Received: 16 February 2024 | Revised: 24 June 2024 | Accepted: 26 June 2024

DOI: 10.1111/apa.17345

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

Paternal adverse childhood experiences are associated with a low risk of atopy in the offspring

Emma Puosi[1,2,3] | Hasse Karlsson[1,3,4] | Heikki Lukkarinen[1,2] | Linnea Karlsson[1,2,3] | Minna Lukkarinen[1,2,3]

[1]FinnBrain Birth Cohort Study, Turku Brain and Mind Center, Department of Clinical Medicine, Faculty of Medicine, University of Turku, Turku, Finland

[2]Tyks Department of Paediatrics and Adolescent Medicine, Turku University Hospital and Paediatrics and Adolescent Medicine, Department of Clinical Medicine, Faculty of Medicine, University of Turku, Turku, Finland

[3]Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland

[4]Psychiatry, Department of Clinical Medicine, Faculty of Medicine, University of Turku and Tyks Psychiatry, Turku University Hospital, Turku, Finland

Correspondence
Emma Puosi, FinnBrain Birth Cohort Study, Turku Brain and Mind Center, Department of Clinical Medicine, University of Turku, FI-20014 Turku, Finland.
Email: emmapu@utu.fi

Funding information
Academy of Finland, Grant/Award Number: 134950, 308258 and 325292; Allergy Research Foundation; Finnish Medical Foundation; Juho Vainio Foundation; Maire Taposen Foundation; Päivikki and Sakari Sohlberg Foundation; Signe and Ane Gyllenberg Foundation; Southwestern Finland Foundation of Allergy Research; TYKS Foundation

Abstract

Aim: Parental adverse childhood experiences (ACE) might affect the offspring health through intergenerational inheritance. The aim of this study was to investigate how paternal ACE associate with offspring sensitisation and allergic rhinitis (AR).

Methods: The study included 590 Finnish father-child dyads from the FinnBrain Birth Cohort Study. Outcomes were offspring sensitisation against allergens and AR at age 5.5 years. Paternal ACE up to 18 years were assessed using the Trauma and Distress Scale (TADS) with the lowest quarter as the reference group.

Results: Of the children, 317 (54%) were males. Sensitisation occurred in 162/533 (30%) and AR in 122/590 (21%). Paternal TADS (median 17 points; interquartile range 11–27) was inversely associated with the risk of sensitisation. Children whose fathers scored the highest quarter had the lowest risk of sensitisation (adjusted odds ratio 0.42; 95% confidence interval 0.24–0.75), followed by those in the second highest quarter (0.58; 0.34–0.99). The association between the highest quarter and reduced risk of AR was similar.

Conclusion: Paternal ACE were associated with a low risk of offspring sensitisation and AR, suggesting paternal childhood stress might influence immune responses in their offspring.

KEYWORDS
adverse childhood experiences, atopy, early-life stress, epigenetics, sensitisation

Abbreviations: ACE, adverse childhood experiences; AR, Allergic rhinitis; EPDS, Edinburgh Postnatal Distress Scale; IgE, immunoglobulin E; IQR, interquartile range; ISAAC, International Study of Asthma and Allergies in Childhood; TADS, Trauma and Distress Scale.

1 | INTRODUCTION

Allergic diseases, consisting of allergic asthma, atopic eczema and allergic rhinitis, are characterised by coexisting sensitisation to allergens, this is especially the case for allergic rhinitis.[1] Major risk factors for atopic diseases include maternal allergic diseases, maternal tobacco smoke and low socioeconomic status.[2] Studies in recent years have also shown that offspring exposed to maternal psychological distress during gestation, especially late gestation, have an elevated risk for atopic diseases.[3–5] These data support the theory that programming of the immune system starts already during foetal development which may result in enhanced susceptibility to atopic diseases.[3] There is also growing evidence for inheritance of parental adverse childhood experiences (ACE) contributing to health outcomes of the offspring.[6,7] Both maternal and parental ACE have been linked to an elevated risk of asthma among the offspring.[8,9] We found only one study[9] that examined how paternal ACE, as a factor independent of maternal ACE, affected offspring health outcomes. That study did show a link between paternal ACE and an elevated risk of autoimmune diseases among the offspring.[9] It is noteworthy that human[7,9–12] and animal[7,13] studies imply that the sex of the ACE-exposed parent may be a significant contributing factor, since the impact on offspring health outcomes could be differently induced by metabolic, behavioural and epigenetic factors expressed by mothers and by fathers.

Human and animal studies have shown that there are different factors that cause epigenetic changes which could affect the risk of atopic diseases for the offspring.[14] For example, exposure to tobacco smoke constitutes a transgenerational risk factor for asthma; this means that exposures experienced by previous generations increase the risk for the offspring across generations.[15] Paternal ACE have been associated with changes in DNA methylation in the gametes, with small non-coding RNAs and with changes in the chromatin architecture of paternal gametes, as summarised in the review by Condon et al.[7] Interestingly, animal studies have demonstrated changes in sperm cell epigenetics after exposure of the subject to psychological trauma in early life and also after puberty.[14] Merrill et al. found changes in the methylation of the DNA in the blood of offspring who had been exposed to paternal ACE.[16] Among humans, a more marked suppression of cortisol secretion was observed among offspring of Holocaust survivors who experienced post-traumatic stress than of the ones who were not exposed. This phenomenon was linked to changes in DNA methylation of the offspring.[16] These associations between paternal ACE and offspring health outcomes have been put in relation to modified metabolism, hypothalamic–pituitary–adrenal axis dysfunction and dysregulation of stress of the offspring.[7] Dysfunction of the hypothalamic–pituitary–adrenal axis could lead to an imbalance in the amount of Type 1 T helper (Th1) cells and Type 2 T helper (Th2) cells and to a shift favouring Th2 responses, predisposing to an increased risk of atopic diseases.[17]

Key notes

- Parental adverse childhood experiences (ACE) have been linked to health outcomes of the offspring, but studies on offspring atopic diseases are scarce.
- Self-reported paternal ACE were associated with a low risk of sensitisation and allergic rhinitis of the offspring at age 5.5 years.
- This indicates that paternal stress in one's own childhood may affect the immune responses of the offspring; however, further research on the possible mechanisms is warranted.

Although our understanding of intergenerational inheritance of paternal ACE and of epigenetic changes that impact the health of offspring is gradually improving, little is known about how these circumstances affect atopic diseases in the offspring.[6,8,9,18] We aimed to investigate the associations between paternal ACE and offspring sensitisation in a population-based birth cohort of 5.5-year-old patients with allergic rhinitis (AR). Sensitisation was measured as elevated immunoglobulin E (IgE) antibody levels against specified allergens. We hypothesised that paternal ACE is harmful for the offspring and is associated with an elevated risk to the offspring for sensitisation or AR. If this was the case, it might be due to underlying epigenetic associations or gene–environment interactions. The result would be an altered risk of atopic diseases to the offspring.

2 | PATIENTS AND METHODS

2.1 | Study subjects and study design

The FinnBrain Birth Cohort is a multidisciplinary, intergenerational, population-based, prospective and observational pregnancy cohort recruