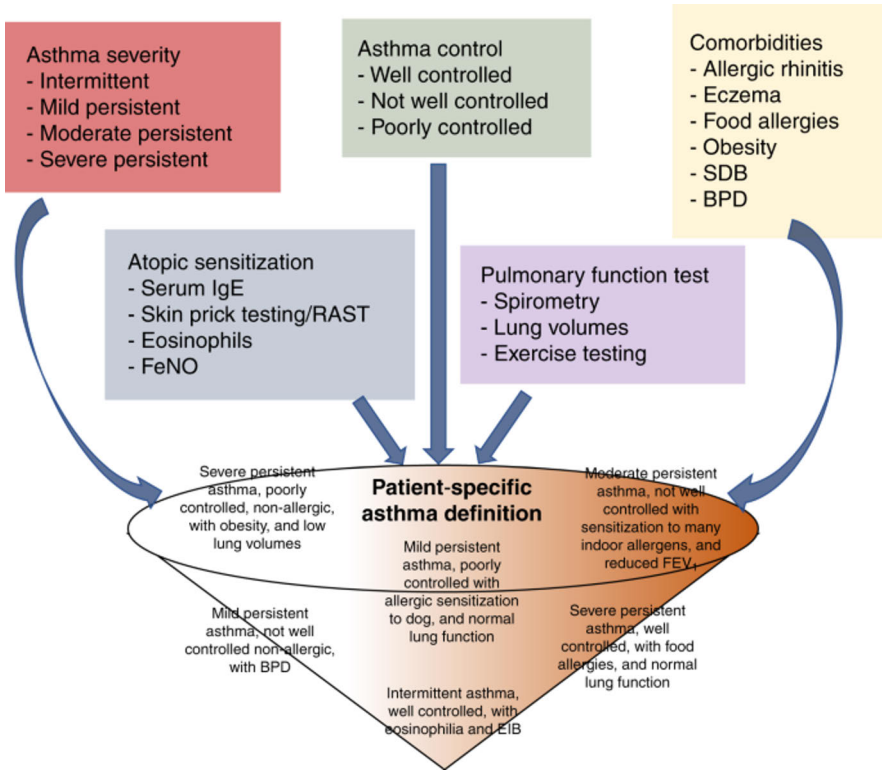

Figure 3. One approach to defining paediatric asthma endotypes, highlighting the complexity of asthma subtypes. Reprinted with permission from Conrad et al. (2020).

Immunologically, asthma features contributions from both the adaptive and innate immune systems. In Th2-high asthma, the most common type, allergens stimulate Th2 cells to release cytokines, particularly IL-4, IL-5 and IL-13, which lead to eosinophilic inflammation and increased IgE production (Hammad & Lambrecht, 2021). This in turn results in mucus overproduction, airway swelling and bronchial hyperreactivity. The newer classifications of type 2 asthma also consider the role of innate lymphoid cells, which produce IL-5 and IL-13 cytokines and enhance type 2 responses in epithelial cells (Kuruvilla et al., 2019; Porsbjerg et al., 2023). In type 2-low asthma, neutrophil activations play a key role without the typical Th2 cytokine signatures found in type 2-high asthma. Neutrophil-predominant asthma is usually more severe, may respond poorly to corticosteroids and is associated with obesity (Grunwell et al., 2019). The complexity of immune responses and interactions in atopic asthma is illustrated in Figure 4.

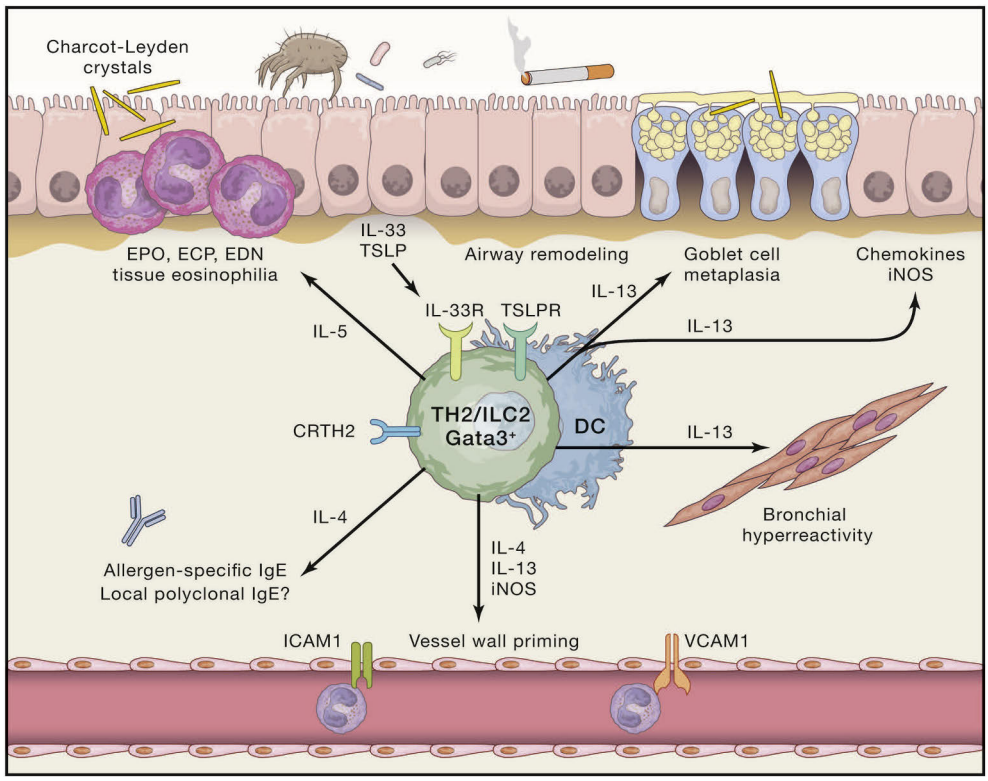

Figure 4. Role of the innate immune system and Th2 cytokines in the pathophysiology of atopic asthma. The reactions can be triggered by exposure to e.g. allergens or tobacco smoke, causing bronchial hyperreactivity. Preprinted with permission from Hammad & Lambrecht (2021).

The risk factors for wheezing and asthma overlap to some extent. The most significant risk factors for wheezing include low birth weight, male sex, low gestational age, a family history of atopic disease, exposure to tobacco smoke or maternal smoking during pregnancy, and symptomatic rhinovirus-induced respiratory infections (Bozaykut et al., 2013; Lemanske et al., 2005). Risk factors for asthma in children include concomitant sensitisation, atopic eczema and a parental history of atopic diseases (NAEPP, 2007; Rubner et al., 2017). Lower respiratory tract infections, most commonly induced by rhinovirus or syncytial virus, are risk factors for paediatric atopic asthma. However, the associations tend to weaken significantly over time, and the exact role of these infections behind the association remains unclear; they could merely be indicators of an increased predisposition (Lukkarinen et al., 2017; Sigurs et al., 2010). Risk factors for non-atopic asthma include household mould exposure, tobacco smoke exposure, and a family history of asthma and preterm birth (Caffarelli et al., 2023; Strina et al., 2014).

2.1.3 Allergic rhinoconjunctivitis

Allergic rhinoconjunctivitis is chronic inflammatory disease characterised by symptoms such as itching, sneezing, nasal congestion and rhinorrhoea in response to allergen exposure. It is triggered by aeroallergens like pollen, dust mites, animal dander and moulds and often coexists with other atopic diseases, most commonly asthma (Bousquet et al., 2012). The diagnosis of allergic rhinoconjunctivitis is based on clinical history, symptoms and testing of allergen sensitisation. Diagnosis may include skin prick testing or serum-specific IgE testing to identify sensitivities to allergens.

The prevalence of allergic rhinoconjunctivitis is substantial and has been increasing globally, particularly in urbanised and industrialised regions. Approximately 20% of the global population is affected by allergic rhinitis, with decreasing rates among the elderly (Eriksson et al., 2012). Allergic rhinoconjunctivitis typically manifests in childhood or adolescence but can occur at any age (Greiner et al., 2011).

The pathogenesis of allergic rhinoconjunctivitis involves a complex interaction of genetic and environmental factors. Exposure to antigens leads to sensitisation and inflammation of the nasal mucosa. Initial sensitisation occurs when an individual is exposed to an allergen that triggers an exaggerated immune response. The allergen penetrates the nasal epithelium, where it is processed by antigen-presenting cells such as dendritic cells. These cells present the allergen to Th2 cells, which in turn produce cytokines like IL-4, IL-5 and IL-13. These cytokines stimulate B cells to produce IgE antibodies specific to the allergen, initiating an allergic immune response releasing histamine and other mediators responsible for the typical symptoms of sneezing, nasal congestion and rhinorrhoea (Greiner et al., 2011).

Risk factors for allergic rhinoconjunctivitis include both genetic predispositions and environmental exposures. A family history of atopic diseases and concomitant asthma are one of the strongest risk factors for developing allergic rhinitis. Additionally, exposure to environments with high levels of pollutants can increase the likelihood of developing allergic rhinoconjunctivitis (Eriksson et al., 2012). Reduced microbial exposure in early childhood may increase the risk of allergic diseases, including allergic rhinitis, by contributing to an underdeveloped immune system (Papadopoulos et al., 2022).

2.1.4 Sensitisation

IgE sensitisation is a process by which the immune system becomes abnormally responsive to otherwise harmless substances, resulting in the production of allergen-specific IgE antibodies. This sensitisation is an underlying mechanism in many allergic diseases, including allergic rhinoconjunctivitis, asthma, atopic eczema and

food allergies (Mackay et al., 2001). Upon re-exposure to the sensitising allergen, individuals experience an allergic reaction mediated by IgE antibodies, which can lead to a range of symptoms depending on the allergen type and the area of exposure.

The presence of significant levels of IgE antibodies to allergens does not necessarily lead to clinical symptoms of allergy, as sensitisation can occur independently (Fiocchi et al., 2015). Testing should therefore be guided by clinical history and a clear suspicion of inhalant or food allergies. Testing can also be done in the presence of other, persistent atopic diseases such as asthma (Sicherer et al., 2012). Sensitisation can be tested with skin prick testing and serum-specific IgE assays. In skin prick testing, a small amount of allergen is introduced into the skin, the reaction is observed for signs of swelling or redness, and the response area is then measured. Serum-specific IgE tests measure IgE levels in the blood specific to individual allergens. Both tests are reliable in adults, but in young children there is a discrepancy between the results of skin prick tests and serum-specific IgE levels (Chafen et al., 2010; Schoos et al., 2015). To diagnose a food allergy, a child must also exhibit symptoms of allergy; a positive result of either a skin prick test or IgE assay alone is not sufficient for diagnosis (Sicherer et al., 2012) Sensitisation to aeroallergens in symptomatic children with rhinoconjunctivitis may also be delayed, with significant sensitisation present only after clinical symptoms have already appeared (Veskitkul et al., 2013).

The prevalence of IgE sensitisation to one or more allergens in developed countries is around 30–40% (Amaral et al., 2015; Sterner et al., 2019). The prevalence varies by age, geographic location and exposure to environmental factors. Sensitisation to specific allergens such as pollens, dust mites and animal dander is more common in urbanised areas with higher levels of pollution and environmental changes. The prevalence is also age-dependent; sensitisation rates are often higher in children and adolescents and can stabilise or decline with age in adulthood (Jarvis et al., 2005).

The pathogenesis of IgE sensitisation involves multifactorial interactions between genetic, environmental and immunological factors. Sensitisation generally occurs through repeated exposure to allergens, leading to initial activation of the immune system in genetically predisposed individuals. Allergens are processed by antigen-presenting cells, which present the allergen to naïve Th cells. In susceptible individuals, these Th cells differentiate into Th2 cells, releasing cytokines such as IL-4, IL-5 and IL-13. The cytokines further promote B cell class switching to IgE production. This initial production of allergen-specific IgE is crucial to sensitisation, as IgE binds to receptors on mast cells and basophils, priming the immune system for a potential allergic response upon subsequent exposure to the allergen (Greiner et al., 2011; Sicherer & Sampson, 2014).

Risk factors for IgE sensitisation include both genetic predisposition and environmental exposures. Atopy is a highly hereditary trait encompassing susceptibility to IgE sensitisation. Therefore, the most important risk factor for IgE sensitisation is a family history of atopic diseases. Environmental factors such as early-life exposure to allergens, pollution, tobacco smoke and microbial agents can influence immune development and the likelihood of sensitisation and atopic diseases (Kilpeläinen et al., 2000; Pfirrman et al., 2024; Svanes et al., 1999).

2.2 The concept of maternal prenatal psychological stress

Interest in risk factors for atopic diseases beyond childhood has emerged in recent decades and sparked a field of research exploring prenatal and even preconception factors. The concept of the prenatal environment shaping the development and health of offspring is not new. Decades ago, David Barker identified a correlation between low birth weight and increased risk of cardiovascular disease, leading to the formulation of the Developmental Origins of Health and Disease (DOHaD) hypothesis. This framework suggests that environmental exposures during critical periods of early development can have long-term effects on health, including the development of atopic diseases (Barker, 1998). Maternal diet, stress, smoking and exposure to environmental pollutants during pregnancy can alter the foetal immune system, predisposing the child to atopic diseases. For instance, maternal exposure to air pollution and tobacco smoke has been linked to an increased risk of childhood asthma (Accordini et al., 2018; Deng et al., 2018). Postnatal factors such as mode of delivery, breastfeeding, early-life antibiotic use and early respiratory infections are also associated with the development of atopic diseases (Alm et al., 2014; Goksör et al., 2013; Wegienka et al., 2014).

Foetal programming suggests that environmental factors during the prenatal period induce lasting changes in physiological systems, causing alterations in the behaviour and health of the developing foetus later in life. The intrauterine period, marked by rapid growth and critical developmental windows, is especially sensitive to factors that influence the programming of the developing foetus. A crucial mediator and modulator in this process is the placenta, which serves as the interface between mother and foetus. The regulation of this maternal–foetal interface is complex, involving both sex-specific and time-dependant mechanisms. The placenta delivers nutrients and oxygen, as well as hormones such as corticosteroids, to the foetus. It plays a key role in mediating and moderating maternal stress signals. Maternal stress has been shown to alter the function of barrier proteins and disrupt the endocrine function of the placenta (Bronson & Bale, 2015; Glover, 2015). A growing body of evidence indicates that early-life adversity, such as maternal

psychological stress during pregnancy, can have lasting effects on the development and health of the offspring in various ways (Bush et al., 2020; Caparros-Gonzalez et al., 2021; Jones et al., 2019; Mepham et al., 2023; Sanjuán et al., 2021; Y. Wu, De Asis-Cruz, et al., 2024; Jones et al., 2019; Van den Bergh et al., 2017).

Symptoms of depression and anxiety, and other psychiatric disorders, affect a significant number of pregnant women worldwide. Around 13% of women experience a mood disorder during the prenatal period (Vesga-López et al., 2008), with an even greater prevalence of subclinical symptoms not meeting the criteria for clinical diagnosis. Perceived psychological stress can, however, be induced by various factors beyond mood disorders, such as the death of a loved one, an event causing post-traumatic stress disorder, or other significantly negative life events. This inherent variability contributes to the heterogeneity in how prenatal maternal stress (PNMS) is defined in the research field. Nonetheless, a common denominator across stressors is the maternal stress response, which leads to alterations in endocrine and immune system function. This can eventually alter the programming of the developing foetus (Cao-Lei et al., 2016). The timing and chronicity of symptoms also play a crucial role, as certain developmental windows are especially sensitive. From the perspective of immune system development, the most significant windows of vulnerability include the stem cell, hepatic, myeloid, immunocompetence and immune memory stages. These key windows span across the gestational period (Veru et al., 2014). Research on offspring atopic diseases and PNMS suggests that stress during late pregnancy appears to represent a particularly critical period (Andersson, Hansen, et al., 2016).

In general, studies show that PNMS during specific periods of gestation—early, mid or late pregnancy—can variably influence foetal immune programming, yet there is no clear understanding of the effects of the timing and possible chronicity of symptoms on the development of atopic diseases (Andersson, Hansen, et al., 2016; Flanigan et al., 2018; Veru et al., 2014). Some studies suggest that the first and third trimesters are especially vulnerable to PNMS and consequent aberrations in offspring HPA axis function (Galbally et al., 2019; Giesbrecht et al., 2017). The first and second trimesters are crucial for establishing the foundational structures of the foetus, including the formation of immune and endocrine system responses, whereas the maturation of these systems occurs during the last trimester. Excessive exposure to stress hormones may disrupt foetal programming, altering the sensitivity of the developing immune system to future allergens and inflammatory stimuli. Maternal stress during different stages of development may have varying impacts on specific organs and physiology (Veru et al., 2014).

Disaster studies offer a more objective perspective on the timing of stress exposure, providing precise timepoints and minimising the influence of individual maternal biophysiological characteristics. Two of the most extensively studied

natural experiments include the Dutch famine of 1944–1945 and the Quebec ice storm of 1998. Children born to mothers who endured the ice storm showed alterations in hippocampal volume (Cao-Lei et al., 2021), cognitive development (King & Laplante, 2005) and an increased likelihood of developing asthma (Turcotte-Tremblay et al., 2014), among other adverse outcomes. The transgenerational outcomes of the Dutch famine included poorer cognitive function among the offspring, a higher prevalence of obstructive airway disease and increased rates of microalbuminuria, to name but a few. These studies also provide a more objective view on the importance of timing of psychological stress, as they reveal organ-specific windows of vulnerability to the intrauterine environment (De Rooij et al., 2022).

Nevertheless, prospective birth cohort studies with well-defined exposure periods covering the entire duration of pregnancy remain relatively scarce. The definition of stress varies considerably, and it is possible that different types of stress exposures have distinct effects. Therefore, examining various forms of stress across different stages of gestation is of particular interest, as it allows for the analysis of sensitive periods in foetal development.

2.3 Maternal prenatal psychological distress as a risk factor for offspring atopic diseases

The study field of PNMS and offspring emerged around 25 years ago, with Wright *et al.* reporting novel findings of positive associations between PNMS and wheezing in infancy (Wright et al., 2002). Since then, several studies, along with systematic reviews and meta-analyses, have added to the body of research.

For the literature review in this study, research on PNMS and atopic diseases published within the last 15 years was collected by searching PubMed and reviewing cited references (Ai et al., 2024; Andersson, Hansen, et al., 2016; S. Chen & Chen, 2021; Flanigan et al., 2018; Suh et al., 2017; Y. Wu, Chen, et al., 2024). The database search was conducted up to December 1st, 2024. Only retrospective and prospective cohort studies were included. While study designs differed significantly, the retrospective studies typically had far larger sample sizes compared to most prospective studies, making them particularly interesting as a group.

The search terms used were: (Stress,'Psychological' OR 'Life'Change'Events' OR 'Anxiety' OR 'Depression' OR 'Bereavement' OR 'Parental'Death' OR 'Abuse' OR Demoralization' OR 'Daily'Hassles' OR 'Job'Strain') AND (Maternal'Exposure' OR 'Prenatal'Exposure' OR ´Pregnancy' OR 'antenatal') AND (Asthma OR Dermatitis OR Atopic OR Rhinitis OR Allergic OR Immunoglobulin E OR IgE OR Sensitization OR Hypersensitivity). This search yielded 881 publications, which were initially screened at the title level. If a title was considered

relevant to the research question, the abstract was reviewed, followed by a more detailed full-text assessment. In total, 831 articles were excluded, either because they did not address the relevant research questions or because the study design was not a prospective or retrospective cohort study. The remaining publications are presented in the subchapters below for each atopic disease, with corresponding tables summarising the methods and results. Due to the abundance of information, only statistically significant results are included in the tables. Studies focusing on PNMS and cord blood samples were excluded, as this topic represents an already extensive area of literature and was not directly aligned with the focus of this thesis.

2.3.1 Prenatal maternal psychological stress and food allergy or sensitisation to foodborne allergens

Paediatric food allergy remains a relatively unexplored condition within the field of PNMS and offspring atopic diseases. Only a few prospective cohort studies have reported outcomes related to food allergy, with some only focusing on the sensitisation to food-related allergens when phenotyping other atopic diseases into atopic and non-atopic subtypes. When only sensitisation was reported, which was observed by skin prick tests or specific IgE levels to food-related allergens, no information on symptoms was available. Some studies did not differentiate between sensitisation to food-related allergens and aeroallergens, which complicates the interpretation of findings specific to food allergy. The type of stress exposure varied considerably across studies, including occupational stress, NLE, symptoms of anxiety and depression, exposure to community violence and perceived stress. The exposure was evaluated by a wide range of questionnaires partly due to differences in the stressors chosen for each study (Table 1).

In three studies, no associations were found between PNMS and offspring food allergy (Elbert et al., 2017; Lau et al., 2022; Smejda et al., 2018). Negative life events up to 1 year before or during pregnancy were associated positively with offspring physician-diagnosed food allergy at 3 years of age (Kojima et al., 2022). Perceived stress, particularly in late pregnancy, was similarly associated with symptoms of food allergy at the age of 2 years when assessed using the ISAAC questionnaire (Shi et al., 2023). A third study reported similar findings, where prenatal depressive symptoms were associated with sensitisation to at least one allergen of milk, egg, peanut and/or cockroach at 12 months of age, with the emphasis placed on sensitisation rather than clinically confirmed food allergy (Wood et al., 2011).

Table 1. Studies on prenatal maternal psychological stress and food allergy and/or sensitisation to food-related allergens from retrospective and prospective cohort studies.

Reference; country; study design	Number of participants included	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Elbert 2017; Netherlands; Prospective cohort study	5,205	Psychiatric symptoms, depression and anxiety during the 2nd trimester	Global Severity index, Brief Symptom Inventory	Skin prick test at 10 years and parent-reported physician-diagnosed food allergy using ISAAC	No associations found
Kojima 2022; Japan; Prospective cohort study	81,337	Negative life events (NLE) and psychosocial job remand during pregnancy or up to 1 year prior	Tailored questionnaires	MR physician-diagnosed food allergy up to 3 years	**NLE** Two events *vs* none: aOR 1.13 (1.02-1.25) Three or more events *vs* none: aOR 1.28 (1.10-1.50)
Lau 2022; Singapore; Prospective cohort study	332	Perceived stress, anxiety and depression, NLE at each trimester	Edinburgh Depression Scale (EPDS), Beck Depression Inventory-II, State-Trait Anxiety questionnaire, Pregnancy Anxiety questionnaire, Life Experiences Survey, General Health Questionnaire, Perceived Stress Scale (PSS)	Skin prick test at 18 months to cow's milk, egg, peanut, soy, wheat, shrimp, crab, house dust mites	No associations found
Shi 2023; China; Prospective cohort study	3,252	Anxiety and depression between 32–36 weeks and perceived stress between 12–16 weeks and 32–36 weeks	Life Events Scale for Pregnant Women, Self-Rating Anxiety Scale, Center for Epidemiologic Studies-Depression Scale	MR food allergy with symptoms during the last 2 weeks up to 2 years assessed with modified ISAAC	**Stress in late pregnancy; high *vs* low** 6 months: aOR 3.2 (1.27.8,12) **Anxiety in late pregnancy; high vs low** 2 years: 1.76 (1.06-2.92)
Smejda 2018; Poland; Prospective cohort study	370	Perceived and occupational stress during the second trimester and NLE during pregnancy	Subjective Work Characteristics questionnaire, PSS, Social Readjustment Rating Scale	Food allergy at 1 year assessed during a study visit with ISAAC	No associations found
Wood 2011; USA; Prospective cohort study	515	Depression, stress, exposure to work stress or community violence during the 2nd or 3rd trimester	Interview using EPDS, PSS	Allergen-specific sensitisation to milk, egg, peanut and/or cockroach at 12 months	**Depression** Sensitisation to at least one allergen: aOR 0.80, *P* = 0.05

aOR, adjusted odds ratio; CI, confidence interval; EPDS, Edinburgh Postnatal Depression Scale; ISAAC, International Study of Asthma and Allergy in Childhood; MR, mother-reported; NLE, negative life events; OR, odds ratio; PSS, Perceived Stress Scale

2.3.2 Prenatal maternal psychological stress and atopic eczema

Atopic eczema (AE) in relation to PNMS is the second most studied atopic condition after wheezing and asthma. Numerous studies within the last 20 years have been published. These studies exhibited substantial variability of PMPS exposure definition. *In lieu,* the definition of atopic eczema was relatively unanimous with the use of ISAAC combined with a previous physician-made diagnosis of the condition.

Five studies did not find associations between PNMS and atopic eczema (Brew et al., 2024; Cheng et al., 2015; Lau et al., 2022; Senter et al., 2021), whereas 14 did (Chang et al., 2016; Elbert et al., 2017; Hartwig et al., 2014; Kawaguchi et al., 2022; Kojima et al., 2022; Larsen et al., 2014; Letourneau et al., 2017; S. et al., 2016; Shen et al., 2020; Shi et al., 2023; van der Leek et al., 2020; I. J. Wang et al., 2013; Wei et al., 2020; J.-X. Zhou et al., 2023). Only two studies (Shen et al., 2020; J. Zhou et al., 2024) examined the stress exposure in each trimester, while some expanded the exposure timing of NLE and stressful life events up to 1 year before recruitment, and therefore in some cases to a timepoint before conception (Kojima et al., 2022; Senter et al., 2021). A range of exposure types of psychological stress resulted in a positive association with atopic eczema in childhood: perceived stress, anxiety, depression, overall psychiatric symptoms, NLE, stressful life events, pregnancy-specific anxiety and occupational stress (Table 2).

Table 2. Studies on prenatal maternal psychological stress and offspring atopic eczema: Findings from retrospective and prospective cohort studies.

Reference; country; study design	Number of participants included	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Braig 2016; Germany; Prospective cohort study	787	Perceived stress, anxiety and depression during pregnancy, recruited after birth	Trier Inventory of Chronic Stress, Pregnancy Related Anxiety Questionnaire (PRAQ), Hospital anxiety and depression scale	Physician-diagnosed atopic eczema (AE) up to 2 years	**Perceived stress; highest quartile *vs* lowest** aOR 1.5 (1.0-2.3) **Anxiety symptoms; highest quartile *vs* lowest** aOR 1.4 (1.0-2.0)
Brew 2024; Sweden; Retrospective cohort study	15,092 twins	At least two mental health diagnoses or dispenses of medication during pregnancy up to child's age of 3 years	National registers	Parent-reported (ISAAC) and register-defined current atopic eczema at age 9	**Maternal mental health disorders** No associations found
Chang 2016; South Korea; Prospective cohort study	Cohort 1: 973, Cohort 2: 1,531	Cohort 1: depression and anxiety at 3rd trimester, Cohort 2: depression any time during pregnancy	Center for Epidemiological Studies-Depression, State-Trait Anxiety-Inventory-Trait subscale (STAI), Kessler Six-question Psychological Distress Scale	Cohort 1: atopic eczema diagnosis by paediatric allergist, Cohort 2: MR current atopic eczema using International Study of Asthma and Allergies questionnaire (ISAAC)	**Cohort 1: maternal depression** aHR 1.31 (1.02-1.69) **Cohort 1: maternal anxiety** aHR 1.41 (1.06-1.89) **Cohort 2: maternal depression** aOR 1.85 (1.06-3.25)
Cheng 2015; Singapore; Prospective cohort study	1,067	Anxiety and depression at 26 weeks	Edinburgh Postnatal Depression Scale (EPDS), STAI	Mother-reported (MR) physician-diagnosed atopic eczema up 1-year old	No associations found
Elbert 2017; Netherlands; Prospective cohort Study	5,205	Psychiatric symptoms, depression and anxiety during the 2nd trimester	Global Severity index, Brief Symptom Inventory	Parent-reported physician-diagnosed atopic eczema using ISAAC	**Overall psychiatric symptoms** aOR 1.21 (1.05-1.39) **Anxiety symptoms** aOR 1.15 (1.02-1.29)
Hartwig 2014; Australia; Prospective cohort study	994	Negative life events (NLE) between 0-18 weeks and 18-32 weeks	Tailored questionnaire	MR physician-diagnosed or self-reported atopic eczema at 6 years and 14 years	**NLE between 18 and 34 weeks and atopic eczema at 14 years** Three or more events *vs* none: aOR 4.19 (1.97-8.89)

Reference; country; study design	Number of participants included	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Kawaguchi 2022; Japan; Prospective cohort study	8,377	Anxiety and depression during the 1st trimester	K6 scale	MR atopic eczema presenting between ages of 1 and 2 years using ISAAC	**Psychological distress** Postnatal only: aRR 1.23 (1.07-1.39) Pre- and postnatal: aRR 1.34 (1.20-1.47)
Kojima 2022; Japan; Prospective cohort study	81,337	NLE and psychosocial job remand during pregnancy or up to 1 year prior	Tailored questionnaire	MR physician-diagnosed eczema up to 3 years	**NLE and eczema** One event *vs* none: aOR 1.11 (1.05-1.18) Two events *vs* none: aOR 1.25 (1.14-1.37) Three or more events *vs* none: aOR 1.28 (1.10-1.48)
Lau 2022; Singapore; Prospective cohort study	332	Perceived stress, anxiety and depression, NLE at each trimester	EPDS, Beck Depression Inventory-II, STAI, PRAQ, Life Experiences Survey, General Health Questionnaire, Perceived Stress Scale (PSS)	MR physician-diagnosed atopic eczema at 18 months using ISAAC	No associations found
Larsen 2014; Denmark; Prospective cohort study	32,271	Job strain during 2nd trimester	Interview	MR physician-diagnosed atopic eczema at 7 years of age	**Work stress (AE without asthma)** High vs low: aOR 1.15 (1.02-1.31)
Letourneau 2017; Canada; Prospective cohort study	242	Depression, anxiety and perceived stress during 13-22 weeks and 32-40 weeks	EPDS, SCL-90-R (anxiety subscale), Pregnancy-Specific Anxiety Scale, Stressful life events questionnaire	MR physician-diagnosed atopic eczema at 18 months	**Pregnancy specific anxiety** aOR 2.74 (1.04-7.19)
van der Leek 2020; Canada; Retrospective cohort study	9,995	Clinical diagnosis of anxiety and depression during pregnancy	Register	Doctor visits for atopic eczema between ages 3-5 years	**Exposure to anxiety and/or depression** aOR 1.27 (1.11-1.46)
Sausenthaler 2009; Germany; Prospective cohort study	3,004	Perceived stress during pregnancy	Assessed from maternity cards	MR physician-diagnosed atopic eczema up to 6 years	No associations found

Reference; country; study design	Number of participants included	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Senter 2021; USA; Prospective	426	Stressful life events 12 months before delivery	Pregnancy Risk Assessment Monitoring System, stressful life events survey	MR atopic eczema assessed between 4 and 6 years using ISAAC	No associations found
Shen 2020; China; Prospective cohort study	1,638	Perceived stress at each trimester	Perceived Stress Scale	Questionnaire based on the UK Working Party diagnostic criteria	2nd trimester: aOR 1.56 (1.08-2.25)
Shi 2023; China; Prospective cohort study	3,252	Anxiety and depression between 32-36 weeks and perceived stress between 12-16 and 32-36 weeks	Life Events Scale for Pregnant Women, Self-Rating Anxiety Scale, Center for Epidemiologic Studies-Depression Scale	MR atopic eczema at 6 months and eczema at 2 months and 2 years assessed with modified ISAAC	**Stress in late pregnancy; high *vs* low** Eczema at 2 months: aOR 1.30 (1.01-1.67)
Wang 2013, Taiwan; Prospective	19,381	Work stress at any time during pregnancy, collected after birth	Tailored questionnaire	MR physician-diagnosed atopic eczema based on ISAAC	Increased from 1st to 2nd trimester: aOR 2.05 (1.33-3.15) Increased from 1st to 3rd trimester: aOR 1.92 (1.22-3.00) High vs low/no stress: aOR 1.34 (1.16-1.54)
Wei 2020; China; Prospective cohort study	5,825	Depression in early (before week 20) and late (after 32 weeks) pregnancy	Self-Rating Depression Scale	Parent-reported physician-diagnosed atopic eczema at 1 year of age	**Depressive symptoms *vs* no symptoms** Persistent symptoms: aOR 1.55 (1.19-2.03)
Wood 2011; USA; Prospective cohort study	515	Depression, stress, exposure to work stress or community violence during the 2nd or 3rd trimester	Interview, EPDS, PSS	Physician-diagnosed atopic eczema during a study visit at 1 year of age	No associations found
Wen 2011; Taiwan; Prospective cohort study	730	Perceived stress during the third trimester	Short Form 36 Health Survey	MR physician-diagnosed atopic eczema via telephone up to 2 years of age	**Maternal stress; high *vs* low/no stress** aOR 2.30 (1.10-5.30)

Reference; country; study design	Number of participants included	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Zhou 2023; China; Prospective cohort study	3,131	Anxiety during all three trimesters	PRAQ	MR physician-diagnosed atopic eczema up to 3 years of age assessed with ISAAC	**Anxiety** 1st trimester: aOR 1.29 (1.01-1.65) 2nd trimester: aOR 1.22 (1.00-1.49) 3rd trimester: aOR 1.30 (1.06-1.46) **Cumulative anxiety during pregnancy** One trimester: aOR 1.30 (1.09-1.59) Two trimesters: aOR 1.31 (1.03-1.65) Three trimesters: aOR 1.45 (1.02-2.07)

AE, atopic eczema; aOR, adjusted odds ratio; CI, confidence interval; EPDS, Edinburgh Postnatal Depression Scale; ISAAC, International Study of Asthma and Allergy in Childhood; MR, mother-reported; NLE, negative life events; OR, odds ratio; PRAQ, pregnancy-related anxiety questionnaire; PSS, Perceived Stress Scale; SCL-90-R, Symptom Checklist 90 Revised; STAI, Anxiety-Inventory-Trait subscale

2.3.3 Prenatal maternal psychological stress and wheezing or asthma

The largest body of evidence on PNMS and offspring atopic diseases pertains to wheezing and asthma, with 36 studies published since 2009. Of these, only one study (Pape et al., 2021) did not report an association between PNMS and asthma, while the remaining studies found a positive association with either wheezing or asthma, as summarised in Table 3 (Adgent et al., 2019; Alcala et al., 2023; Bandoli et al., 2016; Brew et al., 2018, 2024; Viktorin et al., 2018; Cheng et al., 2015; Chiu et al., 2012; Cookson et al., 2009; Fang et al., 2011; Guxens et al., 2014; Hartwig et al., 2014; Hovland et al., 2015; Khashan et al., 2012; Kojima et al., 2022; Larsen et al., 2014; Lau et al., 2022; A. Lee et al., 2016; Liu et al., 2019; Liu, Olsen, Agerbo, et al., 2015; Liu, Olsen, Pedersen, et al., 2015; Magnus et al., 2017; G. T. O'Connor et al., 2018; Radhakrishnan et al., 2019; Ramratnam et al., 2017, 2021; Reyes et al., 2011; Rosa et al., 2016; Shi et al., 2023; Smejda et al., 2018; Turcotte-Tremblay et al., 2014; van der Leek et al., 2020; van Gelder et al., 2023; van Meel et al., 2020; Wood et al., 2011; J.-X. Zhou et al., 2023). The definitions and timing of exposure and outcomes were highly heterogeneous (Table 3).

The approach to defining stress exposure varied across studies. In most cases, outcomes were determined through questionnaires or interviews inquiring about previously diagnosed asthma, wheezing symptoms or hospital and/or physician visits related to wheezing or asthma. Some population register studies had asthma medication use as the outcome measure (Table 3).

Only one of the studies observed PNMS in all three trimesters (J. Zhou et al., 2024), while a few separated early and late pregnancy exposure (Cookson et al., 2009; Hartwig et al., 2014; Shi et al., 2023; van Gelder et al., 2023). Most studies did not examine the effects or adjust for the effects offspring sex, and only a few stratified for this factor. Among those that did, findings on sex-specific sensitivity to PNMS were inconsistent (Table 3).

Table 3. Studies on prenatal maternal psychological stress and offspring wheezing and asthma, from retrospective and prospective cohort studies.

Reference; country; study design	Number of participants	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Adgent 2024; USA; Prospective cohort study	1,157	Stressful events during pregnancy	Modified Prevention Pregnancy Risk Assessment Monitoring System survey	Mother-reported (MR) wheeze and physician-diagnosed asthma, ever or current asthma using International Study of Asthma and Allergies in Childhood questionnaire (ISAAC) between 4 and 6 years	**Stressful events as a continuous variable** Current wheeze: aRR 1.08 (95% CI 1.03-1.13)
Alcala 2022; Mexico; Prospective cohort study	569	Depression during the 2nd or 3rd trimester	Edinburgh Postnatal Depression Scale (EPDS)	MR ever and current wheeze and asthma using ISAAC up to 6 years	**Recurrent depression in the postnatal period and wheeze ever** Current wheeze: aRR 2.22 (1.42-3.49) Asthma ever: aRR 2.14 (1.01-4.54) **Only prenatal depression was not associated with wheeze or asthma**
Bandoli 2016; USA; Prospective cohort study	1,193	Mother-reported (MR) anxiety, negative life events (NLE) and chronic stress at any time during pregnancy	Interviews	MR wheeze and asthma between the ages of 2.3 and 5.8 years	**Maternal pregnancy-related anxiety and wheezing ever** Very much vs none: aRR 1.40 (1.07-1.83) **Maternal NLEs and wheezing ever** One NLE vs none: aRR 1.30 (1.04-1.64) Two or more NLEs vs none: aRR 1.36 (1.06-1.75)
Brew 2018; Brew 2024; Sweden; Retrospective cohort study	360,526 for Brew 2018, 15,092 twins for Brew 2024	2021: Maternal diagnosis or medication for depression or anxiety; 2024: at least two mental health diagnoses or dispenses of medication during pregnancy up to child's age of 3 years	National registers	2021: Register-based diagnosis of current asthma at 5 years of age; 2024: parent-reported (ISAAC) and register-defined current asthma at age 9	**Pre-conception stress** aOR = 1.29 (1.24-1.34) **Prenatal stress** aOR = 1.32 (1.24-1.40) **Postnatal stress** aOR = 1.33 (1.28-1.38) **Maternal mental health disorder** Register-defined asthma aOR 1.37 (1.09-1.64) Parent-reported asthma aOR 1.31 (1.08-1.55)

Reference; country; study design	Number of participants	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Cheng 2015; Singapore; Prospective cohort study	1,067	Anxiety and depression at 26 weeks	EPDS, State-Trait Anxiety Inventory (STAI)	MR physician-diagnosed wheezing up to 1 year of age	**Maternal depression** Wheeze: aOR 2.09 (1.05-4.19)
Chiu 2012; Chiu 2014; USA; Prospective cohort study	653 for Chiu 2012, 718 Chiu 2014	NLE during the last 6 months. Mothers recruited between 20 and 36 weeks of gestation	My Exposure to Violence questionnaire, Crisis in Family Systems-Revised survey (CRISYS-R)	MR physician-diagnosed asthma at 7 years of age or wheezing during the last 12 months	**NLE and wheeze:** 3-4 vs none: aOR 3.55 (1.38-9.15) 5+ vs none: aOR 3.79 (1.39-10.3) **Exposure to violence and wheeze** High vs low: aOR 1.95 (1.13-3.36)
Cookson 2009; UK; Prospective cohort study	5,810	Anxiety at 18 and 32 weeks	Crown-Crisp Experimental Index (CCEI)	MR physician-diagnosed asthma at 7.5 years with current symptoms or treatment	**Anxiety at 18 weeks and non-atopic asthma at 7.5 years** 4th vs 1st quart. aOR 1.78 (1.24-2.57) **Anxiety at 32 weeks and non-atopic asthma at 7.5 years** 2nd vs 1st quart. aOR 1.57 (1.06-2.33) 3rd vs 1st quart. aOR 1.72 (1.17-2.51) 4th vs 1st quart. aOR 1.80 (1.20-2.70)
Fang 2011; Sweden; Retrospective cohort study	Cohort 1: 426,334, Cohort 2: 493,813	Bereavement of a close relative during pregnancy or up to 1 year prior	Population register	Asthma ever up to 4 years and current asthma between ages 7 and 12 years	**Cohort 1: bereavement and asthma onset** Boys: 2nd trimester: aHR 1.55 (1.19-2.02) **Cohort 2: bereavement and current asthma** Any time during pregnancy: bereavement of an older child Boys: aOR 1.58 (1.11-2.25)
Gelder 2023; Netherlands; Prospective cohort study	2,618	Depression at 17 and 34 weeks	EPDS and Hospital Anxiety and Depression scale	Wheezing ever up 2 years of age	**Mid gestation (weeks 15-22)** Wheezing ever aRR 1.36 (1.04-1.78) Current wheezing aRR 1.29 (1.03-1.61) **Late pregnancy (weeks 32-35)** Current wheezing aRR 1.28 (1.02-1.60)

Reference; country; study design	Number of participants	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Guxens 2014; Netherlands; Prospective cohort study	4,848	Anxiety and depression at 20 weeks	Brief Symptom Inventory (BSI)	MR physician-diagnosed asthma, ever at 6 years and wheeze at 4 years of age	**Anxiety and depression** Late wheeze (at 4 yrs): aOR 1.94 (1.04-3.60) Persistent wheeze (1-4 yrs): aOR 2.15 (1.47-3.13) **Depression** Late wheeze (at 4 yrs): aOR 2.04 (1.14-3.64) Persistent wheeze (1-4 yrs): aOR 1.84 (1.24-2.72) **Anxiety** Late wheeze (at 4 yrs): aOR 1.81 (1.05-3.12) Persistent wheeze (1-4 yrs): aOR 1.72 (1.22-2.43)
Hartwig 2014; Australia; Prospective cohort study	994	Negative life events (NLE) between 0-18 weeks and 18-32 weeks	Tailored questionnaire	MR physician-diagnosed current asthma at 6 years and 14 years of age	**Asthma at 14 years** One vs no NLE: aOR 2.24 (1.33-3.75) Two vs no NLE: aOR 1.96 (1.01-3.79)
Hovland 2015; Norway; Prospective cohort study	550	Perceived family stress at birth	Tailored questionnaires	MR physician-diagnosed asthma, asthma medication use or asthma symptoms up to 16 years of age	**Family stress *vs* no stress** Prepubertal asthma: aOR 1.04 (1.01-1.09)
Khashan 2012; Sweden; Retrospective cohort study	3,193,033	Bereavement of a spouse or child during pregnancy or up to 6 months prior	Population register	Asthma hospitalisation between 2 and 34 years of age	**Death of spouse or child** Asthma hospitalisation: aRR 1.43 (1.06-1.92) Asthma hospitalisation and other related outcomes: aRR 1.40 (1.14-1.72) **Death of spouse only** Asthma hospitalisation: aRR 1.59 (1.10-2.30) Asthma hospitalisation + other related outcomes: aRR 1.64 (1.29-2.10)
Kojima 2022; Japan; Prospective cohort study	81,337	NLE and psychosocial job remand during pregnancy or up to 1 year prior	Tailored questionnaires	MR physician-diagnosed asthma up to 3 years of age	**NLE** One event *vs* none: aOR 1.13 (1.07-1.2) Two events *vs* none: aOR 1.24 (1.13-1.36) ≥3 events *vs* none: aOR 1.26 (1.10-1.46)

Reference; country; study design	Number of participants	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Lau 2022; Singapore; Prospective birth cohort	332	Perceived stress, anxiety and depression, NLE at each trimester	EPDS, Beck Depression Inventory-II, STAI, Pregnancy Anxiety questionnaire (PRAQ), Life Experiences Survey, General Health Questionnaire, Perceived Stress Scale (PSS)	MR wheeze assessed with questionnaire based on ISAAC at 18 months of age	**Depression at timepoint of the highest score** BDI score of 20 or over: aOR 2.5 (1.0-5.9)
Larsen 2014; Denmark; Prospective cohort study	32,271	Job strain during the 2nd trimester	Interview	MR physician-diagnosed asthma at 7 years of age or wheezing during the last 12 months	**Work stress and asthma without atopic eczema** Active vs low strain: OR 1.13 (1.03-1.24)
Lee 2016; USA; Prospective cohort study	765	NLE during the last 6 months. Mothers recruited between 20 and 36 weeks of gestation	CRISYS-R	MR physician-diagnosed asthma up to 6 years of age	**NLE, all** ≥5 NLE vs none: aOR 2.02 (1.05-3.87) Continuous: aOR 1.31 (1.07-1.60) **Boys:** Continuous: aOR 1.38 (1.06-1.79)
Liu 2015; Denmark; Retrospective cohort study	733,685	Clinical diagnosis of depression and/or use of antidepressant during pregnancy or up to 1 year prior	Population register	Asthma ever assessed from medication prescription database up to 3 years of age	**Maternal depression vs none** aHR 1.25 (1.20-1.30) **Use of antidepressant vs non-use** aHR 1.25 (1.18-1.33)
Liu 2015; Denmark; Retrospective cohort study	750,058	Bereavement of a close relative during pregnancy or up to 1 year prior	Population register	Asthma ever assessed from medication prescription database up to 15 years of age	**Maternal bereavement vs none** 0-3 years: aHR 1.04 (1.00-1.07) No differences were found between exposure timing during pregnancy

Reference; country; study design	Number of participants	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Liu 2019; Denmark; Retrospective cohort study	547,533	NLE and psychosocial job remand during pregnancy or up to 1 year prior	Population register	Asthma ever assessed from medication prescription database up to 6 years of age	**Low job demands with low job control:** Early-onset transient asthma: aPR 1.14 (1.09-1.19) Early-onset persistent asthma: aPR 1.17 (1.11-1.23) Late-onset asthma: aPR 1.06 (1.00-1.14)
Magnus 2017; Norway, prospective cohort study	63,626	Major depression at 30 weeks	Symptom Check List, 5 domains	Current use of asthma medication and MR physician-diagnosed asthma	**Depression and asthma onset** aRR = 1.17 (1.06-1.29)
O'Connor 2018; USA; Prospective cohort study	422	Perceived stress and depression at any time during pregnancy	PSS, EPDS, tailored questionnaires	Parent-reported physician-diagnosed current asthma, asthma hospitalisation and current asthma symptoms up to 7 years of age	**Prenatal depression and current asthma** aOR 1.03 (1.00-1.06)
Pape 2021; Denmark; Prospective cohort study	75,156	NLE during pregnancy or up to 1 year prior or psychosocial job strain	Population register	Asthma ever assessed from medication prescription database between 3 and 10 years of age	No associations found
Radhakrishnan 2018; Canada; Retrospective cohort study	122,333	Mental health service use during pregnancy	Not applicable	Asthma ever up to 12 years of age	**Maternal stress** aOR 1.16 (1.12-1.20)
Ramratnam 2017; Ramratnam 2021; USA; Prospective cohort study	560	Depression and perceived stress at any time during pregnancy	EPDS, PSS	Wheezing and atopy up to 10 years of age combined into phenotypes	**Recurrent wheeze at 3 years** Depression: aOR 1.54 (1.24-1.91) Perceived stress: aOR 1.28 (1.03-1.58) Hardships: aOR 2.00 (1.29-3.12) **Wheeze phenotypes up to 10 years** Results presented in a figure with a positive, significant association between prenatal depression and moderate wheeze-low atopy phenotype

Reference; country; study design	Number of participants	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Reyes 2011; USA; Prospective cohort study	279	Demoralisation during the 3rd trimester	Psychiatric Epidemiology Research Instrument-Demoralisation scale via study visits	MR wheeze up 5 years of age	**Maternal demoralisation score as a continuous variable** Any wheeze at 5 yrs: aOR 1.66 (1.29-2.14) Transient wheeze (3-30 months): aOR 2.25 (1.34-3.76) Persistent wheeze (3-5 yrs): aOR 2.69 (1.52-4.76)
Rosa 2016; Mexico; Prospective cohort study	417	NLE during the 2nd or 3rd trimester	CRISYS-R	MR ever or current wheeze up 4 years of age	**NLE as a continuous variable and wheeze ever** All: aRR 1.08 (1.00-1.16) Boys: aRR 1.12 (1.02-1.24) **NLE as a continuous variable and current wheeze** All: RR 1.12 (1.00-1.26)
Shi 2023; China; Prospective cohort study	3,252	Anxiety and depression between 32-36 weeks and perceived stress between 12-16 weeks and 32-36 weeks	Life Events Scale for Pregnant Women, Self-Rating Anxiety Scale, Center for Epidemiologic Studies -Depression Scale	MR physician-diagnosed asthma or wheezing with symptoms or medication use during the last 4 weeks up to 2 years of age assessed with modified ISAAC	**High vs low stress in early pregnancy** aOR 1.30 (1.01-1.67) **High vs low stress in late pregnancy** aOR 1.65 (1.14-2.36)
Smejda 2018; Poland; Prospective cohort study	370	Perceived and occupational stress during the 2nd trimester and NLE during pregnancy	Subjective Work Characteristics questionnaire, PSS, Social Readjustment Rating Scale	Wheezing at 1 year assessed during a study visit with ISAAC	**Perceived stress and wheezing** aOR 1.08 (1.02-1.1) **NLE and wheezing** aOR 1.1 (1.02-1.2)
Turcotte-Tremblay 2014; Canada; Prospective cohort study	68	Maternal questionnaire-reported posttraumatic stress disorder at any time during pregnancy	Impact of Events Scale - Revised and a tailored questionnaire	MR physician-diagnosed current asthma and wheeze between the ages of 11 and 12 years	**Maternal stress and wheeze** Girls only: OR 1.11 (1.01-1.23) **Maternal stress and asthma** Girls only: aOR 1.09 (1.00-1.19) **Maternal stress and asthma medication** Girls only: aOR 1.12 (1.01-1.25)
van der Leek 2020; Canada; Retrospective cohort study	9,995	Clinical diagnosis of anxiety and depression during pregnancy	Register	Current asthma at 7 years of age	**Anxiety and/or depression** aOR = 1.57 (1.29-1.91)

Reference; country; study design	Number of participants	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
van Meel 2020; Netherlands; Prospective cohort study	4,231	Psychological distress at second trimester	BSI with Global Severity Index	MR physician-diagnosed current asthma up to 10 years of age assessed by ISAAC	**Anxiety** Clinical cut-off: aOR 1.84 (1.21-2.80) **Depression** Clinical cut-off: aOR 1.64 (1.09-2.47)
Wood 2011; USA; Prospective cohort study	515	Depression, stress, exposure to work stress or community violence during the 2nd or 3rd trimester	Interview and questionnaires of EPDS, PSS	Wheezing at the age of 1 year	**Stress and one wheezing episode** aOR 1.54, *P* = .03 **Depression and several wheezing episodes** aOR 1.37, *P* = <.001 **Stress and several wheezing episodes** aOR 1.59, P = .01
Zhou 2023; China; Prospective cohort study	3,131	Anxiety during all three trimesters	PRAQ	MR physician-diagnosed current asthma up to 4 years using ISAAC	**Medium anxiety trajectory** aOR 1.38 (1.03-1.84) **High anxiety trajectory** aOR 2.18 (1.44-3.28)

aHR, hazard ratio; aOR, adjusted odds ratio; aRR, adjusted risk ratio, BDI, Beck Depression Inventory-II; BSI, Brief Symptom Inventory; CCEI, Crown-Crisp Experimental Index; CI, confidence interval, CRISYS-R, Crisis in Family Systems-Revised Survey; EPDS, Edinburgh Postnatal Depression Scale; IgE, Immunoglobulin E; ISAAC, International Study of Allergy and Asthma in Childhood; OR, odds ratio; MR, mother-reported; NLE, negative life events; PR, prevalence ratio; RR, risk ratio; PRAQ, Pregnancy Related Anxiety Questionnaire; PSS, Perceived Stress Scale; SCL, Symptom Checklist; STAI; State-Trait Anxiety Inventory

2.3.4 Prenatal maternal psychological stress and rhinoconjunctivitis or sensitisation to aeroallergens

Studies on PNMS and allergic rhinoconjunctivitis are relatively scarce. Most of the studies used ISAAC as a tool for assessing allergic rhinoconjunctivitis, often in conjunction with a previous physician-confirmed diagnosis. However, some studies collected data based solely on information of possible allergic rhinoconjunctivitis symptoms without a formal diagnosis. Studies reporting sensitisation to aeroallergens are included in Table 4 alongside those on allergic rhinoconjunctivitis, as these conditions are closely and significantly linked. However, not all children with objective sensitisation to aeroallergens exhibit symptoms of allergic rhinitis. Conversely, all children with allergic rhinitis are sensitised to an allergen which is responsible for triggering the immune system and manifestation of symptoms. As with other atopic diseases, exposure to stressors in the reviewed studies were highly heterogeneous. Exposure was variably defined as symptoms of anxiety or depression, NLE, perceived stress, demoralisation or hardships.

Four studies did not find an association between PNMS and offspring allergic rhinoconjunctivitis and sensitisation to aeroallergens (Brew et al., 2024; Cookson et al., 2009; Lau et al., 2022; Reyes et al., 2011), whereas six studies did report a positive correlation (Cheng et al., 2015; Conrad, Rauh, et al., 2020; Elbert et al., 2017; Hartwig et al., 2014; Shi et al., 2023; J. Zhou et al., 2024). One study by Zhou et al. (2024) examined the cumulative effect and timing of the stress exposure. While no particularly sensitive developmental period was identified, chronic PNMS was associated with a heightened effect. Some of the studies reported allergic rhinoconjunctivitis and sensitisation in very young children with a low prevalence of allergic rhinoconjunctivitis, which could explain why there are some conflicting findings of a positive or non-existing association.

Table 4. Studies on prenatal maternal psychological stress and offspring allergic rhinoconjunctivitis and sensitisation to aeroallergens from retrospective and prospective cohort studies.

Reference, country; and study design	Number of participants	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Brew 2024; Sweden; Retrospective cohort study	15,092 twins	At least two mental health diagnoses or dispenses of medication during pregnancy up to child's age of 3 years	National registers	Parent-reported (ISAAC) and register-defined current allergic rhinitis at age 9	**Maternal mental health disorders** No associations found
Cheng 2015; Singapore; Prospective cohort study	1,067	Anxiety and depression at 26 weeks	Edinburgh Prenatal Depression Scale (EPDS), State-Trait Anxiety Inventory (STAI)	Mother-reported (MR) physician-diagnosed allergic rhinitis up to 12 months of age	**Maternal anxiety state:** Allergic rhinitis: aOR 1.82 (1.17-2.82) **Maternal anxiety trait:** Allergic rhinitis: aOR 1.70 (1.10-2.61)
Cookson 2009; UK; Prospective cohort study	5,810	Anxiety at 18 and 32 weeks	Crown-Crisp Experimental Index (CCEI)	Skin prick test to aeroallergens at 7.5 years of age	No associations found
Elbert 2017; Netherlands; Prospective cohort Study	5,205	Psychiatric symptoms, depression and anxiety during the 2nd trimester	Global Severity index, Brief Symptom Inventory	Skin prick test and parent-reported physician-diagnosed allergic rhinitis using International Study of Asthma and Allergies questionnaire (ISAAC) up to 10 years of age	**Overall psychiatric symptoms** Physician-diagnosed inhalant allergy: aOR 1.96 (1.44-2.65) **Anxiety symptoms** Physician-diagnosed inhalant allergy: aOR 1.61 (1.27-2.03) **Depressive symptoms** physician-diagnosed inhalant allergy: aOR 1.58 (1.25-1.98)
Hartwig 2014; Australia; Prospective cohort study	994	Negative life events (NLE) between 0-18 weeks and 18-32 weeks	A tailored questionnaire	MR physician-diagnosed allergic rhinitis at 6 years and 14 years of age	**NLE between 18 and 34 weeks and allergic rhinoconjunctivitis at 14 years** Three or more events *vs* none: aOR 2.38 (1.21-4.70)
Conrad 2020; USA; Prospective cohort study	578	Maternal hardship during previous year or maternal demoralisation assessed during the 3rd trimester	Psychiatric Epidemiology Research Instrument-Demoralization scale, a tailored questionnaire	MR rhinitis without a cold up to 12 months	**Demoralisation** RR = 1.24 (1.05-1.46) **Hardship** RR = 1.15 (1.02-1.29)

Reference, country; and study design	Number of participants	Time and type of exposure during gestation	Exposure assessment	Outcomes	Key results
Lau 2022; Singapore; Prospective birth cohort	332	Perceived stress, anxiety and depression, NLE during each trimester	EPDS, Beck Depression Inventory-II, STAI, Pregnancy Anxiety questionnaire (PRAQ), Life Experiences Survey, General Health Questionnaire, Perceived Stress Scale	MR allergic rhinitis assessed with questionnaire based on ISAAC at 18 months	No associations found
Shi 2023; China; Prospective cohort study	3,252	Anxiety and depression between 32-36 weeks and perceived stress between 12-16 and 32-36 weeks	Life Events Scale for Pregnant Women, Self-Rating Anxiety Scale, Center for Epidemiologic Studies-Depression Scale	MR allergic rhinitis at 24 months with symptoms within the last 4 weeks assessed with modified ISAAC	**Stress in late pregnancy; high *vs* low** aOR 1.78 (1.01-3.15)
Zhou 2024; China; Prospective cohort study	3,131	Anxiety during all three trimesters	PRAQ	MR physician-diagnosed allergic rhinoconjunctivitis between 6-48 months assessed with ISAAC	1st trimester: aOR 1.38 (1.08,1.78) 2nd trimester: aOR 1.30 (1.06,1.60) 3rd trimester: aOR 1.35 (1.09,1.66) One trimester: aOR 1.34(1.10,1.64) Two trimesters: aOR 1.39 (1.09,1.77) Three trimesters: aOR 1.67 (1.17, 2.37)
Ramratnam 2021; USA; Prospective cohort study	560	Depression and perceived stress at any time during pregnancy	EPDS, PSS	Trajectories of allergen-specific IgE and skin prick test ratios up to 10 years of age	Depression: High skin prick ratio: aOR: 0.93 (0.89, 0.97) Stress: High skin prick ratio: aOR 0.93 (0.86, 1.00)
Reyes 2011; USA; Prospective cohort study	279	Demoralisation during the 3rd trimester	Psychiatric Epidemiology Research Instrument-Demoralization scale via study visits	Total IgE of aeroallergens up 5 years of age	No associations found

aOR, adjusted odds ratio; CCEI, Crown-Crisp Experimental Index; EPDS, Edinburgh Postnatal Depression Scale; IgE, Immunoglobulin E; ISAAC, International Study of Allergy and Asthma in Childhood; MR, mother-reported; NLE, negative life events; RR, risk ratio; PRAQ, Pregnancy Related Anxiety Questionnaire; STAI; State-Trait Anxiety Inventory;

2.4 Maternal prenatal distress and offspring atopic diseases – possible mechanistic pathways

There is no clear consensus on the precise mechanisms linking prenatal maternal stress (PNMS) to offspring health outcomes, including atopic diseases (Suh et al., 2017). One of the most widely proposed pathways involves maternal HPA axis activation, leading to elevated levels of glucocorticoids, such as cortisol, which can cross the placenta and influence foetal immune development. Increased maternal stress may also disrupt immune function, promoting inflammation through elevated cytokine levels that shape the foetal immune environment, potentially increasing susceptibility to atopic conditions (Figure 5).

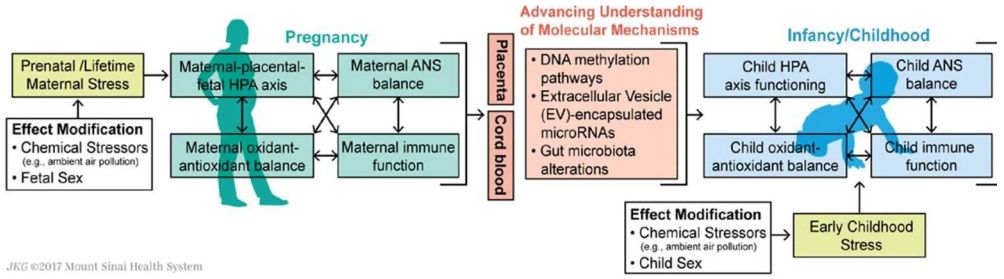

Figure 5. Mechanisms linking maternal prenatal stress to offspring atopic diseases. Reprinted with permission from Rosa et al. (2018).

Beyond direct biological pathways, PNMS may also influence offspring health through epigenetic modifications, which can alter the expression of genes involved in immune regulation and inflammatory responses. Additionally, maternal stress is often linked to poor sleep, suboptimal nutrition and reduced prenatal care, which may indirectly contribute to immune dysregulation in the developing child (Coussons-Read, 2013; Suh et al., 2017).

Studies examining PNMS and childhood atopic diseases have considered various stress exposures, including maternal mood disorders (e.g. anxiety, depression), perceived stress, post-traumatic stress disorder (PTSD), negative life events (e.g. financial hardship, bereavement) and environmental stressors (e.g. natural disasters, neighbourhood violence, poor housing conditions). The vast heterogeneity in how stress is measured and defined complicates generalising findings in this research field. Different stressors may activate the HPA axis in distinct ways, making it challenging to establish a single biological pathway (Mustonen et al., 2018). Furthermore, psychological stress is inherently subjective, influenced by an individual's genetic background, temperament and coping mechanisms. All these factors can consequently also affect maternal caregiving behaviours postpartum.

Although PNMS appears to influence foetal immune programming, the timing and chronicity of exposure remain unclear (Andersson, Hansen, et al., 2016; Flanigan et al., 2018; Veru et al., 2014). Some studies suggest that early and late pregnancy are particularly vulnerable windows, during which maternal stress may lead to altered offspring HPA axis function, yet no single critical period has been universally established (Galbally et al., 2019; Giesbrecht et al., 2017). Early gestation is the critical period of development of organs and organ systems in the foetus, whereas late gestation is characterised by the continued growth and maturation of these systems.

Natural disaster studies offer a more objective assessment of PNMS timing, as they provide precise exposure periods with minimal confounding from maternal psychological traits or lifestyle choices, yet with limited generalisability. Two of the most extensively studied natural experiments are the Dutch famine (1944–1945) and the Quebec ice storm (1998). Offspring of mothers who experienced these events showed changes in hippocampal volume (Cao-Lei et al., 2021), altered cognitive development (King & Laplante, 2005) and a higher prevalence of asthma (Turcotte-Tremblay et al., 2014), among other adverse offspring outcomes. The Dutch famine cohort also demonstrated transgenerational effects, with offspring exhibiting poorer cognitive function, higher rates of obstructive airway disease, and increased metabolic disorders (De Rooij et al., 2022). In relation to PNMS and atopic diseases, late-gestation stress exposure appears particularly critical, possibly due to its role in respiratory system maturation, though cumulative stress exposure over the entire pregnancy may also contribute to these outcomes. However, the evidence on the effects of PNMS timing are inconsistent (Al-Hussainy & Mohammed, 2021; Brew et al., 2018, Cookson et al., 2009; Flanigan et al., 2018; Rosa et al., 2018).

2.4.1 Hypothalamic-pituitary-adrenal axis dysregulation

One of the primary pathways through which PNMS may influence offspring immune function is via the HPA axis, which regulates stress responses through glucocorticoids (e.g. cortisol) (Figure 6). Pregnancy naturally alters HPA axis function, leading to elevated maternal cortisol levels, which peak in the third trimester. While moderate increases in maternal cortisol have an adaptive function, chronic stress and prolonged HPA activation can result in excessive foetal exposure to glucocorticoids, potentially disrupting immune programming and stress regulation in the offspring.

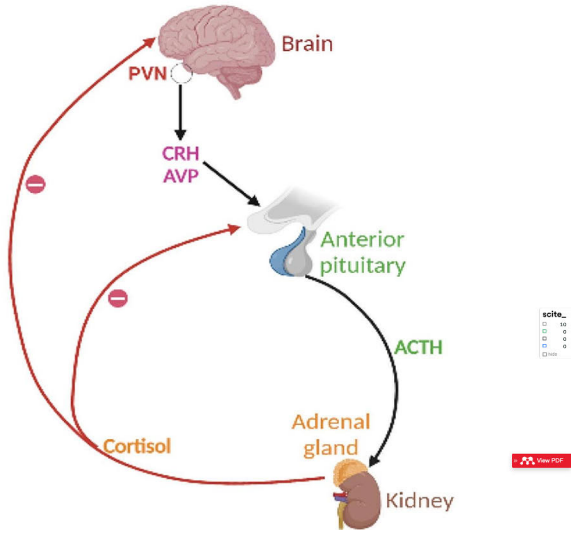

Figure 6. Illustration of the hypothalamic-pituitary-adrenal axis and the production of cortisol. The paraventricular nucleus (PVN) of the hypothalamus responds to perceived stress by releasing arginine vasopressin (AVP) and corticotropin-releasing hormone (CRH). AVP is transported to the anterior pituitary, where it stimulates the secretion of adrenocorticotropic hormone (ACTH) into the bloodstream. ACTH then acts on the adrenal cortex, promoting the production of glucocorticoids (CORT), which exert various physiological effects. To prevent excessive activation of the HPA axis, glucocorticoids form a negative feedback regulation. Preprinted with permission from (Mbiydzenyuy & Qulu, 2024).

The placenta provides partial protection against excessive maternal cortisol exposure via 11β-hydroxysteroid dehydrogenase type-2 (11β-HSD2), an enzyme that converts active cortisol into its inactive form (F. Wu et al., 2016). The balance between maternally and placentally regulated cortisol is complex, but negative feedback inhibition mechanisms help to moderate maternal stress responses to protect the foetus from environmental stressors (Howland et al., 2017). However, animal studies suggest that chronic maternal stress may impair placental 11β-HSD2 function, leading to higher foetal cortisol exposure (Peña et al., 2012). It has also been proposed that PNMS effects may be partially mediated by oxidative stress, potentially altering placental function (Chang et al., 2016). When foetuses are exposed to excess glucocorticoids, their HPA axis sensitivity may be permanently altered, leading to lifelong changes in stress reactivity and immune function (Duthie & Reynolds, 2013; Seckl & Holmes, 2007). These HPA axis alterations are associated with increased risks of psychiatric disorders (e.g. anxiety, depression), metabolic dysfunction and immune dysregulation, including a heightened susceptibility to atopic diseases.

2.4.2 Epigenetics and other possible factors

Another potential mechanism linking PNMS and atopic diseases is epigenetic modification, which alters gene expression without changing DNA sequences (Feinberg, 2018). The major epigenetic regulatory mechanisms include DNA methylation, post-translational histone modifications, non-coding RNA (ncRNA) and higher-order chromatin structure. Maternal stress can trigger HPA axis activation, leading to neurohormonal and corticosteroid release, which can induce epigenetic changes in genes regulating immune responses (Cao-Lei et al., 2016). Psychosocial stress can trigger adaptive responses, causing neurohormonal activation and resulting in the release of corticosteroids mainly mediated through the HPA axis. Glucocorticoids are thought to be one of the key contributors in the mediation of epigenetic changes and psychosocial stress. Exposure to prenatal stress during gestation has been shown to induce several epigenetic changes, marking an especially sensitive period with potentially profound implications for later health outcomes (Zannas & Chrousos, 2017). One possible mediator of later child outcomes, particularly in relation to atopic diseases, could be dysregulated functioning of the child's HPA axis (Al-Hussainy & Mohammed, 2021). Prenatal exposure to maternal stress has been linked to changes in offspring DNA methylation patterns in genes related to HPA axis regulation, such 11β-HSD2 and genes related to glucocorticoid receptors. However, further research is needed to clarify these associations, as causality has not yet been established (Palma-Gudiel et al., 2015; Sosnowski et al., 2018; Turecki & Meaney, 2016). In addition, genome-wide associations of DNA methylation have been observed in children of stressed mothers with dysregulated neuroendocrine function. These alterations have further been linked to an increased risk of persistent wheezing in offspring (Trump et al., 2016).

PNMS can affect offspring through both intergenerational and transgenerational inheritance, but these mechanisms differ in their transmission pathways. In intergenerational inheritance, the stress effects experienced by the mother directly impact the foetus during pregnancy, potentially influencing development through the pathways described previously. This form of inheritance involves only one generation, as PNMS directly affects the child. In contrast, transgenerational inheritance refers to the transmission of stress effects beyond the directly exposed generation. Here, the impacts of stress can be observed in subsequent generations without direct exposure to the original stressor. However, conditions *in utero* can also result in outcomes that manifest across future generations. Epigenetic mechanisms play a key role in transgenerational inheritance, with social and behavioural aspects also contributing to this transmission (Breton et al., 2021).

Other possible parallel factors mediating PNMS associated with the maternal immune system include a shift in the concentration of pro-inflammatory and anti-inflammatory cytokines (L. Karlsson et al., 2017) and serotonin (St-Pierre et al.,

2016) and changes in the maternal sympathetic system. The latter can lead to increased maternal circulatory catecholamines, which may influence placental blood flow (Rakers et al., 2015). Activation of maternal stress responses has been associated with restriction of blood flow to the uterus, potentially affecting foetal growth (Teixeira et al., 1999). Increased oxidative stress has also been proposed as a mediator of PNMS, primarily impacting placental function (Chang et al., 2016; F. Wu et al., 2016). Another proposed mediator of PNMS is the microbiome, with interesting associations reported in recent years (H. J. Chen & Gur, 2019; Mepham et al., 2023). Psychological well-being is often reflected in lifestyle choices and behaviours. Mothers exhibiting higher levels of depressive and anxiety symptoms may be more likely to use harmful substances during pregnancy, such as alcohol and tobacco, which can alter the reactivity and sensitivity of the foetal HPA axis (Pearson et al., 2015). Additionally, twin studies have reported associations between psychological stress, such as depressive symptoms, anxiety and high neuroticism, and atopic diseases. These findings may indicate a possible genetic contribution to their co-occurrence. However, results are inconsistent: some studies have found evidence supporting a genetic link (Lehto et al., 2019), while others have not (Brew et al., 2018; Tedner et al., 2016).

2.4.3 Changes in the offspring immune system

Exposure to PNMS can lead to various changes in the offspring's immune system, impacting the predisposition to adverse health outcomes. Alterations in the offspring HPA axis have been reported in animal and human studies, but with considerable heterogeneity in study design and results. Although the precise pathways through which PNMS influences offspring outcomes remain unclear, several studies have linked PNMS to alterations in the offspring's immune system. Maternal stress-induced neuroimmune changes contribute to altered corticosteroid profiles in offspring, with long-term consequences for immune homeostasis (Entringer et al., 2008; Molenaar et al., 2019).

Cytokine signalling alterations have also been implicated in PNMS-induced immune programming. Elevated maternal stress levels are associated with increased pro-inflammatory cytokines (IL-1β, IL-6 and IL-8) in cord blood, which may influence neonatal immune responses (Andersson et al., 2016). This shift in cytokine balance can impair immune tolerance mechanisms, increasing susceptibility to atopic diseases (Wright et al., 2010). Additionally, PNMS has been linked to sex-specific immune changes, although mostly in animal studies. Male offspring exhibit heightened HPA axis reactivity and a Th2-skewed immune polarisation, whereas females show distinct immune function alterations (Glover, 2015; Veru et al., 2014). Moreover, in animal studies, maternal stress has caused immune alterations in the

offspring, including alterations in lymphocyte populations and natural killer cell activity (Veru et al., 2014).

Epigenetic modifications provide further evidence for PNMS-induced immune alterations. Studies have shown that PNMS is associated with DNA methylation changes in immune-related genes, potentially leading to long-term effects on immune function (Cao-Lei et al., 2014). Moreover, PNMS-induced changes in maternal gut microbiota composition could lead to dysbiosis in offspring, affecting immune system maturation and increasing atopic disease risk (Fyhrquist et al., 2023; Zijlmans et al., 2015). Neuroimmune interactions further contribute to immune dysregulation, with increased microglial activation and inflammatory responses observed in prenatally stressed offspring (Ślusarczyk et al., 2015).

Changes in cytokine production following exposure to PNMS have been widely observed; however, the effects seem to be highly specific and the interactions complex. Notably, a more Th2-dominant cytokine profile has been observed, with increased levels of IL-4 and decreased levels of IFN-y, along with associations to other Th2 cytokines (Andersson, Li, et al., 2016; Entringer et al., 2008; O'Connor et al., 2013; Veru et al., 2014; Wright et al., 2010). This could, at least partially, help explain the observed link between PNMS and an increased risk of atopic diseases in offspring (Figure 7).

These findings highlight the complex interplay between maternal stress and offspring immune programming, though the causal consequences for offspring immune function remain poorly understood.

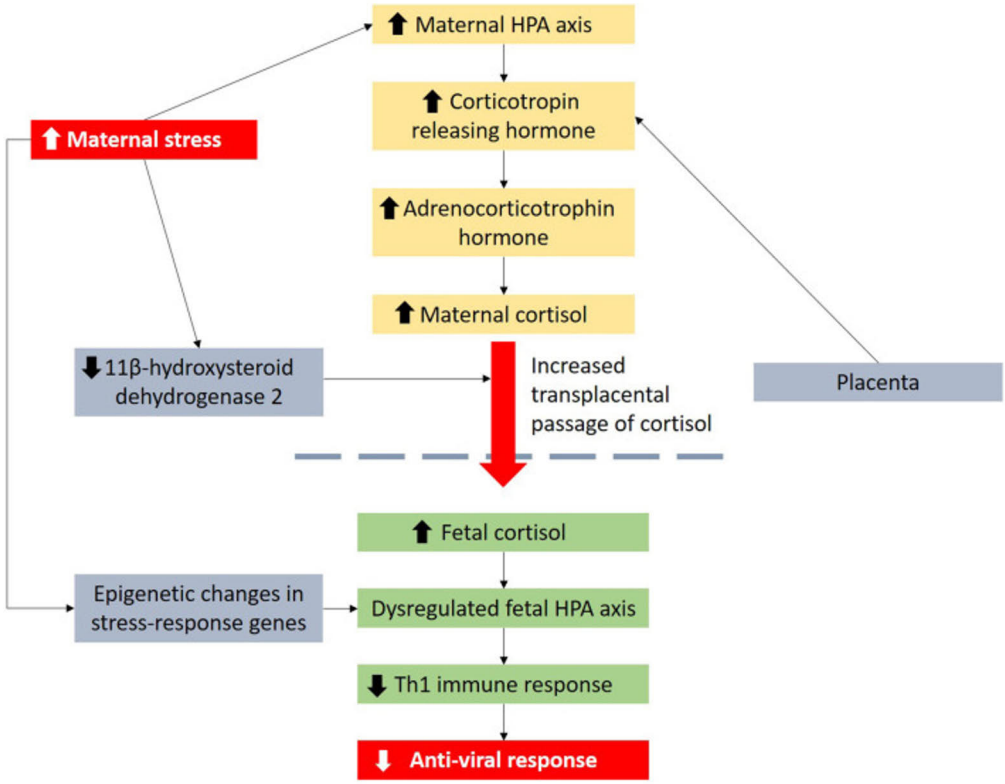

Figure 7. Alteration in the maternal HPA axis functions when exposed to stress and the effects on foetal HPA axis and immune system through placental interphase. Reprinted with permission by Lau et al (2022).

2.5 The concept of paternal adverse childhood experiences as a risk factor for offspring atopic diseases

The influence of paternal environmental factors on a child's growth and diseases is an emerging area of research, offering the advantage of excluding *in utero* exposure effects, which are inherent in maternal influences. The foundation of the research field exploring parental early life stress, which encompasses adverse experiences during a parent's own childhood or early adulthood, and its impact on offspring health and developmental outcomes was established in the 1980s with the pivotal hypothesis by David Barker, as discussed earlier. Advances in epigenetics and neuroscience in recent decades have provided new and valuable insights into the possible mechanisms underlying the impacts of parental stress on the health and development of offspring. The concept of intergenerational inheritance is illustrated in Figure 8. One key area of interest is adverse childhood experiences (ACEs), which

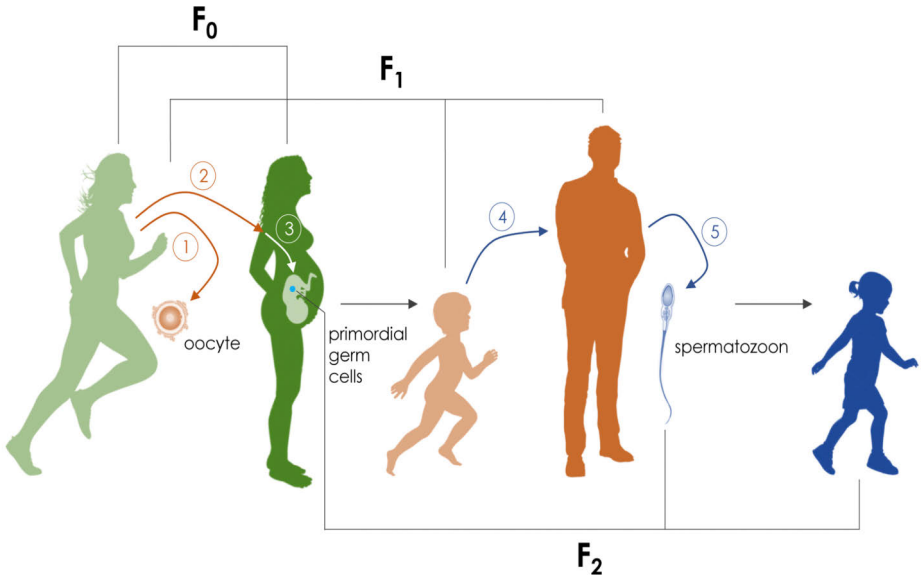

Figure 8. Illustration of transgenerational inheritance and sex-specific environmental factors in the F0 generation may induce epigenetic modifications in the oocyte (1) and/or alter systemic physiology (2). If these changes persist into pregnancy, they could influence the intrauterine environment (3), affecting the developing embryo (F1) and its primordial germ cells, precursors to the F2 generation. These factors may also shape metabolism and behaviour in F1, influencing physiological traits (4) and modifying spermatozoa through sequential programming (5). Alternatively, stable epigenetic changes in gametes across generations (F0, F1, etc.) may lead to transgenerational inheritance. Ultimately, the F2 generation reflects accumulated epigenetic influences from previous generations. Reprinted with permission from (Donkin & Barrès, 2018).

encompass physical, sexual and emotional abuse, neglect and other significant adversities, such as bereavement of a close relative before the age of 18. Offspring of individuals exposed to ACEs are at higher risk of developmental delays, emotional dysregulation, altered brain development and obesity, among other conditions (Arnold et al., 2023; H. Karlsson et al., 2020; Lê-Scherban et al., 2018; Oh et al., 2018). An interesting study by Brew et al. (2022) investigated whether early-life bereavement in parents is associated with an increased risk of inflammatory diseases in their offspring, using a three-generation Swedish cohort. They reported that early-life bereavement experienced by men was associated with autoimmune diseases in offspring.

Theories regarding the mechanisms through which ACEs are transmitted to offspring include alterations in the parent's stress response systems, resulting in changes in epigenetic markers that may modify the offspring's immune responses. Additionally, ACEs can influence parental behavioural patterns, potentially affecting caregiving abilities (Yehuda & Lehrner, 2018). Parental ACEs and offspring outcomes have a more straightforward approach, as the effects of maternal ACEs could be transmitted to the developing foetus during the sensitive prenatal period (Shih et al., 2023). Most studies on parental ACEs and offspring outcomes, however, have focused on mothers, which is beyond the scope of this section of the literature review, which focuses on the paternal aspect (Arnold et al., 2023).

2.6 Paternal adverse childhood experiences and offspring atopic diseases – possible mechanistic pathways

While evidently maternal ACEs play a crucial role in shaping the health and development of a woman's children, intrauterine exposure to the resulting psychiatric symptoms complicate the interpretation of findings. ACEs have been linked to chronic psychiatric symptoms affecting exposed individuals also in adulthood (Ertel et al., 2011). ACEs are linked to negative patterns in parenting, and fathers exposed to ACsS tend to have more conflicts with the mother of their children, potentially affecting *in utero* exposure to maternal psychological stress (Hughes & Cossar, 2016; Noel & Misra, 2021). Although fathers do not directly influence prenatal environments, their ACEs may indirectly impact their offspring through paternal germline epigenetic modifications or behavioural factors that may influence maternal prenatal stress (Choi et al., 2021). Male sperm cells are constantly generated after puberty, making them susceptible to environmental factors (Rowold et al., 2017). In contrast, oocytes in female ovaries are all developed at birth. This does not exclude the possibility of environmental factors also causing alterations to the epigenome of oocytes, especially before puberty (Cortessis et al., 2012).

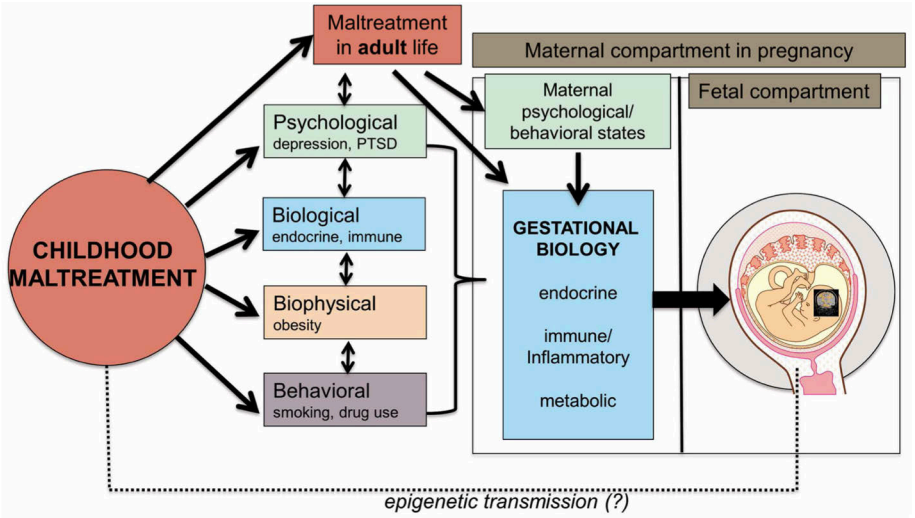

Figure 9. Illustration of potential transmitting pathways of early-life adversity to offspring. Reprinted with permission from (Buss et al., 2017).

ACEs have been shown to affect the exposed individual's immune system and stress responses, with long-lasting effects spanning into the adulthood. These effects are often mediated by disrupted hormonal and immune functions, including elevated cortisol levels (Yehuda & Lehrner, 2018). Several models have been proposed to explain the neurobiological mechanisms ultimately affecting offspring health and development, incorporating potential hormonal, neural, genetic and psychophysiological factors (Figure 9). Cumulative exposure to adversity has been associated with alterations in immune function, stress responses, inflammation and epigenetic changes (Blair et al., 2013; Fagundes et al., 2013; O'Connor et al., 2020; Rowold et al., 2017; Van Steenwyk et al., 2018). Individuals exposed to similar types of adversity may exhibit significantly different psychological and stress responses, as observed in a study examining psychopathology in children with both objective and subjective exposure to maltreatment (Danese & Widom, 2020). In addition, sex-specific differences in the effects of exposure to ACEs have been observed, suggesting that males and females may exhibit distinct vulnerabilities and coping mechanisms, potentially mediated by differences in hormonal regulation, neurobiological responses and sociocultural factors (McCabe et al., 2017; Tang et al., 2020).

One of the putative mechanisms of intergenerational transmission of ACEs is changes of the epigenome in the germline. Epigenetics plays an important role in development by regulating gene expression without altering the underlying DNA sequence, thereby influencing individual traits and shaping susceptibility to environmental influences. Epigenetic factors include DNA methylation, histone

modification and non-coding RNA. These epigenetic modifications could be transmitted to offspring, potentially affecting their health by modulating susceptibility to disease, including atopic and stress-related conditions (Alashkar Alhamwe et al., 2020; Klibaner-Schiff et al., 2024). Recent human studies have investigated paternal ACEs and epigenetic modifications, particularly DNA methylation patterns in children and adults within candidate gene and epigenome-wide approaches (Parade et al., 2021; Rowold et al., 2017). Some of these genes and systems are illustrated in Figure 10, with systems spanning from the HPA axis to immune function. Evidence suggests that paternal exposure to early-life stressors can lead to epigenetic alterations in sperm, which may be transmitted to the next generation, potentially influencing offspring development and health outcomes (Roberts et al., 2018). For instance, research indicates that paternal stress in humans can result in changes in DNA methylation and sperm non-coding RNA content, affecting gene expression (Rodgers et al., 2013; Tuulari et al., 2025; Zheng et al., 2021). Non-coding RNA could exert a more profound influence in the shorter term, undergoing dynamic and active alterations after exposure. These changes can further induce other epigenetic changes, such DNA methylation and histone modification, which are more stable and long-lasting (Mattick et al., 2023; Perez-Pereira et al., 2013). Furthermore, paternal ACEs have been linked to differential DNA methylation in offspring genes involved in neurological and immune functions (Yehuda et al., 2014, 2016). Still, there is no clear understanding on how paternal ACEs affect offspring outcomes, but epigenetic factors are one plausible pathway. Examples of genes showing changes in DNA methylation and in various physiological systems following exposure to ACEs are illustrated in Figure 10 below. Other suggestions on the mediating pathways include oxidative damage to sperm DNA. Markers of oxidative stress following exposure to childhood adversities have been identified in adults and children, yet there are no studies on the transgenerational aspect of transmission (Horn et al., 2019; Schiavone et al., 2013). Exposure to ACEs has also been shown to cause long-term dysregulation of the HPA axis, which can lead to altered reactivity of cortisol and testosterone levels and ultimately affect offspring outcomes, such as immune function and atopic diseases (Maniam et al., 2014; E. L. Rodgers & Kuhlman, 2023). Childhood experiences can influence parenting practices, and fathers' exposure to ACEs may affect their relationships, potentially increasing the risk of family conflict and contributing to maternal prenatal stress. Recent studies have highlighted seminal fluid composition as an interesting factor carrying signalling molecules, hormones, proteins and cytokines, which influence the uterine environment and embryonic development (Lane et al., 2014; Rando, 2012). There is no comprehensive understanding of how paternal ACEs affects offspring outcomes, yet the hypothesis has been that it predisposes the offspring especially to adverse health and developmental outcomes.

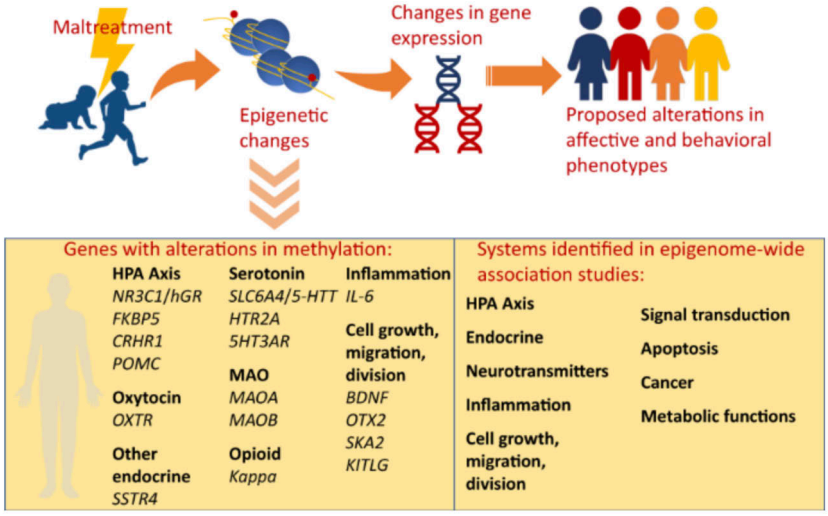

Figure 10. Synopsis of genes with DNA methylation alterations and associated physiological systems linked to childhood maltreatment. Reprinted with permission from (Parade et al., 2021).

2.7 Summary

Evidence suggests that prenatal maternal stress (PNMS) may influence the risk of atopic diseases in offspring, particularly asthma and wheezing. However, the findings for other atopic conditions such as atopic eczema, food allergy and allergic rhinitis have been inconsistent. These inconsistencies are likely due to methodological differences across studies, including variation in study designs, timing and type of exposure measurements, and outcome definitions. Furthermore, little is known about specific phenotypes of asthma and wheezing in relation to PNMS, despite their potential etiological heterogeneity.

In addition, while intergenerational effects of paternal early life adversity have been increasingly recognised in other health domains, their role in the development of offspring atopic diseases remains virtually unexplored. To date, only one study has examined paternal adverse childhood experiences in relation to offspring atopic outcomes, indicating a major gap in current knowledge (Brew et al., 2022).

There is thus a clear need for prospective birth cohort studies that include repeated and well-timed assessments of maternal psychological stress during pregnancy, allowing for the evaluation of not only overall exposure but also the potential impact of its timing. In addition, further research in needed regarding less studied atopic diseases such as food allergy, allergic rhinitis and atopic eczema. Outcomes of wheezing and asthma phenotypes associated with PNMS would offer new, intricate insights. Furthermore, such cohorts are essential for assessing novel

intergenerational exposures, such as paternal ACEs, using validated measures and prospectively collected offspring health outcomes, while also offering new avenues for research exploration.

3 Aims

The primary aim of this thesis was to study how parental prenatal stress, specifically prenatal maternal psychological stress and paternal adverse childhood experiences, is associated with the development of atopic diseases in offspring during early childhood. Maternal psychological stress was defined as symptoms of depression or anxiety. Paternal ACEs were defined as neglect and abuse.

The specific aims of the thesis were:

1) To assess the association between maternal prenatal depressive and anxiety symptoms and:
    a) Infant food allergy at 6 months (Study I)
    b) Toddler wheezing at 24 months, with particular focus on atopic *vs.* non-atopic wheezing phenotypes (Study II)
    c) Childhood current asthma and the phenotypes of atopic *vs.* non-atopic asthma at 5.5 years (Study IV)
2) To assess the association between paternal adverse childhood experiences and child sensitisation and allergic rhinitis at 5.5 years (Study III)

4 Materials and Methods

4.1 Study designs and subjects

This thesis was a part of a paediatric subdivision of the FinnBrain Birth Cohort, which is a multidisciplinary, population-based, prospective observational birth cohort. The birth cohort aims to investigate the intergenerational effects of prenatal and early life exposures to child health and development. The study subjects of the birth cohort were recruited between December 2011 and April 2015 during free-of-charge ultrasound appointments at maternity clinics in the Southwestern Hospital District and the Åland Islands. The cohort included 3808 mothers, 2,623 fathers and their children. The number of participants in each study included in this thesis is presented in the following sections. The follow-up points adhered to the study protocol established at the beginning of FinnBrain Birth Cohort Study and continued until the child's age of 5.5 years. Separate questionnaires were sent via mail or email to the mothers and their partners at gestational weeks 14, 24 and 34, as well as at the child's ages of 6 and 12 months and 5.5 years. A questionnaire assessing abuse and neglect during their own childhood was sent to the fathers at gestational week 12. At the child's age of 5.5 years, the families took part in a study visit conducted by a study paediatrician, during which blood samples were collected. The birth cohort and its substudies included additional study points and/or visits that were not included in this specific substudy. The timeline of data collection points across the studies is presented in Figure 11. Final sample sizes for each study, after the exclusion of participants due to missing data, are shown in the flowcharts below. The exposures in Studies I–IV were selected based on the available data within the birth cohort, as all children had already been born at the time the studies included in this thesis were designed. The outcomes were chosen to encompass several age-typical atopic diseases to provide a broader perspective on the potential associations between parental stress and offspring atopic conditions.

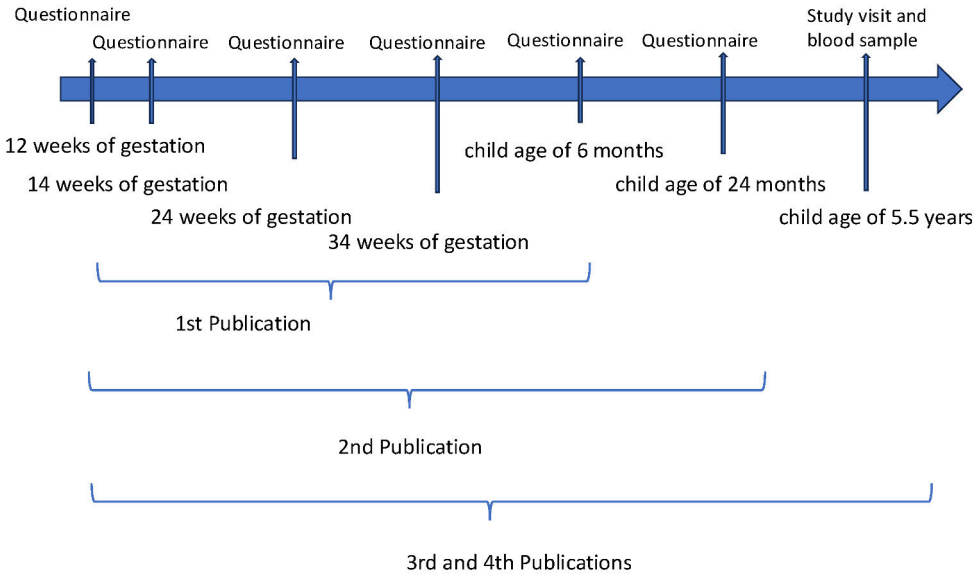

Figure 11. Timeline of data collection points included in Studies I-IV.

4.2 Data collection

4.2.1 Background information

After recruitment, the mothers and fathers received a self-report questionnaire via mail or email at gwks 14, 24 and 34. Background information included parental age at delivery, parental and sibling atopic diseases, parental smoking during pregnancy, number of siblings, area of living (rural or urban) years of parental education, maternal pre-pregnancy body mass index (BMI; kg/m^2) and delivery type (vaginal or caesarean section). Infant background information included sex, birth weight, birth height and duration of gestation. If information on the birth date and delivery type were not provided in the self-report questionnaires, this information was drawn from the Finnish Institute for Health and Welfare.

4.2.2 Exposure of maternal prenatal psychological stress

The information on maternal prenatal psychological stress was self-reported at each study point at gwks 14, 24 and 34 by validated questionnaires assessing depressive and anxiety symptoms (Bergink et al., 2011; Cox et al., 1987; Derogatis et al., 1973; Holi et al., 1998).

Depressive symptoms were assessed with the Edinburgh Postnatal Depression Scale (EPDS). The questionnaire includes 10 items with a score ranging from 0 to

30. A score over 10 indicates possible depressive symptoms and over 13 a likely depression disorder. Anxiety symptoms were assessed using the anxiety subscale of the Symptom Checklist-90 (SCL-90), which includes ten items specifically designed to evaluate symptoms of anxiety and has total score range of 0–40 (for questions 17, 23, 33, 39, 57, 72, 78, 80 and 86, see the questionnaire form in the Appendices). No clear cut-off value for a clinically significant score for SCL-90 anxiety exists, but a mean score of 1 or more has been suggested in the population (Olsen et al., 2006). Symptom trajectories were built using latent growth curve modelling for Studies I and II (See section 5.3.1 for details).

4.2.3 Exposure of paternal adverse childhood experiences

Paternal ACEs were self-reported at 12 gwks using the validated Trauma and Distress Scale (TADS) questionnaire. (Salokangas et al., 2016). The TADS comprises five domains: emotional neglect and abuse, physical neglect, and physical and sexual abuse. The questionnaire also includes two questions (18 and 27) designed to detect potential reporting bias by identifying exaggerated positive responses. Although the TADS is structured around thematic domains of early-life adversity, scores within these domains do not necessarily reflect experiences of severe abuse or maltreatment. The questionnaire is provided in the Appendices.

4.2.4 Follow-up at the child age of 6 months (Study I)

Study I included 1,976 infant–mother pairs. Participants were excluded if data data on exposure, outcomes or covariates were insufficient (Figure 12). The outcome of offspring food allergy was assessed through a self-reported questionnaire completed by the mothers. In addition, to enhance the validity of the outcome, mothers who reported a food allergy in the questionnaire were contacted by the author of this thesis via phone. During the call, they were asked whether the child's allergy was physician-diagnosed and whether an oral food challenge had been conducted. In an oral food challenge, the suspected allergen is firstly completely avoided and then reintroduced while monitoring for possible symptoms. A food allergy is diagnosed if symptoms subside during the avoidance period and re-emerge when the allergen is reintroduced. Additionally, the specific symptoms caused by the allergen (skin, intestine or both) were identified during the call.

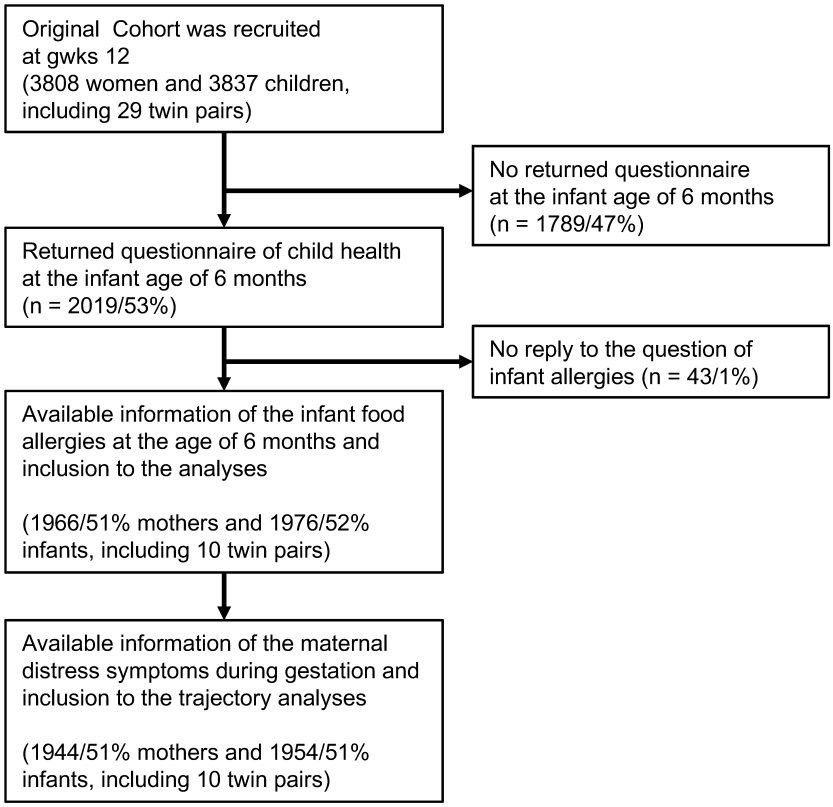

Figure 12. Flowchart of Study I. From original Publication I. Gestational weeks, gwks.

4.2.5 Follow-up at the child age of 24 months (Study II)

For Study II, the outcomes of wheezing and eczema were mother-reported via a questionnaire administered at the 24-month data collection point, based on the ISAAC questionnaire (Asher et al., 1995). The core questionnaires for eczema and asthma were used with questions 7 for eczema and 1 for asthma (see questionnaires in the Appendices). Offspring wheezing ever was determined at the 24-month follow-up point as a mother-reported outcome. Offspring eczema was assessed at the 24-month follow-up point as a physician-diagnosed mother-reported outcome. Data on wheezing and atopic eczema, as well as covariates, were available for 1,305 and 1,276 children, respectively. Preterm children were excluded (Figure 13). To illustrate the different phenotypes of wheezing, a four-class variable was created combining wheezing and atopic eczema: neither wheezing nor eczema, wheezing with eczema, wheezing without eczema and eczema without wheezing.

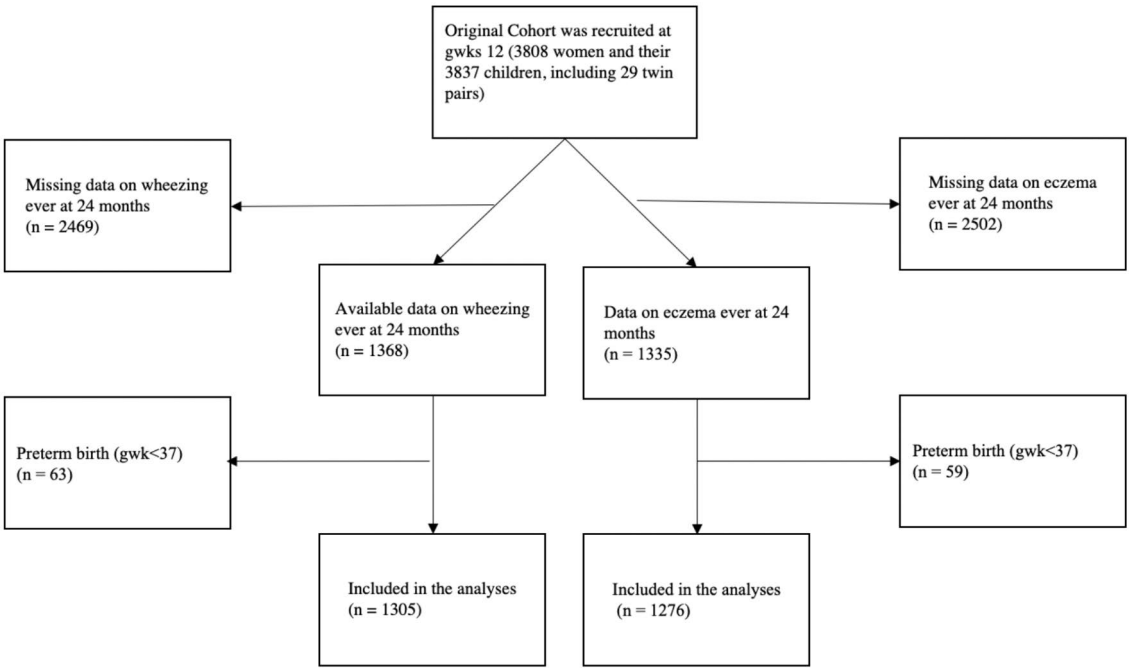

Figure 13. Flowchart of Study II. From original Publication II. Gestational weeks, gwks.

4.2.6 Follow-up at the child age of 5.5 years (Studies III and IV)

The children visited the study centre with their parents at the age of 5.5 years. Outcome data listed below were gathered through a phone interview by a study paediatrician, and a blood sample was drawn. Questions related to atopic disease outcomes were based on the ISAAC questionnaire (Asher et al., 1995). The core questionnaires for asthma and allergic rhinitis were used, specifically question 6 for asthma and question 6 for allergic rhinitis (see the questionnaires in the Appendices). Sensitisation was assessed by measuring the IgE antibody levels against common allergens (codfish, cow's milk, egg, peanut, soybean, wheat, cat, dog, horse, birch, mugwort, timothy, *Cladosporium herbarum* and *Dermatophagoides pteronyssinus*; fluoro-enzyme immunoassay, CAP FEIA, Phadiatop Combi®, Phadia, Uppsala, Sweden). The analyses were conducted by the Central Laboratory of Turku University Hospital as part of routine diagnostics. An IgE level of 0.35 kU/L for one or more allergens was considered moderate sensitisation, while 0.70 kU/L was considered significant sensitisation.

4.2.6.1 Study III

Participants were excluded if data on exposure, outcome or covariates were unavailable. The number of participants included in each model is presented below in Figure 14.

Model 5 for sensitisation included 430 father–child dyads, while the allergic rhinitis model included 473 pairs. A child was considered to have allergic rhinitis if a physician had diagnosed the condition within the last 12 months. If symptoms of allergic rhinitis had been present during the same period, this was classified as current allergic rhinitis. The outcome of clinically diagnosed offspring allergic rhinitis at age 5.5 years was determined during the interview conducted by the study paediatrician during the study visit.

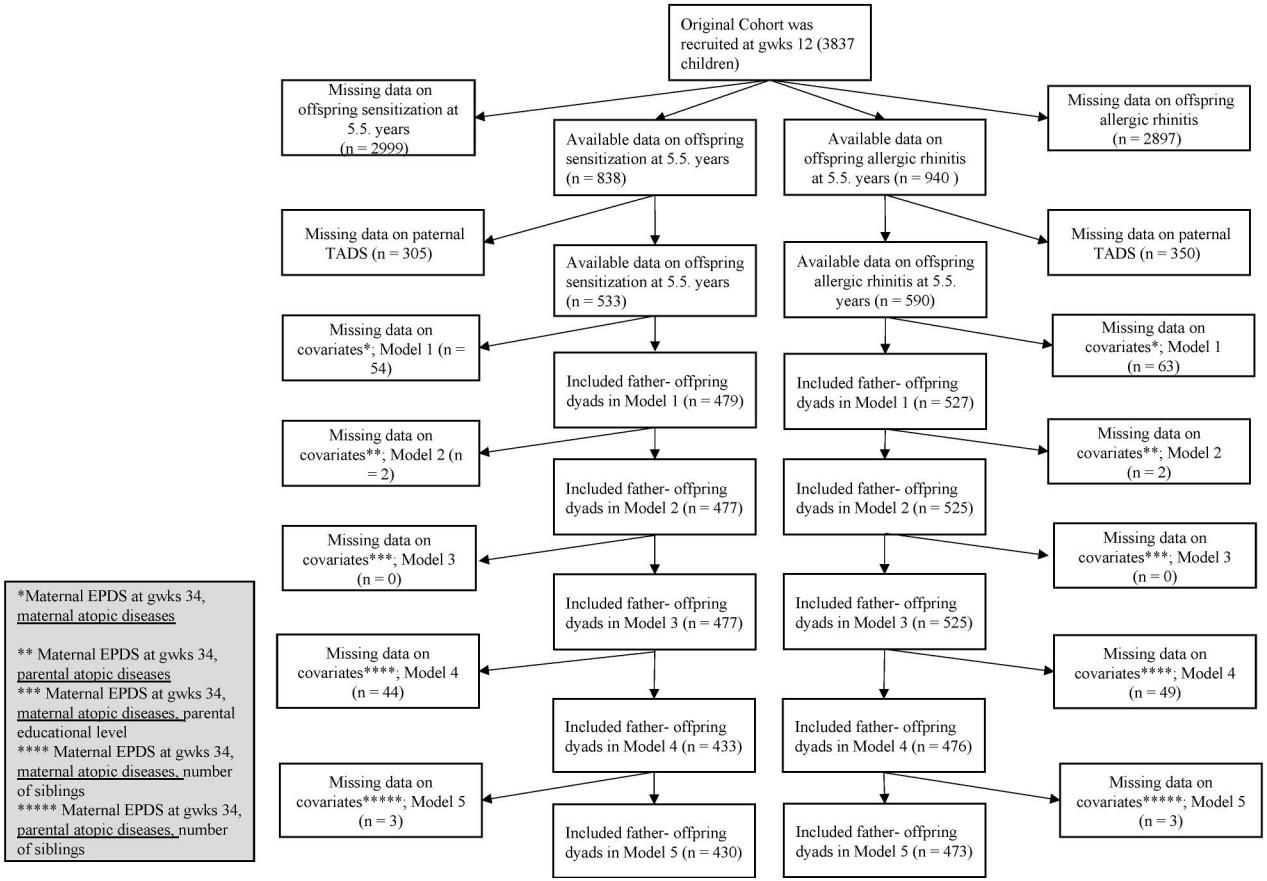

Figure 14. Flowchart of Study III. From original Publication III. Gestational weeks, gwks. Flow chart. EPDS, Edinburgh Postnatal Distress Scale; gwks, gestational weeks; TADS, Trauma and Distress Scale. *Maternal EPDS at gwks 34, maternal atopic diseases; **Maternal EPDS at gwks 34, parental atopic diseases; ***Maternal EPDS at gwks 34, maternal atopic diseases, parental educational level; ****Maternal EPDS at gwks 34, maternal atopic diseases, number of siblings; *****Maternal EPDS at gwks 34, parental atopic diseases, number of siblings.

4.2.6.2 Study IV

This study included 940 mother-child pairs who attended the study paediatrician's visit at age 5.5 years (Figure 15). The child's current asthma status was verified from the medical records for children with an affirmative response to the question of ever having experienced wheezing. The definition of current asthma required a prior diagnosis by a paediatrician and evidence of active asthma symptoms between the ages of 4.5 and 5.5 years, indicated by the need for follow-up visits and the use of inhaled corticosteroids. All asthma diagnoses and prescriptions had been made previously by attending paediatricians, not by the study paediatricians. As a secondary outcome, non-atopic *vs.* atopic asthma phenotypes were investigated to assess susceptibility to different asthma phenotypes. To examine the effect of PNMS timing and severity on the outcome, continuous, two- and three-class variables were derived from EPDS and SCL-90 scores

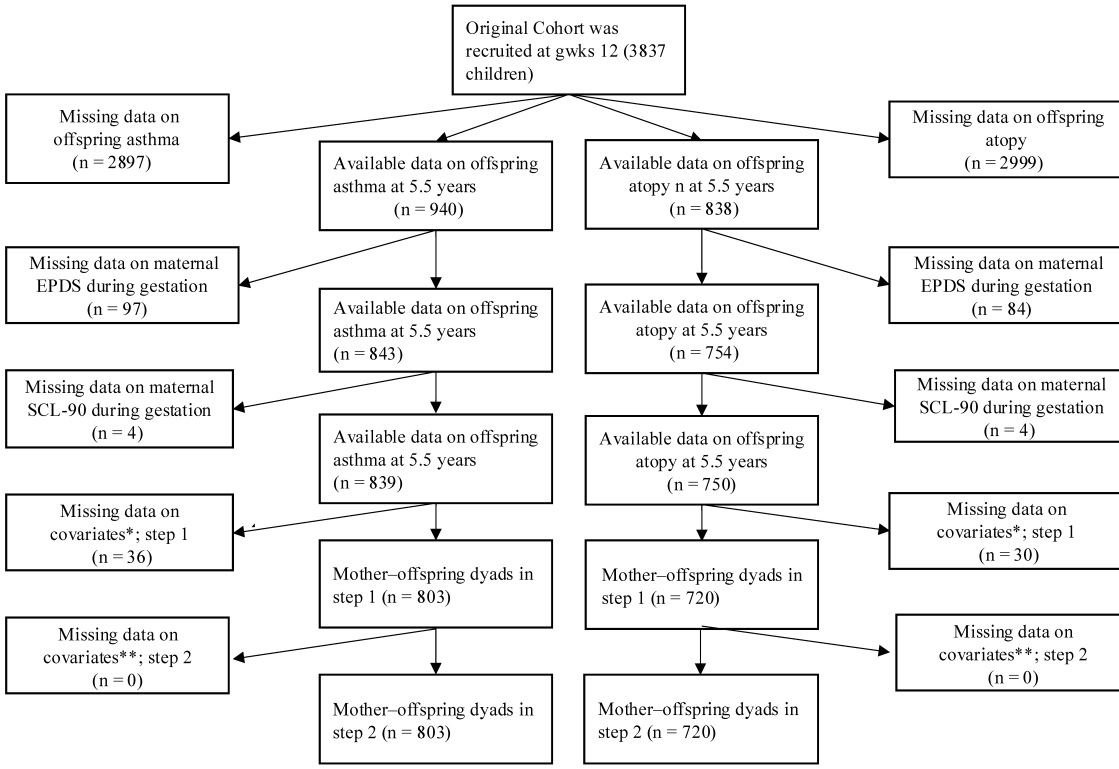

Figure 15. Flowchart of Study IV. From original Publication IV. *Maternal asthma and/or atopic diseases, child's sex, parental educational level, **Maternal asthma and/or atopic diseases, child's sex, parental educational level, maternal smoking during pregnancy. EPDS, Edinburgh Postnatal Depression Scale; gwks, gestational weeks; SCL-90, the Symptom Checklist 90.

4.3 Statistical analysis

Analyses were performed using the IBM SPSS 26.0-30.0 software (IBM Corp, 2019-2024) and R (version 4.2.2, 2022). Associations between background variables and subgroups with the outcome variables were assessed using the unpaired t-test, Mann–Whitney U test, Pearson's correlation coefficient, Spearman's rank correlation coefficient, binary logistic regression and multinominal regression, depending on the type of variable.

4.3.1 Trajectories

In Studies I and II, separate symptom trajectories for the EPDS and SCL-90 anxiety scale were constructed to capture the chronicity and severity of PNMS symptoms. The trajectories were modelled using latent growth mixture modelling with Mplus 6.0 (StatModel) (Muthén & Muthén, 2012). Missing data were imputed. Longitudinal confirmatory factor analysis showed a good fit for both questionnaires. Secondly, latent growth mixture modelling determined the number of latent curves by increasing subgroups and comparing fit indices. The optimal number of groups was defined using Bayesian information criteria, posterior probabilities, entropy rates and likelihood ratio tests (Bootstrapping Likelihood Ratio Test and Vuong-Lo-Mendell-Rubin likelihood ratio test) (Asparouhov & Muthén, 2012) The meaningfulness of the curves was visually inspected, and the group sizes were additionally considered when choosing the final models (NAGIN, 2005; Nylund et al., 2007). Entropy rate indexing classification accuracy was evaluated to assess accuracy (Lubke & Muthén, 2007a) Based on these principles, four latent growth curves were formed separately for EPDS and SCL-90 in Study I. Similarly, in Study II, five and three symptom trajectories were formed for EPDS and SCL-90, respectively. In both studies, the consistently low symptom trajectory was used as the reference group.

4.3.2 Study I

The odds of food allergy in relation to prenatal depression and anxiety symptoms was assessed using binary logistic regression. Continuous variable symptom scores for individual trimesters captured the timing of depressive and anxiety symptoms. Symptom trajectories throughout pregnancy reflected chronicity and severity. These trajectories were analysed using multinomial regression, with consistently low symptom trajectories serving as the reference group. In the unadjusted sensitivity analyses, trajectories with high PNMS symptoms were excluded due to the small number of infants in the corresponding food allergy group (Table 5). The adjusted analyses were performed separately for the same EPDS and SCL-90 trajectories

including covariables of maternal atopic diseases, a known and significant risk factor for offspring atopic diseases. A significance level of $p<0.10$ was used in unadjusted analyses to account for other confounders. A two-sided value of $p<0.05$ was considered statistically significant in the subsequent analyses. All analyses were performed with SPSS Statistics 26.0 (IBM Corp 2019).

4.3.3 Study II

In the primary analyses, the odds of wheezing ever or physician-diagnosed eczema ever was assessed using binary logistic regression, first in univariable and then in multivariable analyses. The multivariable models were adjusted for established risk factors: for wheezing, adjustments included prenatal maternal smoking, parental education level, child's sex, and maternal history of asthma; for eczema, adjustments included child's sex, maternal history of atopic diseases, and parental education level. The impact of chronic depressive and anxiety symptoms on the outcomes was evaluated using symptom trajectories with multinomial logistic regression, where the trajectory of consistently low symptoms served as the reference group.

In the secondary analyses, the odds of belonging to one of the four outcome categories were assessed using multinomial logistic regression, with the "neither wheezing nor eczema" group as the reference category. These analyses were adjusted for parental education level, child's sex, maternal prenatal smoking, and a combined variable representing a maternal history of asthma and/or atopic diseases. In supplementary analyses, stress symptom scores were analysed as continuous variables at each timepoint to explore the role of stress exposure separately across gestation. Correlation analysis of maternal perinatal depressive symptom scores was conducted, including maternal depressive symptoms at the child's age of 24 months as a potential confounder for reporting bias in paediatric outcomes. A p-value of <0.05 was considered statistically significant, and 95% confidence intervals were reported. All analyses were conducted using SPSS Statistics 27.0 (IBM Corp. 2020).

4.3.4 Study III

The odds of sensitisation and allergic rhinitis were analysed using binary logistic regression, first in unadjusted models and subsequently adjusted for potential confounders. The TADS was treated as a four-class categorical variable, divided into quartiles, with the lowest quartile serving as the reference group. The analyses accounted for established risk factors, including parental atopic diseases, parental education level, maternal depressive symptoms at gwk 34, and the number of older siblings (models 1 to 5). These models were designed to test for potential residual confounding, incorporating various combinations of significant covariates.

The genetic contribution of atopic diseases was examined by adjusting for parental atopic diseases: maternal atopic diseases only in models 1, 3 and 4, and both maternal and paternal atopic diseases in model 2. Model 3 additionally adjusted for parental education level, model 4 for the number of older siblings, and model 5 for all covariates mentioned. Supplementary analyses were conducted separately for sensitisation to aeroallergens and food allergens. Furthermore, a combined variable was created, representing sensitisation to aeroallergens (cut-off >.70 kU/L) and allergic rhinitis.

To further assess potential residual confounding, models 6 to 8 included all covariates from model 5, plus additional factors: the maternal TADS score (model 6), area of residence (rural or city; model 7), and population density (greater or fewer than 100 people per 250m × 250m grid; model 8). A two-tailed *p*-value of <0.05 was considered statistically significant, and adjusted odds ratios and 95% confidence intervals were reported. All analyses were conducted using SPSS version 29.0 (IMP Corp. 2022).

4.3.5 Study IV

The primary outcomes assessed were atopy and current asthma at 5.5 years. Associations between these primary outcomes and EPDS and SCL-90 (continuous, two- and three-class variables) and these primary outcomes were examined using binary logistic regression, with the lowest group as the reference group when analysing categorical variables. Models were adjusted stepwise to account for known risk factors for childhood asthma. In Step 1, adjustments included the parental educational level, maternal history of asthma and/or allergies, and sex of the child. In Step 2, maternal smoking during pregnancy was added as a confounder.

To analyse the secondary outcomes related to asthma phenotypes, the data was stratified by atopy to ensure appropriate comparison groups—atopic asthmatics were compared with atopic non-asthmatics, and non-atopic asthmatics were compared with non-atopic non-asthmatics (Pekkanen et al., 2012). Associations between EPDS and SCL-90 variables (continuous and two-class variables) and asthma phenotypes were assessed. The three-class variable of EPDS and SCL-90 was excluded due to insufficient sample size in some categories preventing meaningful statistical analysis. Logistic regression models were applied separately for each stratified sample, with adjustments conducted in Steps 1 and 2. A two-tailed *p*-value <0 .05 was considered statistically significant. Adjusted odds ratios and 95% confidence intervals were calculated for all analyses, which were conducted using R (version 4.2.2, 2022) while the subgroup and population characteristics were performed with SPSS Statistics version 30.0 (IBM Corp. 2024).

4.4 Ethics

The studies adhered to the principles outlined in the Declaration of Helsinki and received ethical approval from the Ethics Committee of the Hospital District of Southwest Finland (ETMK:57/180/2011). The research commenced only after obtaining written informed consent from the children's guardians. The child's cooperation was also required for any procedures involving them.

Each study participant was assigned a unique personal ID code, and all data have been handled exclusively using these codes to ensure confidentiality. Data storage protocols were developed in collaboration with the IT department of the University of Turku. Statistical analyses and publications have been prepared in a way that ensures that no individual can be identified. Participants were informed that their participation was voluntary and that they could withdraw from the study at any time without consequence, and that their privacy would be strictly maintained.

Artificial intelligence was used in conducting literature searches for the thesis, evaluating references and improving the grammar and fluency of parts of the text. The university's guidelines on the use of artificial intelligence were followed.

5 Results

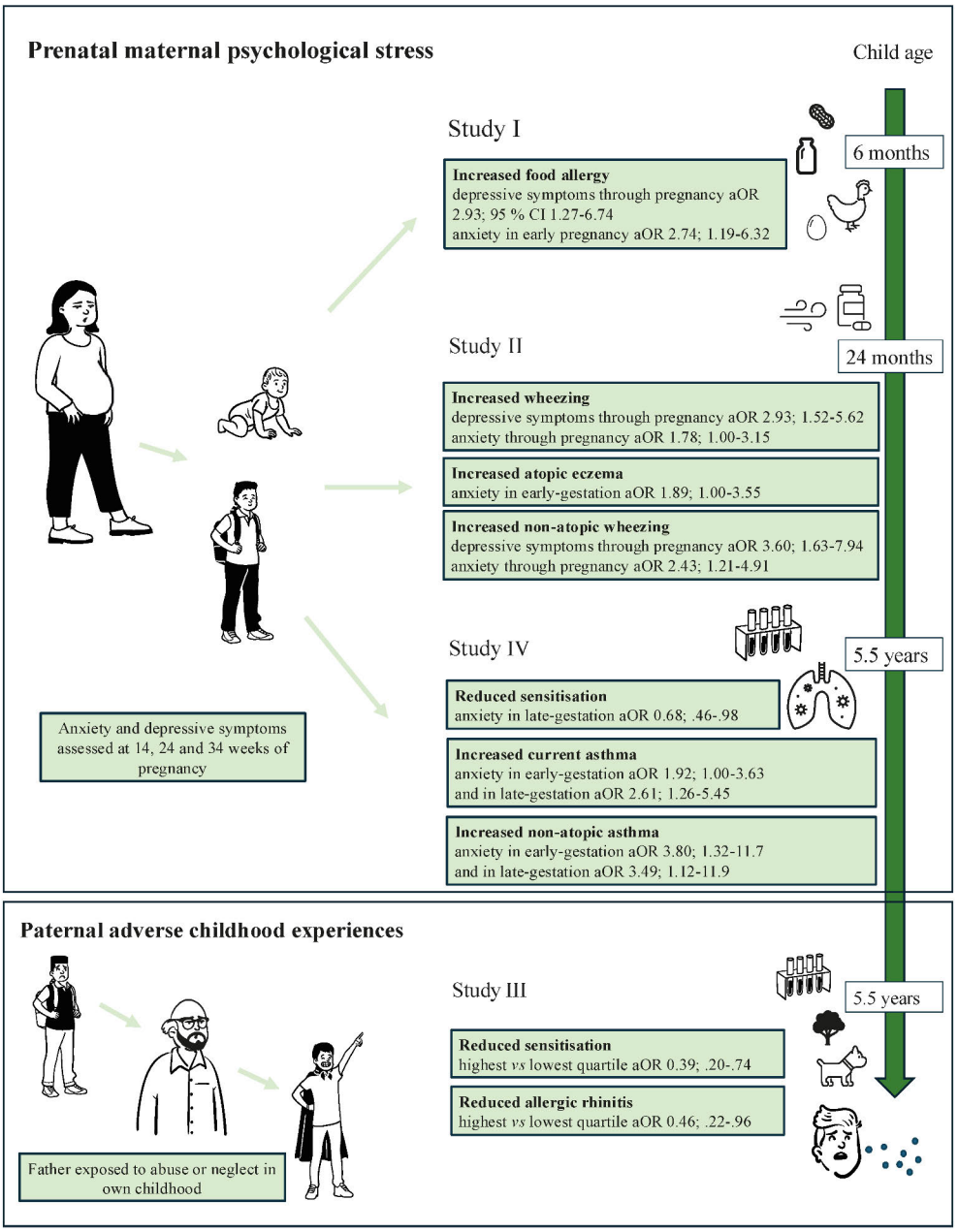

Figure 16. Summary of the main results from Studies I-IV. Due to space limitations, textual detail in the figure is minimal; however, it should be noted that the results indicate either reduced or increased odds of a specific outcome. aOR, adjusted odds ratio

5.1 The association between maternal PNMS and food allergy at 6 months (Study I)

5.1.1 Study population and characteristics

The study included 1,976 mothers and their offspring who had replied to the questionnaire at the 6-month follow-up point. From this population, 80 mother–infant dyads were excluded from the adjusted analyses due to missing data on the maternal allergy covariate (Figure 12). The excluded mothers had slightly higher EPDS and SCL scores than those who were included in the study.

The median EPDS score of the included mothers was 4.0 (interquartile range [IQR] 2.0–7.0) across all follow-up points and the SCL score 2.0 (IQR 0–4.0 at gwks 12 and 34, and 1.0–5.0 at gwk 24). Mothers were grouped into symptom trajectories, most of them consistently scoring low on both the EPDS (1401/1954) and the SCL (1704/1954). Of these children, 45 had a physician-diagnosed food allergy, of whom 30 were diagnosed through an oral food challenge. The most common allergy was to milk protein, affecting 40/45 (89%) of the children. Specific symptoms following allergen exposure were not reported for 6/45 (13%) children. Gastrointestinal symptoms (16/45) and skin symptoms (15/45) were reported with nearly equal frequency. Only 18% (8/45) of the children exhibited both gastrointestinal and skin symptoms. Maternal allergies and asthma, as well as allergies in older siblings, were associated with food allergy in the child, while paternal allergies and offspring characteristics at birth were not.

5.1.2 Trajectories of depressive and anxiety symptoms

Four distinct latent trajectory curves were generated from the EPDS (range 0–40 points) and SCL-90 (range 0–30 points) scores, based on data from the follow-up points at gestational weeks 14, 24 and 34. The trajectories were named to best reflect their shape (Figure 17).

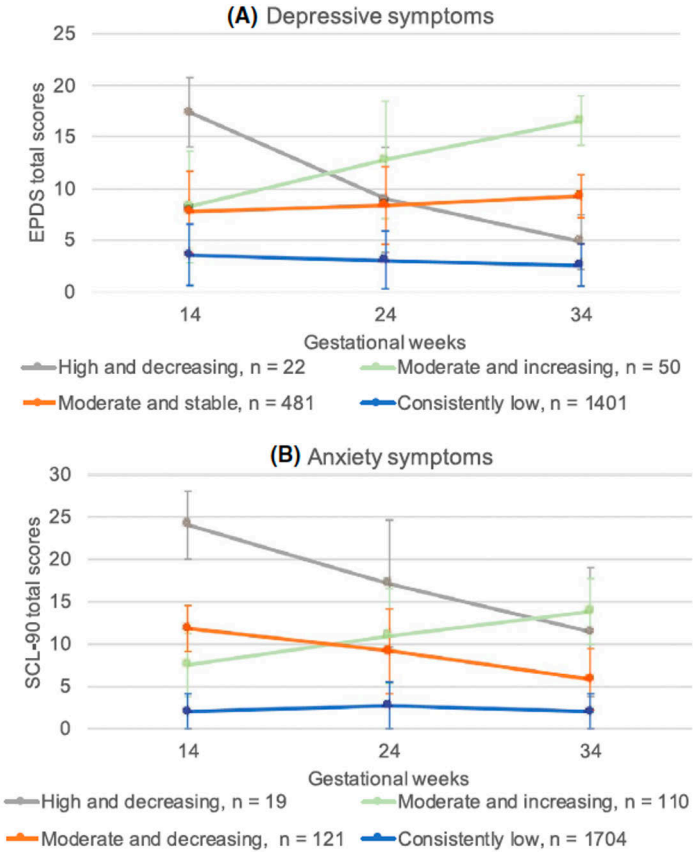

Figure 17. Latent growth curve trajectories of maternal depressive (A) and anxiety symptoms (B) during gestation at three timepoints from Study I. The whiskers illustrate the standard deviations of the scores at each timepoint, and the dots show the means. EPDS, Edinburgh Postnatal Scale (range 0-30 points); SCL-90, Symptom Checklist-90, anxiety subscale (range 0-40 points). From original Publication I.

5.1.2.1 Depressive symptoms

The largest group, classified as 'consistently low' (n=1401), exhibited minimal depressive symptoms, with EPDS scores stable at around 2–4 points from gestational weeks 14 to 34. The 'moderate and stable' group (n=481) showed consistently moderate symptoms, maintaining stable EPDS scores around 8 points throughout the observed period. A smaller subset, 'moderate and increasing' (n=50), began with moderate depressive symptoms of around 8 points at gestational week 14, which gradually increased, reaching approximately 17 points by week 34. Conversely, the 'high and decreasing' group (n=22) initially presented strong depressive symptoms, around 17 points at week 14, which notably decreased over time to approximately 5 points by week 34.

5.1.2.2 Anxiety symptoms

Regarding anxiety symptoms measured by SCL-90, the largest group of 'consistently low' (n=1704) reported minimal anxiety throughout pregnancy, with scores consistently around 3 points from weeks 14 to 34. The 'moderate and decreasing' group (n=121) started with moderate anxiety symptoms scoring approximately 12 points, decreasing gradually to about 6 points by week 34. A 'moderate and increasing' group (n=110) demonstrated an increase in anxiety symptoms from approximately 8 points at week 14 to about 14 points at week 34. The smallest group, 'high and decreasing' (n=19), initially showed very high anxiety scores of around 24 points at gestational week 14, which substantially declined to approximately 12 points by week 34.

5.1.3 Maternal PNMS associated with offspring food allergy

Maternal prenatal depressive and anxiety symptoms were associated with offspring food allergy at 6 months throughout pregnancy at each follow-up point, except for depressive symptoms at gwks 24 in the unadjusted analysis. The EPDS trajectory of 'moderate and stable' and the SCL trajectory of 'moderate and decreasing' were associated with an increased odds of offspring food allergy when compared with the 'consistently low' trajectory as reference (OR 2.19, 95% CI 1.16–4.15 and 2.93, 1.27–6.74, respectively). After adjusting for maternal allergy, both the EPDS 'moderate and stable' and the SCL 'moderate and decreasing' trajectories remained positively associated with offspring food allergy (OR 2.93, 95% CI 1.27–6.74 and 2.74, 1.19–6.32).

5.2 Association between maternal PNMS and wheezing or eczema at 24 months (Study II)

5.2.1 Study population and characteristics

After excluding children born preterm, the study population included 1,305 children and their mothers with available data on offspring wheezing at 24 months. A further 13 children were excluded due to missing maternal prenatal EPDS and SCL data regarding wheezing, and 21 due to missing data on atopic eczema. For multivariable analyses, data were available from 1,221 mother–child dyads for offspring wheezing and from 1,183 dyads for atopic eczema.

From the included population, 219/1,305 (17%) of children were reported to have had wheezing ever and 285/1276 (22%) had been diagnosed with atopic eczema. Participants were divided into a four-class variable, where the most common group after 'neither wheezing nor eczema' (829/1267; 65%) was 'eczema without wheezing' (231/1267; 18%), followed by 'wheezing without eczema' (154/1267; 12%) and lastly 'wheezing with eczema' (53/1267; 4.2%). Children with wheezing

had a higher prevalence of maternal asthma and maternal atopic diseases, while mothers of children with atopic eczema and asthma were more likely to have atopic diseases. Male children were more likely to wheeze (66% vs 34%).

5.2.2 Trajectories of depressive and anxiety symptoms

The latent growth curve models that best described the data included five trajectories for EPDS (range 0–40 points) and three for SCL-90 (range 0–30 points) with scores measured at gwks 14, 24 and 34.

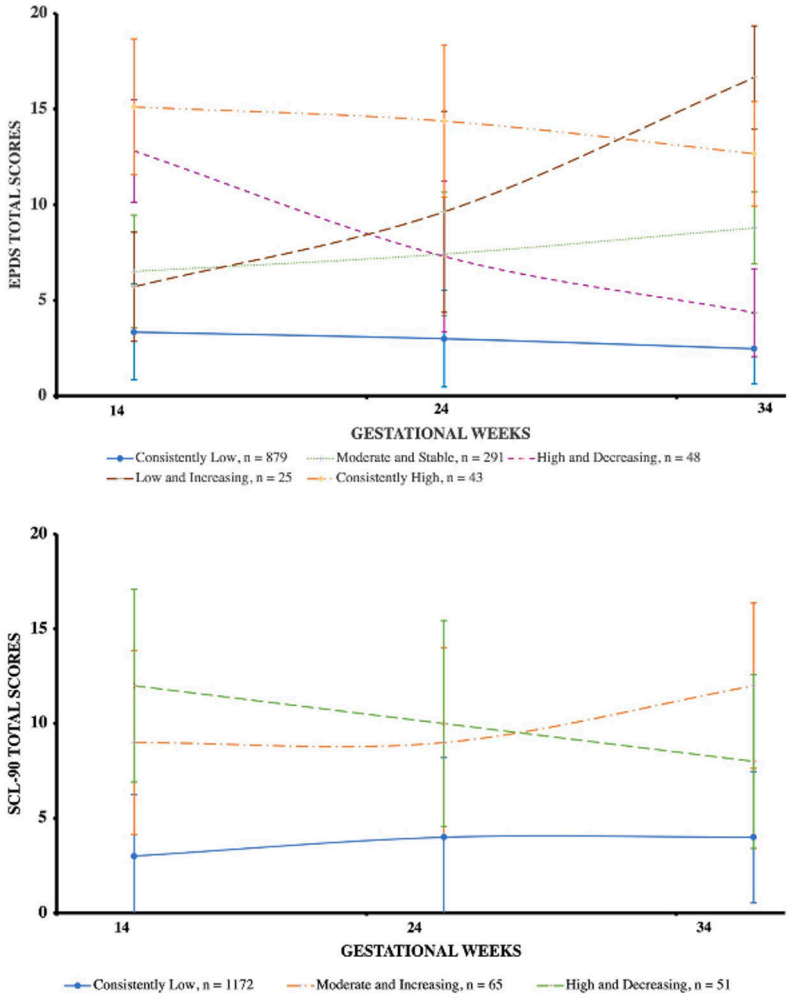

Figure 18. Latent growth curve trajectories of maternal depressive (above) and anxiety (below) symptoms during gestation at three timepoints from Study II. EPDS, Edinburgh Postnatal Scale (range 0-30 points); SCL-90, Symptom Checklist-90, anxiety subscale (range 0-40 points). From original Publication II.

5.2.2.1 Depressive symptoms

The largest group, ‘consistently low’ (n=879), demonstrated minimal depressive symptoms across pregnancy, maintaining stable and low EPDS scores ranging from approximately 2 to 3 points. The second-largest group, ‘moderate and stable’ (n=291), displayed consistently moderate depressive symptoms with minor fluctuations around an EPDS score of approximately 7 points from week 14 through week 34. The smaller ‘high and decreasing’ (n=48) group initially exhibited elevated depressive symptoms, with scores around 13 points at gwk 14. This group's depressive symptoms significantly decreased over the course of pregnancy, reaching approximately 4 points by week 34. Conversely, another small group, ‘low and increasing’ (n=25), started with low depressive symptoms of around 6 points and showed a notable rise, peaking at around 16 points by week 34. Finally, the ‘consistently high’ group (n=43) presented with persistently elevated depressive symptoms, maintaining high EPDS scores fluctuating between 13 and 15 points throughout pregnancy.

5.2.2.2 Anxiety symptoms

Regarding psychological stress measured by SCL-90 scores, the largest group of ‘consistently low’ (n=1172) reported stable, minimal symptoms of around 3 points throughout pregnancy, indicative of low psychological stress. A second, smaller group, ‘moderate and increasing’ (n=65), showed a gradual upward trend in stress symptoms, rising from approximately 9 points at gwk 14 to around 12 points by week 34. Additionally, the ‘high and decreasing’ group (n=51) initially presented with elevated stress symptoms, at around 12 points, but demonstrated significant improvement, with scores dropping to approximately 8 points by week 34 (Figure 18).

5.2.3 PNMS associated with offspring wheezing

In the unadjusted analysis, male sex, lower parental educational level, presence of older siblings, maternal asthma and maternal atopic diseases were associated with offspring with wheezing ever. The EPDS trajectory of ‘consistently high’ (OR 2.93, 95% CI 1.52–5.62) and the SCL-90 trajectory of ‘moderate and increasing’ (OR 1.78, 95% CI 1.00–3.15) were also associated with offspring wheezing ever. The association remained significant after adjustment (aOR 2.74, 95% CI 1.37–5.50 and 1.94, 1.1–3.5, respectively).

5.2.4 PNMS associated with offspring atopic eczema

In the unadjusted analyses, EPDS and SCL-90 trajectories were not associated with eczema. In the adjusted analysis, however, the SCL-90 trajectory of the 'high and decreasing' group was positively associated with atopic eczema (OR 1.89, 95% CI 1.00–3.55).

5.2.5 PNMS associated with offspring non-atopic wheezing

In the supplementary analysis, a four-class variable of wheezing ever and eczema was created to illustrate atopic and non-atopic wheezing phenotypes: wheezing with eczema, eczema without wheezing, wheezing without eczema and neither wheezing nor eczema.

In the unadjusted analysis, the EPDS trajectory of 'consistently high' and the SCL-90 trajectory of 'moderate and increasing' were positively associated with wheezing without eczema (OR 4.40, 95% CI 1.75–7.81 and OR 2.08, 95% CI 1.05–4.14, respectively). Additionally, the 'SCL-90 trajectory of 'high and decreasing' was positively associated with eczema without wheezing (OR 2.19, 95% CI 1.14–4.21). These associations remained significant for all trajectories after adjusting for maternal asthma and/or atopic diseases, parental SES, child's sex and maternal prenatal smoking (Table 5). The results also remained consistent and statistically significant after including maternal EPDS scores at child age 24 months as a confounder.

Table 5. Association of prenatal maternal psychological stress with wheezing and/or atopic eczema at child age 24 months. Modified from Publication II.

	Wheezing with eczema			**Wheezing without eczema**			**Eczema without wheezing**		
	OR	95% CI	*p**	OR	95% CI	P*	OR	95% CI	*p**
Adjusted analyses									
EPDS trajectories									
'Moderate and stable"'	1.21	0.60-2.45	0.59	1.17	0.76-1.81	0.49	1.31	0.92-1.88	0.13
'Low and increasing'	2.72	0.56-13.18	0.21	1.27	0.36-4.48	0.71	0.96	0.31-2.95	0.96
'Consistently high	0.86	0.11-6.80	0.89	3.60	1.63-7.94	**0.002**	1.43	0.58-3.52	0.44
'High and decreasing'	0.64	0.08-4.98	0.67	1.68	0.70-4.00	0.25	1.98	0.97-4.08	0.062
SCL-90 trajectories									
'High and decreasing'	0.71	0.09-5.46	0.74	1.85	0.77-4.44	0.17	2.5	1.28-5.02	**0.008**
'Moderate and increasing'	2.44	0.80-7.34	0.12	2.43	1.21-4.91	**0.013**	1.7	0.89-3.34	0.11

CI, confidence interval; EPDS, Edinburgh Postnatal Depression Scale; OR, odds ratio; SCL-90, Symptom Checklist-90, anxiety scale. The 'consistently low' group was used as reference.
*Indicates comparison with "Neither wheezing nor eczema" as the reference group.

5.3 Association between maternal PNMS and asthma and sensitisation at 5.5 years (Study IV)

5.3.1 Study population and characteristics

The prevalence of atopy, using a cut-off level of 0.70 kU/L, was 29.4% (246/838). Asthma was present in 49 out of 940 children (5.2%), with non-atopic asthma diagnosed in 16 out of 838 (1.9%) and atopic asthma in 49 out of 838 (5.2%). A comparison between included and excluded children revealed no significant differences in maternal or paternal asthma or atopic diseases. However, the median maternal SCL-90 and EPDS scores at gestational weeks 14, 24 and 34 were slightly higher among the excluded children. Additionally, mothers of the included children were older, more highly educated and smoked less during pregnancy. Among children with current asthma, male sex was predominant (66%; p <.001). Maternal atopic diseases and/or asthma were more frequently reported in children with atopy compared to those without atopy (53% vs. 47%; p <.001) and in children with current asthma compared to those without asthma (65% vs. 35%; p <.001). Furthermore, children with atopy had a higher prevalence of maternal atopic diseases. Children with asthma had a significantly higher prevalence of maternal atopic diseases but not maternal asthma.

5.3.2 PNMS associated with offspring atopy

Maternal stress was inversely associated with offspring atopy, but only in the third trimester (Table 6). The two-class variable of SCL-90 at gestational week 34 was associated with lower odds of atopy (aOR 0.68; 95% CI 0.46–0.98; p = .041). Similarly, the three-category SCL-90 variable at gestational week 34 was also associated with reduced odds of atopy (aOR 0.64; 95% CI 0.42–0.97; p = .038). The results were similar with continuous variables of EPDS and SCL-90 and these findings remained consistent when the additional confounder of maternal prenatal smoking was added (Table 6). Depressive symptoms were not associated with atopy (Table 6).

Table 6. Associations with atopy and current asthma at 5.5 years. Modified from Publication IV.

	Atopy total, total N = 838				Current asthma, total N = 940			
Adjusted analyses	**n (%)**	**OR**	**95% CI**	***p***	**n (%)**	**OR**	**95% CI**	***p***
Two-class SCL-90 with the lower 75% as the reference								
at gwk 14 step 1	786 (94)	1.11	.78-1.56	.57	878 (93)	**1.92**	**1.00-3.63**	**.046**
at gwk 14 step 2	786 (94)	1.11	.78-1.56	.57	878 (93)	**1.92**	**1.00-3.63**	**.046**
at gwk 24 step 1	740 (88)	.94	.65-1.35	.74	828 (88)	.96	.43-1.98	.92
at gwk 24 step 2	740 (88)	.94	.65-1.35	.75	828 (88)	.96	.43-1.98	.92
at gwk 34 step 1	720 (86)	**.68**	**.46-.98**	**.041**	803 (85)	**2.61**	**1.26-5.45**	**.010**
at gwk 34 step 2	720 (86)	**.68**	**.46-.99**	**.047**	803 (85)	**2.62**	**1.26-5.47**	**.010**
Three-class SCL-90 with the lowest quartile (25%) as the reference								
at gwk 14 step 1	786 (94)				878 (93)			
Highest quartile (>75%)		1.12	.74-1.71	.58		1.91	.86-4.57	.12
Middle quartiles (25-75%)		1.13	.70-1.51	.58		1.00	.43-2.44	.99
at gwk 14 step 2	786 (94)				878 (93)			
Highest quartile (>75%)		1.13	.74-1.72	.57		1.91	.86-4.57	.12
Middle quartiles (25-75%)		1.03	.70-1.52	.87		1.00	.43-2.44	.99
at gwk 24 step 1	740 (88)				828 (88)			
Highest quartile (>75%)		.86	.58-1.28	.46		1.19	.49-2.82	.69
Middle quartiles (25-75%)		.81	.55-1.20	.30		1.55	.70-3.49	.28
at gwk 24 step 2	740 (88)				828 (88)			
Highest quartile (>75%)		.86	.58-1.28	.47		1.19	.49-2.83	.69
Middle quartiles (25-75%)		.82	.55-1.20	.30		1.56	.70-3.49	.27
at gwk 34 step 1	720 (86)				803 (85)			
Highest quartile (>75%)		**.64**	**.42-.97**	**.038**		**3.27**	**1.31-9.29**	**.016**
Middle quartiles (25-75%)		.90	.61-1.32	.59		1.51	.53-4.56	.44
at gwk 34 step 2	720 (86)				803 (85)			
Highest quartile (>75%)		**.65**	**.42-.98**	**.041**		**3.28**	**1.32-9.31**	**.015**
Middle quartiles (25-75%)		.90	.61-1.32	.59		1.50	.53-4.55	.44
Two-class EPDS with the lower 75% as the reference								
at gwk 14 step 1	786 (94)	1.14	.80-1.60	.54	878 (93)	1.34	.67-2.58	.39
at gwk 14 step 2	786 (94)	1.15	.80-1.62	.99	878 (93)	1.35	.67-2.60	.38
at gwk 24 step 1	741 (88)	.99	.69-1.42	.97	829 (88)	1.34	.64-2.67	.42
at gwk 24 step 2	741 (88)	.99	.69-1.42	.95	829 (88)	1.34	.64-2.68	.42
at gwk 34 step 1	723 (86)	.85	.58-1.23	.38	806 (86)	1.38	.63-2.90	.40
at gwk 34 step 2	723 (86)	.86	.58-1.24	.42	806 (86)	1.39	.63-2.93	.39

Adjusted analyses	Atopy total, total N = 838				Current asthma, total N = 940			
	n (%)	OR	95% CI	*p*	n (%)	OR	95% CI	*p*
Three-class EPDS with the lowest quartile (25%) as the reference								
at gwk 14 step 1	786 (94)				878 (93)			
Highest quartile (>75%)		1.13	.76-1.69	.53		1.04	.49-2.21	.91
Middle quartiles (25-75%)		1.00	.69-1.46	1.0		.59	.26-1.30	.19
at gwk 14 step 2	786 (94)				878 (93)			
Highest quartile (>75%)		1.14	.76-1.71	.51		1.05	.49-2.23	.90
Middle quartiles (25-75%)		1.00	.69-1.46	.99		.59	.26-1.30	.19
at gwk 24 step 1	741 (88)				878 (93)			
Highest quartile (>75%)		1.01	.67-1.52	.96		.96	.43-2.04	.91
Middle quartiles (25-75%)		1.04	.71-1.52	.83		.96	.43-1.02	.91
at gwk 24 step 2	741 (88)				878 (93)			
Highest quartile (>75%)		1.02	.67-1.53	.94		.96	.43-2.05	.91
Middle quartiles (25-75%)		1.15	.72-1.53	.81		.45	.18-1.03	.07
at gwk 34 step 1	723 (86)				806 (86)			
Highest quartile (>75%)		.75	.48-1.16	.20		**2.70**	**.90-9.94**	**.01**
Middle quartiles (25-75%)		.81	.55-1.21	.30		2.51	.91-8.85	.10
at gwk 34 step 2	723 (86)				806 (86)			
Highest quartile (>75%)		.75	.48-1.18	.21		2.73	.91-10	.09
Middle quartiles (25-75%)		.81	.55-1.21	.30		2.51	.91-8.85	.10

CI, confidence interval; EPDS, Edinburgh Postnatal Depression Scale; gwk, gestational week; IQR, interquartile range; n (%), number and percentage of children included in the analysis from the total number; OR, odds ratio; SCL-90: Symptom Checklist-90, anxiety scale.

All models were adjusted stepwise: Step 1 adjustments were the family's highest educational level, maternal history of asthma and/or allergies and child's sex; in step 2, maternal smoking during gestation was added. In analyses with two- and three-class variables, the lowest class was the reference class. p <.05 in bold.

5.3.3 PNMS associated with offspring asthma

Maternal anxiety was associated with offspring current asthma during the first and third trimesters. The two-class variable of SCL-90 at gwk 14 (aOR 1.92; 95% CI 1.00–3.63; p = .046) and at gestational week 34 (aOR 2.61; 95% CI 1.26–5.45; p = .010) was significantly associated with current asthma. Similarly, the three-class variable of SCL-90 at gwk 34 showed a strong association with current asthma (aOR 3.27; 95% CI 1.31–9.29; p = .016). These associations remained unchanged with an additional confounder of maternal prenatal smoking (Table 7). Depressive symptoms were not associated with current asthma (Table 7).

5.3.4 PNMS associated with offspring non-atopic asthma

Maternal anxiety influenced the odds of non-atopic asthma, particularly during the first and third trimesters. In step 1, using continuous symptom scores, the odds of non-atopic asthma increased by 11% per SCL-90 point in the third trimester (aOR 1.11; 95% CI 1.00–1.21; p = .030). The highest quartile of the two-class variable of SCL-90 at gwk 14 (aOR 3.80; 95% CI 1.32–11.7; p = .014) and at gwk 34 (aOR 3.49; 95% CI 1.12–11.9; p = .034) was significantly associated with non-atopic asthma in step 1. These associations remained unchanged in step 2. Depressive symptoms, assessed using EPDS scores, showed no significant associations with non-atopic asthma.

For atopic asthma, the odds increased by 14% per SCL-90 point in the third trimester (aOR 1.14; 95% CI 1.01–1.28; p = .031) when using continuous symptom scores in step 1. Step 2 analyses, however, which included adjustments for maternal smoking during pregnancy, were deemed inappropriate due to insufficient sample size. The two-class variable of SCL-90 during gestation was not significantly associated with atopic asthma. Similarly, depressive symptoms, analysed using the same variables, showed no significant associations (Table 7).

Table 7. Associations with non-atopic and atopic asthma at 5.5 years. Modified from Publication IV.

	Non-atopic asthma, total N = 592				Atopic asthma, total N = 246			
	n (%)	OR	95% CI	*p*	n (%)	OR	95% CI	*p*
Two-class SCL-90 with the lower 75% as the reference								
at gwk 14 step 1	558 (94)	**3.80**	**1.32-12**	**.014**	228 (93)	1.31	.50-3.25	.56
at gwk 14 step 2	558 (94)	**3.90**	**1.35-12**	**.013**	228 (93)	1.37	.52-3.42	.51
at gwk 24 step 1	528 (89)	1.13	.29-3.73	.84	212 (86)	.79	.25-2.14	.66
at gwk 24 step 2	528 (89)	1.08	.28-3.61	.90	212 (86)	.76	.24-2.07	.61
at gwk 34 step 1	516 (87)	**3.49**	**1.12-12**	**.034**	204 (83)	2.57	.85-7.48	.08
at gwk 34 step 2	516 (87)	**3.47**	**1.11-12**	**.035**	204 (83)	2.91	.95-8.73	.06
Two-class EPDS with the lower 75% as the reference								
at gwk 14 step 1	559 (94)	1.63	.53-4.67	.37	227 (92)	1.30	.50-3.17	.58
at gwk 14 step 2	559 (94)	1.55	.50-4.49	.42	227 (92)	1.36	.52-3.36	.51
at gwk 24 step 1	529 (89)	3.02	.97-9.66	.053	212 (86)	.59	.16-1.71	.37
at gwk 24 step 2	529 (89)	2.96	.95-9.50	.06	212 (86)	.61	.17-1.78	.41
at gwk 34 step 1	518 (88)	1.53	.44-4.79	.48	205 (83)	1.80	.58-5.10	.28
at gwk 34 step 2	518 (88)	1.47	.42-4.68	.52	205 (83)	1.81	.58-5.18	.28

CI, confidence interval; EPDS, Edinburgh Postnatal Depression Scale; gwk, gestational week; IQR, interquartile range; n (%), number and percentage of children included in the analysis from the total number; OR, odds ratio; SCL-90: Symptom Checklist-90, anxiety scale.
All models were adjusted stepwise: step 1 adjustments were the family's highest educational level, maternal history of asthma and/or allergies and sex of the child; in step 2 maternal smoking during gestation was added. In analyses with two- and three-class variables, the lowest class was the reference class. *P* <.05 in bold.

5.4 Association between paternal adverse childhood experiences and offspring sensitisation and allergic rhinitis at 5.5 years of age. (Study III)

5.4.1 Study population and characteristics

The study population included 590 father–child dyads after excluding participants with missing data on the exposure variable of paternal TADS or the outcome variable of allergic rhinitis. The number of participants included in each model is detailed in the flowchart (Figure 14).

The prevalence of significant sensitisation of the offspring at the age of 5.5 years was 30% (162/533) for moderate sensitisation 38% (206/533) and 21% for allergic rhinoconjunctivitis (122/590). For all included fathers the median of TADS was 17 (IQR 11–27). Maternal atopic diseases were strongly associated with an increased odds of both sensitisation and allergic rhinitis in offspring, whereas paternal atopic diseases were only linked to increased odds of allergic rhinitis. Additionally, parental education level and paternal smoking showed no significant association with offspring outcomes, and factors such as maternal smoking during pregnancy, the number of older siblings and the child's sex did not exhibit consistent significant associations.

5.4.2 PNMS associated with offspring sensitisation

In the unadjusted analysis, the two highest quartiles of paternal TADS were negatively associated with significant sensitisation in offspring. Moderate sensitisation in offspring was not associated with paternal TADS. Only maternal atopic diseases were associated with increased odds of offspring sensitisation.

In the multivariable analysis (Model 1), in addition to the associations observed the unadjusted analyses, the highest quartile of paternal TADS was negatively associated with moderate offspring sensitisation and allergic rhinitis. When paternal atopic diseases were included as a confounder in Model 2, also the third highest quartile of paternal TADS became significantly associated with moderate offspring sensitisation, with all previous associations remaining as well. In Models 3 and 4, the highest quartiles of paternal TADS were associated with both sensitisation categories, but other associations were lost. These associations remained with both paternal education level and number of older siblings as a covariate in Model 5 (Table 8). In supplementary analyses, the relationship between the highest quartile of TADS and sensitisation (>0.7 IU/L) remained after adjusting for covariates of

maternal TADS, area of residence (city or rural) and population density (under of over 100 people/km^2).

5.4.3 PNMS associated with offspring allergic rhinitis

In the unadjusted analyses, paternal TADS, whether treated as a continuous or categorical variable, was not associated with offspring allergic rhinitis. However, in Models 1–3 and 5, the highest quartile of paternal TADS was inversely associated with offspring allergic rhinitis (Table 8).

Table 8. Association of paternal TADS and offspring sensitisation and allergic rhinitis. Modified From Publication III.

	Sensitisation, cut-off 0.35 kU/L (n = 533)			Sensitisation, cut-off 0.70 kU/L (n = 533)			Allergic rhinitis (n = 590)		
Exposures	**OR**	**95% CI**	***P****	**OR**	**95% CI**	***P****	**OR**	**95% CI**	***P****
Adjusted analyses									
Model 1*:									
Paternal TADS between 0 and 18 years of life, quartiles									
• **< 11 points**		ref			ref			ref	
• **11–17 points**	0.62	0.37-1.0	0.074	0.61	0.36-1.1	0.078	0.91	0.51-1.6	0.74
• **18–27 points**	0.83	0.50-1.4	0.48	**0.58**	**0.34-0.99**	**0.045**	0.70	0.39-1.3	0.24
• **> 27 points**	**0.49**	**0.29-0.84**	**0.009**	**0.42**	**0.24-0.75**	**0.003**	0.55	0.30-1.0	0.053
Model 2:**									
Paternal TADS between 0 and 18 years of life, quartiles									
• **< 11 points**		ref			ref			ref	
• **11–17 points**	**0.59**	**0.35-1.0**	**0.055**	0.59	0.34-1.0	0.058	0.93	0.52-1.7	0.81
• **18–27 points**	0.82	0.49-1.4	0.44	**0.57**	**0.33-0.98**	**0.040**	0.69	0.38-1.3	0.23
• **> 27 points**	**0.48**	**0.28-0.82**	**0.007**	**0.41**	**0.23-0.73**	**0.002**	**0.52**	**0.28-0.97**	**0.040**
Model 3*:**									
Paternal TADS between 0 and 18 years of life, quartiles									
• **< 11 points**		ref			ref			ref	
• **11–17 points**	0.64	0.38-1.1	0.096	0.63	0.37-1.1	0.10	0.95	0.53-1.7	0.86
• **18–27 points**	0.87	0.52-1.5	0.60	0.61	0.36-1.1	0.079	0.75	0.42-1.4	0.75
• **> 27 points**	**0.51**	**0.30-0.88**	**0.015**	**0.45**	**0.25-0.80**	**0.006**	0.60	0.32-1.1	0.099

Exposures	Sensitisation, cut-off 0.35 kU/L (n = 533)			Sensitisation, cut-off 0.70 kU/L (n = 533)			Allergic rhinitis (n = 590)		
	OR	**95% CI**	***P****	**OR**	**95% CI**	***P****	**OR**	**95% CI**	***P****
Model 4**:**									
Paternal TADS between 0 and 18 years of life, quartiles									
• **< 11 points**		ref			ref			ref	
• **11–17 points**	0.68	0.40-1.2	0.16	0.68	0.40-1.2	0.17	1.0	0.54-1.8	1.0
• **18–27 points**	0.88	0.50-1.5	0.65	0.57	0.31-1.0	0.060	0.76	.040-1.4	0.40
• **> 27 points**	**0.48**	**0.26-0.88**	**0.018**	**0.38**	**0.20-0.074**	**0.004**	**0.44**	**0.21-0.89**	**0.022**
Model 5***:**									
Paternal TADS between 0 and 18 years of life, quartiles									
• **< 11 points**		ref			ref			ref	
• **11–17 points**	0.66	.038-1.2	0.15	0.65	0.36-1.1	0.13	1.1	0.58-2.0	0.80
• **18–27 points**	0.96	0.55-1.7	0.88	0.65	0.36-1.2	0.15	0.83	0.43-1.6	0.57
• **> 27 points**	**0.47**	**0.26-0.86**	**0.014**	**0.39**	**0.20-0.74**	**0.004**	**0.46**	**0.22-0.96**	**0.038**

CI, confidence interval; EPDS, Edinburgh Postnatal Depression Scale; gwks, gestational weeks; IQR, interquartile range; OR, odds ratio; TADS, Trauma and Distress Scale.

*Model 1 adjusted for maternal atopic diseases and maternal EPDS score at pregnancy week 34

**Model 2 adjusted for * and paternal atopic diseases

***Model 3 adjusted for * and parental educational years

****Model 4 adjusted for * and number of siblings

*****Model 5 adjusted for **, parental educational years and number of siblings

6 Discussion

The aim of this thesis was primarily to examine the relationship of maternal symptoms of prenatal psychological stress and offspring atopic diseases. Secondly, the aim was to explore the associations of paternal adverse childhood experiences with offspring atopy. This thesis reinforces prior evidence on the link between PNMS and atopic diseases, particularly in food allergies, wheezing, asthma and atopic eczema (Studies I, II, IV). However, contrary to previous studies, our findings also indicate that early gestational exposure may be a sensitive period, providing new insight into the late-gestation sensitivity hypothesis. Paternal ACEs and offspring atopy had not been previously studied in this context, making this thesis a novel contribution to understanding parental influences on offspring health (Study III).

The link between PNMS and offspring atopic diseases, particularly asthma, is well supported by existing research. Studies suggest that prenatal psychological stress increases the risk of asthma and atopic eczema; however, evidence regarding allergic rhinitis, food allergy and sensitisation remains partly inconclusive. These studies reported either positive associations or no associations (Tables 1-4), except for papers by Wood et al. (2011) and Ramratnam et al. (2021). They reported a reduced sensitisation towards a few common allergens if exposed to prenatal maternal depressive (Ramratnam et al., 2021; Wood et al., 2011) symptoms and perceived stress (Ramratnam et al., 2021). However, these results align with the results from Study IV. In this study, maternal anxiety and depressive symptoms were inversely associated with offspring sensitisation at 5.5 years.

PNMS was assessed at three timepoints, enabling the evaluation of timing as well as severity, whereas most previous studies have not used such rigorous assessment. Many of the studies included in the literature review examined PNMS at only a single timepoint during pregnancy, often without a clearly defined time frame, making interpretation impossible. There is some preliminary evidence of late gestation being a particularly sensitive period for PNMS exposure in relation to atopic diseases in offspring, but no clear understanding of the subject exists (Tables 1-4). The findings of this thesis corroborate these finding but further suggest that early gestation may represent a sensitive timeframe during which PNMS can affect

offspring development, potentially altering the risk of atopic diseases later in life. Moreover, chronic versus short-term PNMS seems to impact the disease risk more significantly, contributing to the idea of cumulative exposure. While PNMS in late pregnancy seems to be an especially sensitive period, it is possible that it only represented chronic and cumulative exposure, overestimating the effect of late pregnancy *per se* (Brew et al., 2018, Rosa et al., 2018). It could also be proposed that risk does not increase linearly but levels off after a critical threshold has been reached, or the increase in risk is more subtle. However, the studies within this thesis did observe did a dose-dependent increase in risk, which could be explained by the inclusion of mothers with relatively low levels of symptomatic symptoms.

The type of PNMS exposure and offspring outcomes have been widely heterogeneous across published studies, with only a few using objective outcomes of atopic diseases. The exposures have included stress, depression, anxiety, hardships, bereavement, job stress, financial difficulties, negative life events, psychiatric diagnosis, pregnancy related anxiety, demoralisation, antidepressant use, exposure to community violence and hardships (Tables 1-4). Most studies relied on mother- or parent-reported, though physician-diagnosed, outcomes without employing unequivocal, objective measures of the offspring disease history. Reporting bias could distort the results when using parent-reported offspring outcomes if parents fail to report the outcomes objectively, although the diagnosis was supposed to have been made by a physician. The considerable heterogeneity of the exposures, as well as outcomes, limits the generalisability of findings and could partly explain the varying results across studies. In addition, it is likely that some stress exposure does not elicit similar maternal activation of the HPA axis or other neuroimmune responses and may not, therefore, affect the developing foetus similarly. Despite these restrictions, the link between PNMS and offspring asthma and atopic eczema is quite well established, whereas other atopic diseases warrant further research. Studies I, II and IV offered new insights into the sensitive periods of PNMS exposure and offspring food allergy, sensitisation, atopic eczema, wheezing and asthma. Although the evidence on PNMS, asthma and wheezing is quite substantial, asthma and wheezing phenotypes are less reported, with only a few studies having examined atopic and non-atopic asthma district outcomes. This gap in the literature underscores the rationale behind Study IV. Dividing wheezing and asthma into atopic and non-atopic phenotypes offers a valuable perspective, as these forms of the disease differ in both their immunological profiles and associated risk factors. Atopic asthma is typically linked to IgE-mediated allergic sensitisation and a Th2-dominant immune response, whereas non-atopic asthma is more often associated with non-allergic inflammation, such as neutrophilic pathways. Exploring the association between prenatal PNMS and these distinct asthma phenotypes may help clarify whether stress influences asthma development through shared or

differing biological mechanisms. While food allergy, wheezing, asthma, atopic eczema, allergic rhinitis and sensitisation all fall within the disease group of allergic diseases, they all have district pathophysiology with their own characteristic immunological pathways and differing risk factors. In addition, only some phenotypes of these diseases are truly atopic, with predominant Th2 immune responses. It is therefore understandable that PNMS does not affect the disease risk similarly or with the same magnitude.

In contrast to PNMS and atopic diseases, the link between paternal ACEs and offspring atopic diseases remains underexplored. To date, only one study by Brew et al. (2022) has shown a trend toward a lowered incidence of atopic diseases if the father had experienced the bereavement of a parent during childhood. The results from Study III align with this finding and show an inverse association of paternal ACEs and offspring allergic rhinitis and sensitisation at child age 5.5 years. Further research on the topic is warranted, as all hypotheses regarding possible mediating mechanisms are completely speculative.

6.1 Maternal prenatal anxiety and depressive symptoms and offspring food allergy

In Study I, the association between maternal prenatal depressive and anxiety symptoms and offspring food allergy/intolerance at 6 months of age was examined. Symptom trajectories were constructed to assess the effect of timing and severity of symptoms on the outcome of offspring food allergy. Our findings support the idea that chronic maternal PNMS symptoms predispose offspring to infant food allergy, while the exact mechanisms are unknown.

Paediatric food allergies can manifest through various symptoms affecting both the intestinal tract and the skin. Symptoms can include gastrointestinal issues such as vomiting, diarrhoea and abdominal pain, as well as cutaneous symptoms like eczema and hives. These manifestations are caused by immune responses to allergens introduced through food and consist predominantly of IgE-mediated and non-IgE-mediated mechanisms. Skin symptoms often result from IgE-mediated allergic reactions, while gastrointestinal tract symptoms can involve both IgE and non-IgE-mediated mechanisms (Calvani et al., 2020). For this reason, in this study, specific symptoms were evaluated in detail via a telephone interview. The detailed characterisation of symptoms endorsed the reliability of the diagnosis, as parents could be asked simultaneously whether the diagnosis had been confirmed through an oral food challenge. Allergen-specific IgE testing was not performed, as it is common for the test to yield false negative results in young children (Incorvaia et al., 2013) and is not suitable for assessing allergies involving gastrointestinal symptoms (Sicherer & Sampson, 2018).

The prevalence of food allergy reported in Study I is consistent with previous literature. Roughly 2.3% of infants were reported to have physician-diagnosed food allergies at 6 months of age, which is slightly lower than the prevalence rates reported for paediatric food allergy (Soriano et al., 2024). However, it is likely that a significant incidence of food allergy would follow the introduction of cow's milk, for example, which many infants at 6 months of age have not yet been exposed to.

Previous studies suggest that the third trimester is a particularly sensitive period during which maternal psychological stress may increase the risk of atopic diseases in offspring (Flanigan et al., 2018). This observation was supported by the findings of Study I, as depressive symptoms in both the first and third trimesters were particularly associated with infant food allergy. This indicates that early and late pregnancy could be critical periods during which maternal psychological well-being can influence the development of child's immune system.

The findings from Study I align with existing literature on the association between maternal prenatal psychological stress and food allergies.

6.2 Maternal prenatal anxiety and depressive symptoms and offspring wheezing and asthma

Study II examined the association between PNMS and the odds of wheezing and eczema in offspring at 24 months of age. Study IV investigated the relationship between PNMS and offspring asthma, including asthma phenotypes, at 5.5 years of age. Anxiety and depressive symptoms were evaluated using EPDS and SCL-90 (anxiety subscale) at three timepoints during pregnancy. Consistent with prior research, our findings suggest a significant link between PNMS and offspring wheeze and later asthma (Flanigan et al., 2018). The prevalence of wheezing (17%) and current asthma (5.2%) were slightly lower in the study populations, as reported previously, indicating a possible sampling bias (Akinbami et al., 2016; Patel et al., 2008). However, the definition of current asthma requires the use of inhaled corticosteroids and visits to physicians within the last year and could explain why the prevalence was lower than expected.

The findings of Study II demonstrate that chronically elevated PNMS throughout gestation is significantly associated with increased odds of both wheezing and eczema in children. Using latent growth curve modelling, the chronicity and severity of maternal PNMS symptoms was assessed at three distinct timepoints during pregnancy spanning from 14 to 34 weeks. Symptom trajectories of PNMS were constructed to illustrate the chronicity and severity of symptoms during pregnancy. Anxiety symptoms were both associated with increased odds of wheezing as well as eczema, while depressive symptoms throughout pregnancy were associated with wheezing. Additionally, in supplementary analyses, non-atopic

wheezing was associated only with depressive symptoms. This finding was previously reported by Ramratnam et al. (2021) and aligns with the findings of Study II. However, it is important to note that the small sample sizes within the wheezing phenotype subgroups limit the reliability of the results.

The finding of PNMS and offspring asthma, likewise, is supported by previous studies (S. Chen & Chen, 2021). Asthma was further categorised into atopic and non-atopic subtypes by stratifying for atopy. Atopy was classified with a cut-off value of 0.70 kU/L for IgE levels to common allergens. This classification enabled the exploration of nuanced differences in how PNMS impacts atopic and non-atopic asthma. As reported by Ramnatnan et al. (2021), it is possible that PNMS predisposes offspring to the non-atopic endotype of wheezing and asthma, not through the dysfunctional shift in Th2/Th1 balance of characteristic atopic asthma, but rather other immunological factors and changes in the respiratory system. Impaired lung development and a shift towards airway inflammation has been observed in animal studies supporting this theory (Pincus-Knackstedt et al., 2006; Zazara et al., 2018).

The analyses in Studies II and IV considered known risk factors such as maternal atopic diseases and asthma, maternal smoking during pregnancy, parental educational level, and child's sex. The observed associations persisted after adjusting for covariates, indicating that the relationships are more likely to be driven by maternal PNMS exposure itself. However, residual confounding cannot be entirely excluded.

In conclusion, Studies II and IV contribute to the growing body of evidence linking maternal psychological stress during pregnancy with adverse health outcomes in offspring.

6.3 Maternal prenatal anxiety and depressive symptoms and offspring atopic eczema

The association between PNMS and offspring atopic eczema at 24 months was investigated in Study II. PNMS was evaluated as depressive and anxiety symptoms throughout the pregnancy. The symptoms were assessed using the EPDS and SCL-90 (anxiety subscale) questionnaires. The chronicity and severity of symptoms were analysed using latent growth mixture modelling. Maternal depressive symptoms were not significantly associated with offspring atopic eczema after adjusting for confounding factors. However, there was a modest association between high maternal anxiety and atopic eczema in early pregnancy. The results are generally in line with previous studies, although results from several studies have been somewhat mixed, with some reporting an association between PNMS and offspring atopic eczema and others failing to do so (Table 2). As discussed previously, the

heterogeneous definitions of atopic eczema and the potential for reporting bias could account for these discrepancies.

Previous studies have proposed potential mechanisms, with a leading hypothesis suggesting that PNMS may exert programming effects on the offspring's immune system and skin barrier function. The mechanisms are multifactorial and complex, with no clear understanding of causal effects following exposure to PNMS (Glover, 2015; Molenaar et al., 2019; O'Connor et al., 2020). Maternal factors during pregnancy have been reported to influence the skin barrier function of the offspring (Vaughn et al., 2017) and PNMS has been linked to epigenetic alterations in the filaggrin gene, which is crucial to maintaining skin barrier integrity (DeVries et al., 2017). Despite these advances, the mediating factors and mechanisms behind PNMS and atopic eczema remain poorly understood.

A limitation of the study is the relatively small sample size within some PNMS trajectory subgroups, resulting in limited statistical power to detect associations with eczema, particularly in supplementary analyses. The analyses were adjusted for maternal asthma and/or atopic diseases, child's sex and maternal smoking during pregnancy. The size of the study population did not allow for additional covariates, which could have helped better to control for residual confounding. However, the most important risk factors were accounted for.

The findings of this study suggest that prenatal maternal psychological stress, particularly chronic anxiety, may have a role in the development of atopic eczema. There has been some discrepancy in the results regarding PNMS and atopic eczema, which could in part be explained by varying study population as well as exposure and outcome definitions. The largest body of studies have reported positive associations, and the results of Study II align with these.

6.4 Maternal prenatal anxiety and depressive symptoms and offspring allergic rhinitis and sensitisation

Studies on PNMS and its association with offspring allergic rhinitis and sensitisation are relatively scarce. In this thesis, PNMS was not assessed in relation to allergic rhinitis, but only in relation to sensitisation to common allergens at 5.5 years (Study IV).

Six previous studies have reported a positive association of PNMS with offspring allergic rhinitis. Three studies examining sensitisation to allergens and one study with mother-reported allergic rhinitis as an outcome did not find significant associations (Table 4). Interestingly, one study by Ramratnam et al. (2017) found a negative association between skin prick ratios and maternal prenatal depression and perceived stress. These findings align with the results of Study IV and with the study

by Wood et al. (2011) indicating an inverse relationship between PNMS and offspring sensitisation. One hypothetical explanation for the discrepancy between clinical allergic rhinitis and absence of sensitisation could be the higher incidence of local allergic rhinitis without the presence of systemic atopy indicators. Local allergic rhinitis is thought to be relatively common in children (Colavita et al., 2017). The differences in exposures, outcomes and the timing of both also account for the reported differences. Some studies have assessed clinical allergic rhinitis in children aged 12–18 months, a stage at which allergic rhinitis is relatively uncommon, increasing the likelihood that rhinitis symptoms could have been misdiagnosed as allergy (Kulig et al., 2000).

6.5 Paternal childhood adverse experiences and offspring sensitisation and allergic rhinitis

Study III investigated the association between paternal ACEs and the odds of allergic rhinitis and sensitisation in offspring at age 5.5 years. Unexpectedly, paternal ACEs were found to be inversely associated with offspring sensitisation and allergic rhinitis. Children whose fathers scored in the highest quartile on the TADS had the lowest odds of sensitisation and allergic rhinitis. These findings suggest that paternal ACEs may influence offspring immune system development in ways that reduce the likelihood of sensitisation, potentially mediated by epigenetic mechanisms.

The existing literature has focused primarily on maternal ACEs and their intergenerational impacts, with relatively little attention given to paternal influences. A study by Brew et al. (2022), however, demonstrated associations between paternal childhood bereavement and an increased risk of autoimmune diseases in offspring. While autoimmune and atopic diseases represent distinct immune dysregulations, autoimmune diseases are characterised by a shift to Th1-predominant immune responses, whereas atopic diseases are often driven by Th2, intertwining autoimmune and atopic diseases to a degree. There is limited evidence of paternal ACEs and offspring health outcomes and no previous studies on atopic diseases. However, some studies have reported ACEs inducing epigenetic modifications in paternal sperm, including changes in DNA methylation and chromatin architecture, which could influence immune programming in offspring (Condon et al., 2022; Merrill et al., 2021; Müller & Kenney, 2024; Tuulari et al., 2025). These mechanisms may explain why this study found that paternal ACEs could unexpectedly confer a protective effect against sensitisation in offspring. One possible, hypothetical explanation could be that fathers with high ACEs scores may have developed resilience mechanisms that contribute to offspring health through parenting behaviours, environmental factors or epigenetic modifications. However, alternative

explanations, such as selection bias in paternal ACEs reporting or residual confounding by socioeconomic factors, must be considered.

Extensive steps were taken to account for potential confounding variables, including parental atopic history, educational level, maternal depressive symptoms in late gestation, and number of siblings in the household. Additional models adjusted for maternal ACEs and population density to address residual confounding. The main outcome of sensitisation was the objective levels of IgE, reducing reliance on self-reported data. The stratification of sensitisation outcomes by food and aeroallergens provided nuanced insights into the specific effects of paternal ACEs.

Nevertheless, several limitations warrant consideration. As an observational study, it cannot establish causality, and while epigenetic pathways are hypothesised, these mechanisms were not directly examined. The reliance on self-reported TADS scores for assessing paternal ACEs introduces the possibility of recall bias, which may affect the accuracy of the data. Additionally, attrition bias is a possible concern, as fathers with higher ACEs scores may have been underrepresented in the study due to difficulties in participation. The association could be entirely explained with other than epigenetic or other direct mechanisms and causality cannot be presumed.

The results align with previous research suggesting that paternal early-life environment and experiences can have an impact on offspring health, yet there are no previous studies on offspring atopic diseases. This contrasts with studies linking ACEs to higher atopic risks, particularly through maternal exposure, yet it provides direct insight into the intergenerational aspect of heritage without the gestational period inseparably linked to maternal exposures. This growing body of research emphasises the importance of distinguishing between the maternal and paternal contribution to intergenerational health outcomes that can also arise from parental stress exposures.

These findings challenge conventional assumptions that ACEs universally increase health risks across generations, and highlight the need for further research into the biological mechanisms underlying these associations. Future studies should investigate sperm epigenetics to eventually better understand how paternal ACEs influence offspring immune development. Longitudinal research is also needed to determine whether the observed protective effects against sensitisation persist into later childhood and adulthood.

6.6 Strengths and limitations

The strengths and limitations of the studies should be considered when interpreting the results.

Their key strength is that they derive their data from a large birth cohort study. However, this also introduces also some of the limitations. During the follow-up

period, participant dropout was more common among parents with lower educational attainment, who also experienced more psychological symptoms at the early follow-up timepoints (Karlsson et al., 2018). The study population is from a restricted area in Finland. This can lead to an incline within the study population and somewhat limit the generalisability of the findings. However, the use of a population-based rather than a risk-based cohort enhances the generalisability of the results. Similarly, the scoring distributions for the SCL-90, EPDS and TADS are concentrated toward the lower spectrum for healthy individuals, who tend to score relatively low on the questionnaires and are slightly overrepresented. This may be due to the unintended exclusion of participants with missing data, who tended to have higher scores on average for PNMS and ACEs. A key strength of this thesis is the repeated PNMS assessments across pregnancy, enabling a more granular analysis of sensitive exposure windows. Unlike many previous studies that rely on a single measurement, this approach allows for more detailed and precise measurement of stress exposure patterns.

The main limitation across Studies I–IV lies in the reliance on self-reported data. The exposures and most of the covariates were self-reported through questionnaires and interviews. Parental anxiety and depressive symptoms, as well as paternal ACEs, were assessed using validated questionnaires (Bergink et al., 2011; Holi et al., 1998; Salokangas et al., 2016). Outcomes were mainly physician-diagnosed and parent-reported, omitting objective levels of offspring IgE in Study III. All questions regarding a family history of atopic diseases and outcomes of offspring atopic diseases were based on the validated and widely used ISAAC questionnaire (Asher et al., 2006). The use of self-reported data leaves the validity of the data vulnerable to recalling and reporting biases. To enhance the validity of the infant food allergy outcome in Study I, the author of this thesis contacted each family that reported infant food allergy/intolerance and confirmed whether the diagnosis had been made by a physician following an oral food challenge, as well as the specific symptoms triggered by the allergen. In Studies III and IV, mothers were interviewed by study paediatricians regarding the outcomes of child asthma and allergic rhinitis. While paternal ACEs between the ages of 0 and 18 years are especially susceptible to recall bias, this limitation is inherent to the study design of this thesis given the limited follow-up period.

In this thesis, PNMS was defined as symptoms of depression and anxiety, assessed using the validated EPDS and SCL-90 questionnaires. Although the EPDS questionnaire was originally developed for screening for postnatal depression, it has since been validated and widely accepted as a valid tool for screening for depression outside the postnatal period as well (Cox et al., 1996). The median symptom scores were relatively low across Studies I, II and IV, while Study III did not use these exposures. Some attrition related to poorer psychological health likely contributed

to lower scores. However, subclinical levels of psychological symptoms are common among pregnant women (Korja et al., 2018), making the low median scores of EPDS and SCL-90 still relevant for understanding broader population-level effects (Holi et al., 1998; Matijasevich et al., 2014). This suggests that the psychological profiles of the participants are acceptably representative and do not significantly hinder the generalisability of the findings. However, the included mothers were more educated and smoked less, which could mean that their children were at lower risk of atopic diseases altogether.

The strengths of the studies include a large study population and the assessment of PNMS throughout pregnancy. This enabled the construction of symptom trajectories and allowed for the analysis of especially sensitive timepoints. Studies I, II and IV utilised the SCL-90 and EPDS questionnaires to assess maternal psychological stress. In Studies I and II, this enabled the creation of symptom trajectories, a novel approach that supports previous literature suggesting that late gestation is particularly sensitive for the development of atopic diseases in offspring following PNMS exposure (Flanigan et al., 2018; Van De Loo et al., 2016; J. Zhou et al., 2024).

Although atopic diseases are common, the number of children with specific diseases in each study remained moderate. When adjusting for confounders and creating subgroups of atopic and non-atopic children, for example, the study population dropped significantly within the subgroup analyses, partly due to the use of symptom trajectories, which resulted in multiple exposure groups. This forced us to exclude some desired confounders from the main analysis; however, they were included in the supplementary analyses in Study II. Despite efforts to adjust for known risk factors, it is likely that some relevant confounders or mediators were not fully accounted for. Some cofactors of smaller significance were undoubtedly omitted due to a lack of available data within the birth cohort, but they would most likely been excluded regardless for the same reasons described previously. Some cofactors known to be risk factors for atopic diseases include air pollution, pet ownership and duration of breastfeeding (Collin et al., 2015; Koukou et al., 2023; Ziou et al., 2023). Impaired parental care during the postnatal period, resulting from poorer psychological well-being, could represent an additional confounder in studies focusing solely on prenatal factors. Postnatal psychological symptoms have, for example, been associated with an increased risk of offspring asthma. However, the often significant correlation between prenatal and postnatal psychological symptoms complicates model adjustments for these factors (Jia et al., 2024; Wright et al., 2004).

The relationship between prenatal psychological stress and atopic diseases is complex and likely influenced by multiple interacting factors. Stress may act both as an independent risk factor and as a modifier of other exposures. For instance, stress could alter immune function directly, but it may also increase susceptibility to

environmental influences such as air pollution or reactions to environmental microbes. In addition, it is possible that some environmental or behavioural factors may mediate or confound the relationship between stress and atopic outcomes. Poorer psychological well-being may, for example, increase the likelihood of smoking, which in turn can affect the child's risk of developing atopic diseases.

Lastly, although the original cohort was large, attrition over time reduced the number of participants with complete follow-up data. This further constrained the ability to include a wider set of covariates without compromising statistical power. Therefore, while the aim was to adjust for the most relevant and available confounders, residual confounding cannot be fully excluded. A more comprehensive understanding of the interplay between psychological stress and other established risk factors still requires further investigation.

Another limitation of the studies included in this thesis relates to conclusions drawn from the results. Due to the nature of the research, mechanisms underlying the observed associations cannot be determined, and only associations can be reported. The hypotheses drawn from existing literature may offer potential explanations for these relationships, but further research is needed to investigate the underlying mechanisms in more detail.

6.7 Mechanistic considerations

The following section explores the mechanistic pathways through which PNMS and paternal ACEs could influence offspring immune function, highlighting the roles of HPA axis dysregulation, immune alterations and epigenetic modifications.

6.7.1 Prenatal maternal psychological stress

PNMS has been implicated in shaping offspring immune function and increasing the risk of atopic diseases. The underlying mechanisms connecting PNMS to allergic disease susceptibility are complex and involve multiple biological pathways, including neuroendocrine, immune, epigenetic and microbiome-related processes. The placenta plays a dynamic and bidirectional role at the maternal-foetal interface, serving as a key mediator of maternal stress responses and potentially influencing foetal immune development.

One of the most studied pathways linking PNMS to offspring atopic diseases is the HPA axis. Psychological stress leads to HPA axis activation, increasing glucocorticoid secretion and triggering neuroimmune changes, including elevated pro-inflammatory immune responses (Ruffaner-Hanson et al., 2022; Ulrich-Lai & Herman, 2009). Sustained maternal glucocorticoid exposure can impair the function of placental 11β-HSD2, reducing its ability to inactivate maternal cortisol (Peña et

al., 2012). As a result, the foetus is exposed to elevated glucocorticoids, potentially impacting immune system maturation and increasing susceptibility to atopic diseases (Bronson & Bale, 2015; Welberg et al., 2005). Animal studies indicate that excessive prenatal cortisol exposure suppresses Th1 responses while promoting a Th2-skewed immune profile (Pincus-Knackstedt et al., 2006). Th2 predominance is strongly associated with atopic diseases such as asthma and allergic rhinitis (Hammad & Lambrecht, 2021; Mackay et al., 2001). PNMS has been linked to impaired HPA axis function of the offspring and altered corticosteroid profiles (Entringer et al., 2008; Molenaar et al., 2019; O'Donnell et al., 2009; Veru et al., 2014; Wright et al., 2010).

Th2-skewed immune response is a widely accepted paradigm in atopic diseases, where a bias towards Th2-associated cytokines promotes IgE production and eosinophilic inflammation, contributing to conditions such as asthma, allergic rhinitis and eczema (Hammad & Lambrecht, 2021). This aligns with findings linking maternal stress to increased levels of Th2 predominant cytokines in cord blood and reinforces the theory that atopy would be the link between PNMS and the witnessed increase of atopic disease. It has been thought that PNMS causes changes in the offspring immune system that emphasise atopy and immune responses of Th2 over Th1. Contrary to this classical Th2 paradigm, several previous publications, and studies within this thesis, indicate that PNMS may surprisingly increase the risk of non-atopic asthma and wheezing while reducing the likelihood of allergic sensitisation (Ramratnam et al., 2021; Wood et al., 2011). This suggests that maternal stress may influence immune programming through mechanisms beyond Th2 polarisation.

An interesting notion has been the observed sex-specific differences in offspring outcomes, such as asthma, following exposure to PNMS. Studies by Rosa et al. (2016) and Lee et al. (2016) have reported higher odds of offspring asthma in girls compared to boys. On the other hand, male foetuses are thought to exhibit increased HPA axis reactivity and greater Th2-skewed immune polarisation, while females exabit other immune function changes (Glover, 2015; Veru et al., 2014). These observations could at least in part be explained by sex-specific methylation and function of 11β-HSD in the placenta (Appleton et al., 2013).

One possible explanation is HPA axis overactivation leading to altered glucocorticoid signalling pathways, which may alter adaptive immune responses and promote a heightened innate immune response (Veru et al., 2014). Additionally, maternal autonomic nervous system activation due to PNMS may play a part in addition to altered cytokine signalling *in utero*, which could all affect the developing immune system of the foetus. Another intriguing aspect is placental biomarkers, such as microRNA, which have been shown to transfer from mother to foetus via extracellular vesicles and could alter foetal gene expression (Li et al., 2015). Other

possible mechanisms connecting PNMS to offspring immune functions include oxidative stress, reduced placental circulation, epigenetic modifications and alterations in the gut microbiota. The activation of neuroimmune reactions to chronic stress has been observed to decrease blood flow to the uterus and therefore to the placenta, altering the stress reactivity of the offspring (Dreiling et al., 2018; Teixeira et al., 1999). Emerging evidence suggests that PNMS can impact the microbiota of the child, which plays a crucial role in the development and education of the immune system. Imbalances in the microbiota are linked to atopic diseases (Fyhrquist et al., 2023). Stress-induced alterations in maternal gut microbiota composition can lead to dysbiosis, characterised by reduced microbial diversity and an increase in pro-inflammatory bacteria. These changes could contribute to heightened allergic sensitisation and increased risk of atopic diseases in early life (H. J. Chen & Gur, 2019; S.-Y. Lee et al., 2019; Mepham et al., 2023).

PNMS is associated with increased offspring susceptibility to atopic diseases, particularly wheezing and asthma. The mechanistic pathways underlying this relationship could involve neuroendocrine disruption, maternal immune activation, oxidative stress, epigenetic modifications, microbiome alterations and glucocorticoid resistance. It is likely that they work in parallel, although HPA axis-mediated changes have been the main area of interest. Although the foetal programming concept is well justified, other early-life factors could also contribute to the association of PNMS with atopic diseases. These include exposure to tobacco smoke and pollution. For example, low parental socioeconomic status has been linked to an increased risk of paediatric atopic diseases. Moreover, lower education is often correlated with psychological symptoms of anxiety and depression. Interestingly, recent evidence suggests that PNMS may preferentially increase the risk of non-atopic asthma and wheezing while reducing allergic sensitisation, challenging the classical Th2 paradigm in atopy. This finding underscores the need for further studies addressing the possible differences of atopic disease phenotypes and the contributing alterations to the immune system.

6.7.2 Paternal adverse childhood experiences

The impact of paternal adverse childhood experiences on offspring health, particularly atopic diseases, is an emerging field of research that highlights the importance of transgenerational influences beyond maternal factors. While maternal effects are often emphasised in foetal programming, growing evidence suggests that paternal experiences before conception can shape offspring immune function and predisposition to allergic diseases, possibly through epigenetic modifications, altered sperm quality and modifications in offspring stress response (Van Steenwyk et al., 2018; Zheng et al., 2021). These mechanisms are not yet fully understood, but

especially animal studies have provided evidence for a biological link between a father's early-life environment and immune-related health outcomes in his children. Alterations in HPA axis reactivity have been observed even in adulthood among individuals exposed to ACEs, and such dysregulated stress reactions may influence the susceptibility of paternal germ cells to reprogramming (Kalmakis et al., 2015; A. B. Rodgers & Bale, 2016).

One of the primary hypotheses of mechanisms linking ACEs to offspring outcomes, such as atopic diseases, involves epigenetic inheritance, particularly DNA methylation, histone modifications and non-coding RNAs (ncRNA). ACEs in fathers, such as exposure to stress, abuse, neglect or trauma, could induce lasting epigenetic changes in sperm that are transmitted to offspring (Sharma, 2019). Although evidence is still scarce, a growing body of literature suggests that especially ncRNA could play a crucial role. Specific epigenetic patterns of non-coding RNA and DNA methylation in sperm have been linked to ACEs (Dickson et al., 2018; Essex et al., 2011; Tuulari et al.). Similar results have previously been reported in mice, showing that paternal exposure to early-life stress correlated with altered DNA methylation patterns in immune-related genes in offspring, along with dysregulation of the HPA axis. Interestingly, these epigenetic modifications have been found to persist even when miRNA is injected into the zygote of an unexposed male (Gapp et al., 2014; Rodgers et al., 2013). This process may lead to a dysregulated immune response or affect the development and maturation of the nervous system. Although there is a growing body of evidence that ACEs and early-life adversity may leave lasting epigenetic marks, the mechanisms linking paternal ACEs to offspring atopic diseases remain largely hypothetical (Donkin & Barrès, 2018). Intergenerational inheritance has gained increasing support, with recent studies illustrating a link between paternal ACEs and offspring DNA methylation signatures in blood and buccal mucosa (Merrill et al., 2021; Mohazzab-Hosseinian et al., 2024).

However, it is important to consider other environmental factors that could influence paternal sperm-related features after exposure to ACEs and to remember that there is still no clear evidence of causality, even though animal studies have provided new insights into the hypothesis of causality. Still, early life adversities are linked to a poorer lifestyle, including smoking and unhealthy dietary habits (Yang et al., 2022), which can influence sperm quality (Wogatzky et al., 2012). Interestingly, paternal dietary and lifestyle factors have also been observed to cause intergenerational, epigenetic changes (Dimofski et al., 2021; Dupont et al., 2019; Klastrup et al., 2019). Paternal lifestyle habits have been linked to various offspring outcomes, including obesity and cardiovascular diseases, as reviewed by Q. Shi and Qi (2023).

However, in addition to direct epigenetic transmission, paternal influences on offspring immune function may be mediated through changes in maternal physiology during pregnancy. Fathers who have experienced early-life adversity may have altered stress responses, which in turn affect maternal stress levels through behavioural and psychosocial interactions. The mechanistic pathways of increased maternal stress during pregnancy have been discussed earlier. Overall, the evidence linking paternal early-life adversities to offspring outcomes is largely derived from animal studies and is still poorly understood. Studies suggest a multifaceted interplay of epigenetic inheritance, immune programming and environmental influences. These findings challenge the traditional view that maternal factors are the predominant determinants of offspring health and provide new insights into the intergenerational aspects of health and disease. In the future, it will be of interest to further assess the clinical relevance of these findings in relation to disease outcomes and in older children, as effect sizes may be critical in determining the clinical significance of the observed associations.

6.8 Future research directions

Emerging research indicates that prenatal maternal psychological stress (PNMS) may significantly influence the development of atopic diseases in children. The findings of this thesis align with prior literature highlighting maternal prenatal psychological stress and increased risk of various atopic outcomes in offspring. However, many questions remain regarding the underlying mechanisms and potential avenues for prevention.

Future studies should aim to investigate the specific biological pathways through which maternal stress during pregnancy influences foetal immune development and the subsequent risk of atopic diseases. This includes the roles of the axis, inflammatory mediators and epigenetic modifications in immune-related genes. Studies focusing on epigenomics, transcriptomics and metabolomics could be employed to uncover molecular changes in the offspring that may mediate the association between maternal stress and atopic diseases.

Future research should also explore the potential effectiveness of prenatal interventions aimed at reducing psychological stress symptoms in expectant mothers. These interventions could include behavioural therapy, stress reduction techniques, or integrating more profound mental health support into antenatal care. A randomised controlled trial within a population-based birth cohort could evaluate whether these interventions ultimately reduce the incidence of atopic diseases in offspring.

The intergenerational impact of paternal early-life stress, particularly ACEs, on paediatric atopic diseases is an emerging area of interest that warrants further

investigation. The results presented in this thesis suggest that paternal ACEs may be associated with immunological outcomes in offspring, and future research should aim to replicate these findings. Mechanistic studies are particularly needed to investigate the biological plausibility of these associations. In humans, this may involve analysis of epigenetic patterns in paternal sperm, in combination with offspring health outcomes, to trace possible transmission pathways. Although animal models have demonstrated causal links between paternal stress and offspring immune phenotypes, translational research in human cohorts remains scarce. Studies incorporating both maternal and paternal factors, including psychosocial histories, biological samples and child health outcomes, would allow for a more comprehensive understanding of parental influences on child health.

It would be valuable to incorporate in a prospective longitudinal birth cohort study setting both maternal and paternal psychosocial histories, repeated psychological assessments during pregnancy, and biological sampling across the prenatal and early postnatal period. Biological sampling could include maternal blood and saliva samples during pregnancy to assess cortisol levels, inflammatory markers and other stress-related biomarkers; cord blood at birth to examine neonatal immune status and epigenetic profiles; placental tissue to investigate gene expression related to immune development; and possibly even stool samples from the child to assess microbiome development.

In addition, children's medical information would be obtained from medical history registers to ensure more reliable data and rule out parental reporting bias. Such a study should be large enough to allow for stratified analyses and span into late childhood to capture later-emerging atopic conditions and examine the course of early-onset atopic diseases. Additionally, incorporating interventional components aimed at stress reduction would offer insights into preventive strategies. Exploring postnatal exposures and atopic diseases in the next generation would also be interesting, with a cumulative aspect of psychological stress. The surprising association of paternal ACEs and offspring sensitisation warrants more follow-up studies on the clinical aspect of atopic diseases, and the study design would be interesting to replicate with older children to examine the stability of the observed association.

In conclusion, future research should integrate mechanistic, longitudinal and interventional approaches to better understand and ultimately mitigate the transgenerational risk of atopic diseases associated with parental stress exposure.

7 Conclusions

Maternal prenatal psychological stress (PNMS) was associated with various offspring atopic diseases. Prenatal anxiety and depressive symptoms were positively associated with infant food allergy/intolerance at 6 months, non-atopic wheezing at 24 months and non-atopic asthma at 5.5 years. Prenatal anxiety was further associated with an increased risk of atopic eczema at 24 months. Symptoms occurring during late gestation and/or chronic symptoms appear to be more significant than transient symptoms experienced in early gestation. Even subclinical levels of symptoms seem to influence the risk of atopic diseases in offspring. Exposure to PNMS could affect the developing immune system and subsequently predispose the child to an altered risk of atopic diseases. The finding that risk was particularly elevated for non-atopic wheezing and asthma suggests that the transmission of PNMS exposure through the offspring's immune system may involve other pathways than a Th2/Th1immune response imbalance. The observed variability in risk profiles within the group of atopic diseases following the exposure to PNMS highlights the heterogeneity of the disease group and the differences in their underlying risk factors and pathogenesis.

Paternal adverse childhood experiences (ACEs), which in this thesis were defined as experiences of abuse and maltreatment, were negatively associated with offspring sensitisation and allergic rhinitis at 5.5 years. The possible mechanisms behind this finding are beyond the scope of this thesis; however, it may suggest the involvement of epigenetic changes in male sperm resulting from adaptation to ACEs.

Taken together, the findings of this thesis contribute to the understanding of the complex pathogenesis of atopic diseases. Although offspring atopic diseases, PNMS and paternal ACEs are examined here within a shared framework of parental stress, these exposures are not directly comparable in the context of offspring atopic diseases and should be treated as distinct entities. The examination of paternal ACEs separately from maternal prenatal exposures allows for a clearer assessment of exposures prior to conception. In contrast, maternal ACEs may be partially mediated through psychological symptoms during pregnancy, making them an interesting area of research. However, paternal and maternal exposures are not comparable within the scope of this thesis. The studies included in this thesis provide novel evidence on

the timing-specific effects of PNMS on offspring atopic diseases, and they identify previously unreported associations between paternal ACEs and sensitisation and allergic rhinitis in the next generation. These findings also contribute to the limited body of research examining PNMS in relation to the phenotypes of wheezing asthma. A key strength of the studies is the use of a large birth cohort design. However, this does not provide evidence of causality. Nonetheless, the results generate new research ideas based on the observed associations and underscore the need for mechanistic studies and intervention protocols aimed at supporting the mental health of pregnant women, particularly within maternal welfare clinical settings.

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Appendices

Edinburgh Postnatal Depression Scale (EPDS)

Patient Label

Mother's OB or Doctor's Name:

Doctor's Phone #: _____

Since you are either pregnant or have recently had a baby, we want to know how you feel. Please place a **CHECK MARK** (✔) on the blank by the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**—*not just how you feel today.* Complete all 10 items and find your score by adding each number that appears in parentheses (#) by your checked answer. This is a screening test; not a medical diagnosis. If something doesn't seem right, *call your health care provider regardless of your score.*

Below is an example already completed.

I have felt happy:
Yes, all of the time ____ (0)
Yes, most of the time ✔ (1)
No, not very often ____ (2)
No, not at all ____ (3)

This would mean: "I have felt happy most of the time" in the past week. Please complete the other questions in the same way.

1. I have been able to laugh and see the funny side of things:
   As much as I always could ____ (0)
   Not quite so much now ____ (1)
   Definitely not so much now ____ (2)
   Not at all ____ (3)

2. I have looked forward with enjoyment to things:
   As much as I ever did ____ (0)
   Rather less than I used to ____ (1)
   Definitely less than I used to ____ (2)
   Hardly at all ____ (3)

3. I have blamed myself unnecessarily when things went wrong:
   Yes, most of the time ____ (3)
   Yes, some of the time ____ (2)
   Not very often ____ (1)
   No, never ____ (0)

4. I have been anxious or worried for no good reason:
   No, not at all ____ (0)
   Hardly ever ____ (1)
   Yes, sometimes ____ (2)
   Yes, very often ____ (3)

5. I have felt scared or panicky for no good reason:
   Yes, quite a lot ____ (3)
   Yes, sometimes ____ (2)
   No, not much ____ (1)
   No, not at all ____ (0)

6. Things have been getting to me:
   Yes, most of the time I haven't been able to cope at all ____ (3)
   Yes, sometimes I haven't been coping as well as usual ____ (2)
   No, most of the time I have coped quite well ____ (1)
   No, I have been coping as well as ever ____ (0)

7. I have been so unhappy that I have had difficulty sleeping:
   Yes, most of the time ____ (3)
   Yes, sometimes ____ (2)
   No, not very often ____ (1)
   No, not at all ____ (0)

8. I have felt sad or miserable:
   Yes, most of the time ____ (3)
   Yes, quite often ____ (2)
   Not very often ____ (1)
   No, not at all ____ (0)

9. I have been so unhappy that I have been crying:
   Yes, most of the time ____ (3)
   Yes, quite often ____ (2)
   Only occasionally ____ (1)
   No, never ____ (0)

10. The thought of harming myself has occurred to me:*
    Yes, quite often ____ (3)
    Sometimes ____ (2)
    Hardly ever ____ (1)
    Never ____ (0)

TOTAL YOUR SCORE HERE ▶

Thank you for completing this survey. Your doctor will score this survey and discuss the results with you.

Verbal consent to contact above mentioned MD witnessed by:

_____

Edinburgh Postnatal Depression Scale (EPDS). Adapted from the *British Journal of Psychiatry*, June, 1987, vol. 150 by J.L. Cox, J.M. Holden, R. Segovsky.

Name_____ ID# _____Date _____

SCL-90

Below is a list of problems and complaints that people sometimes have. Please read each one carefully. After you have done so, select one of the numbered descriptors that best describes HOW MUCH THAT PROBLEM HAS BOTHERED OR DISTRESSED YOU DURING THE PAST WEEK, INCLUDING TODAY. Circle the number in the space to the right of the problem and do not skip any items. Use the following key to guide how you respond:

Circle 0 if your answer is NOT AT ALL
Circle 1 if A LITTLE BIT
Circle 2 if MODERATELY
Circle 3 if QUITE A BIT
Circle 4 if EXTREMELY

Please read the following example before beginning:

Example: In the previous week, how much were you bothered by:

Backaches 0 (1) 2 3 4

In this case, the respondent experienced backaches a little bit (1).
Please proceed with the questionnaire.

	HOW MUCH WERE YOU BOTHERED BY:	NOT AT ALL	A LITTLE BIT	MODERATELY	QUITE A BIT	EXTREMELY
1.	Headaches	0	1	2	3	4
2.	Nervousness or shakiness inside	0	1	2	3	4
3.	Unwanted thoughts, words, or ideas that won't leave your mind	0	1	2	3	4
4.	Faintness or dizziness	0	1	2	3	4
5.	Loss of sexual interest or pleasure	0	1	2	3	4
6.	Feeling critical of others	0	1	2	3	4
7.	The idea that someone else can control your thoughts	0	1	2	3	4
8.	Feeling others are to blame for most of your troubles	0	1	2	3	4
9.	Trouble remembering things	0	1	2	3	4
10.	Worried about sloppiness or carelessness	0	1	2	3	4
11.	Feeling easily annoyed or irritated	0	1	2	3	4
12.	Pains in heart or chest	0	1	2	3	4
13.	Feeling afraid in open spaces or on the streets	0	1	2	3	4
14.	Feeling low in energy or slowed down	0	1	2	3	4
15.	Thoughts of ending your life	0	1	2	3	4
16.	Hearing voices that other people do not hear	0	1	2	3	4
17.	Trembling	0	1	2	3	4
18.	Feeling that most people cannot be trusted	0	1	2	3	4
19.	Poor appetite	0	1	2	3	4

SCL-90 (*continued*)

	HOW MUCH WERE YOU BOTHERED BY:	NOT AT ALL	A LITTLE BIT	MODERATELY	QUITE A BIT	EXTREMELY
20.	Crying easily	0	1	2	3	4
21.	Feeling shy or uneasy with the opposite sex	0	1	2	3	4
22.	Feeling of being trapped or caught	0	1	2	3	4
23.	Suddenly scared for no reason	0	1	2	3	4
24.	Temper outbursts that you could not control	0	1	2	3	4
25.	Feeling afraid to go out of your house alone	0	1	2	3	4
26.	Blaming yourself for things	0	1	2	3	4
27.	Pains in lower back	0	1	2	3	4
28.	Feeling blocked in getting things done	0	1	2	3	4
29.	Feeling lonely	0	1	2	3	4
30.	Feeling blue	0	1	2	3	4
31.	Worrying too much about things	0	1	2	3	4
32.	Feeling no interest in things	0	1	2	3	4
33.	Feeling fearful	0	1	2	3	4
34.	Your feelings being easily hurt	0	1	2	3	4
35.	Other people being aware of your private thoughts	0	1	2	3	4
36.	Feeling others do not understand you or are unsympathetic	0	1	2	3	4
37.	Feeling that people are unfriendly or dislike you	0	1	2	3	4
38.	Having to do things very slowly to insure correctness	0	1	2	3	4
39.	Heart pounding or racing	0	1	2	3	4
40.	Nausea or upset stomach	0	1	2	3	4
41.	Feeling inferior to others	0	1	2	3	4
42.	Soreness of your muscles	0	1	2	3	4
43.	Feeling that you are watched or talked about by others	0	1	2	3	4
44.	Trouble falling asleep	0	1	2	3	4
45.	Having to check and double-check what you do	0	1	2	3	4
46.	Difficulty making decisions	0	1	2	3	4
47.	Feeling afraid to travel on buses, subways, trains	0	1	2	3	4
48.	Trouble getting your breath	0	1	2	3	4
49.	Hot or cold spells	0	1	2	3	4
50.	Having to avoid certain things, places, or activities because they frighten you	0	1	2	3	4
51.	Your mind going blank	0	1	2	3	4
52.	Numbness or tingling in parts of your body	0	1	2	3	4
53.	A lump in your throat	0	1	2	3	4
54.	Feeling hopeless about the future	0	1	2	3	4
55.	Trouble concentrating	0	1	2	3	4

SCL-90 (*continued*)

	HOW MUCH WERE YOU BOTHERED BY:	NOT AT ALL	A LITTLE BIT	MODERATELY	QUITE A BIT	EXTREMELY
56.	Feeling weak in parts of your body	0	1	2	3	4
57.	Feeling tense or keyed up	0	1	2	3	4
58.	Heavy feelings in your arms or legs	0	1	2	3	4
59.	Thoughts of death or dying	0	1	2	3	4
60.	Overeating	0	1	2	3	4
61.	Feeling uneasy when people are watching or talking about you	0	1	2	3	4
62.	Having thoughts that are not your own	0	1	2	3	4
63.	Having urges to beat, injure, or harm someone	0	1	2	3	4
64.	Awakening in the early morning	0	1	2	3	4
65.	Having to repeat the same actions such as touching, counting, washing	0	1	2	3	4
66.	Sleep that is restless or disturbed	0	1	2	3	4
67.	Having urges to break or smash things	0	1	2	3	4
68.	Having ideas or beliefs that others do not share	0	1	2	3	4
69.	Feeling very self-conscious with others	0	1	2	3	4
70.	Feeling uneasy in crowds, such as shopping or at a movie	0	1	2	3	4
71.	Feeling everything is an effort	0	1	2	3	4
72.	Spells of terror or panic	0	1	2	3	4
73.	Feeling uncomfortable about eating or drinking in public	0	1	2	3	4
74.	Getting into frequent arguments	0	1	2	3	4
75.	Feeling nervous when you are left alone	0	1	2	3	4
76.	Others not giving you proper credit for your achievements	0	1	2	3	4
77.	Feeling lonely even when you are with people	0	1	2	3	4
78.	Feeling so restless you couldn't sit still	0	1	2	3	4
79.	Feelings of worthlessness	0	1	2	3	4
80.	Feeling that familiar things are strange or unreal	0	1	2	3	4
81.	Shouting or throwing things	0	1	2	3	4
82.	Feeling afraid you will faint in public	0	1	2	3	4
83.	Feeling that people will take advantage of you if you let them	0	1	2	3	4
84.	Having thoughts about sex that bother you a lot	0	1	2	3	4
85.	The idea that you should be punished for your sins	0	1	2	3	4
86.	Feeling pushed to get things done	0	1	2	3	4
87.	The idea that something serious is wrong with your body	0	1	2	3	4
88.	Never feeling close to another person	0	1	2	3	4
89.	Feelings of guilt	0	1	2	3	4
90.	The idea that something is wrong with your mind	0	1	2	3	4

Reference: Derogatis, L.R., Lipman, R.S., & Covi, L. (1973). SCL-90: An outpatient psychiatric rating scale—Preliminary Report. *Psychopharmacol. Bull. 9*, 13–28.

Appendix

The traumatic and distress experiences scale

TADS – *EPOS* version 1.2

Instructions

These questions ask about personal experiences you may have had in your life so far.

Many questions refer to *'when you were young':* this means the period of your life when you were growing up and before you left school. When we talk about *'parents'* this means the adults who had the main responsibility for your upbringing as a child and teenager.

If your parents behaved differently, please answer the questions thinking about the parent whose behaviour was worse.

Read each item carefully and tick the box that most accurately describes the experience from your point of view. Please answer all the questions as honestly as you can.

Thank you for your time

	Never	Rarely	Some-times	Often	Nearly Always
1. When I was young, I felt safe and protected by somebody.					
2. When I was young, I was often hungry.					
3. I was bullied at school.					
4. I often had to wear ragged or dirty clothes to school.					
5. When I was young, I felt valued or important.					
6. My parents / caregivers were often drunk, stoned or wasted.					
7. I have been bullied at work.					
8. My family were emotionally warm and loving.					
9. When I was young, I was hit so hard that it left marks, cuts or bruises.					
10. I felt rejected by my parents / caregivers.					
11. When I was young, there was an adult I could confide in.					
12. When I was young, I was humiliated by people in my family.					
13. When I was young, my family looked after each other.					
14. I believe that I am a bad person.					
15. I believe that somebody died because of me.					
16. I have experienced serious physical assault.					
17. Adults (like teachers, doctors or nurses) noticed cuts, bruises or marks from when I was beaten.					
18. My childhood was perfect.					
19. I am bothered by a very shameful secret.					
20. I think I was physically abused when I was young.					
21. I respect myself.					
22. When I was young, someone touched me or tried to make me touch them in a sexual way.					
23. I have had experiences that I feel very guilty about.					
24. I have been involved in life-threatening situations.					
25. I was forced to keep secrets about someone sexually interfering with me when I was young.					
26. When I was young, I felt hated by a member or members of my family.					
27. My family was the greatest ever.					
28. Other people have acted badly because of me.					
29. When I was young, I felt like the odd one out in my family.					
30. I have experienced sexual assault.					
31. If I needed treatment someone would always take me to see a doctor or nurse when I was young.					
32. I feel that I was put down, criticized and made to feel inferior when I was young.					
33. Someone sexually molested me when I was young.					
34. I feel responsible for harm or injury to another person.					
35. When I was young, I had friends I could talk to about personal problems.					
36. I have experienced harassment / persecution from other ethnic groups.					
37. I did well at school.					
38. I have experienced the loss of somebody who was very important to me.					
39. I believe that I do not deserve to do well in life.					
40. My family was supportive and encouraging when I was young.					
41. I believe that I was sexually used when I was young.					
42. I felt afraid of someone in my family.					
43. When I was young I could make friends easily					

ISAAC Questionnaire

8. Study instruments for 6/7 year olds

8.1 Instructions for completing questionnaire and demographic questions

Examples of instructions for completing questionnaire and demographic questions are given below.
The content of the questionnaires is fixed. *(see pages 72–73 for 'office use only' boxes example)*

On this sheet are questions about your child's name, school, and birth dates. Please write your answers to these questions in the space provided.

All other questions require you to tick your answer in a box. If you make a mistake put a cross in the box and tick the correct answer. Tick only one option unless otherwise instructed.

Examples of how to mark questionnaires: Age [6] years

To answer Yes/No, put a tick in the appropriate box as per example	YES	NO
	☐	☑

SCHOOL: ☐

TODAY'S DATE: ☐ Day ☐ Month ☐ Year

CHILD'S NAME: ☐

CHILD'S AGE: ☐ years

CHILD'S DATE OF BIRTH: ☐ Day ☐ Month ☐ Year

(Tick all your answers for the rest of the questionnaire)

Is your child a: MALE ☐ FEMALE ☐

Optional questions on ethnicity here

8.2 Core questionnaire for asthma

8.2.1 Questionnaire for 6/7 year olds (strongly recommended)

1 Has your child ever had wheezing or whistling in the chest at any time in the past?
- Yes ☐
- No ☐

IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 6

---

2 Has your child had wheezing or whistling in the chest in the past 12 months?
- Yes ☐
- No ☐

IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 6

---

3 How many attacks of wheezing has your child had in the past 12 months?
- None ☐
- 1 to 3 ☐
- 4 to 12 ☐
- More than 12 ☐

4 In the past 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?
- Never woken with wheezing ☐
- Less than one night per week ☐
- One or more nights per week ☐

5 In the past 12 months, has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths?
- Yes ☐
- No ☐

---

6 Has your child ever had asthma?
- Yes ☐
- No ☐

7 In the past 12 months, has your child's chest sounded wheezy during or after exercise?
- Yes ☐
- No ☐

8 In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?
- Yes ☐
- No ☐

8.3 Core questionnaire for rhinitis

8.3.1 Questionnaire for 6/7 year olds (strongly recommended)

1 Has your child ever had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?
Yes ☐
No ☐

IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 6

2 In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu?
Yes ☐
No ☐

IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 6

3 In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?
Yes ☐
No ☐

4 In which of the past 12 months did this nose problem occur? (Please tick any which apply)

January	☐	May	☐	September	☐
February	☐	June	☐	October	☐
March	☐	July	☐	November	☐
April	☐	August	☐	December	☐

5 In the past 12 months, how much did this nose problem interfere with your child's daily activities?:

Not at all ☐
A little ☐
A moderate amount ☐
A lot ☐

6 Has your child ever had hayfever?
Yes ☐
No ☐

8.4 Core questionnaire for eczema

8.4.1 Questionnaire for 6/7 year olds (strongly recommended)

1	Have your child ever had an itchy rash which was coming and going for at least six months?	Yes No	☐ ☐
	IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 7		
2	Has your child had this itchy rash at any time in the past 12 months?	Yes No	☐ ☐
	IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 7		
3	Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?	Yes No	☐ ☐
4	At what age did this itchy rash first occur?	Under 2 years Age 2-4 years Age 5 or more	☐ ☐ ☐
5	Has this rash cleared completely at any time during the past 12 months?	Yes No	☐ ☐
6	In the past 12 months, how often, on average, has your child been kept awake at night by this itchy rash?	Never in the past 12 months Less than one night per week One or more nights per week	☐ ☐ ☐
7	Has your child ever had eczema?	Yes No	☐ ☐

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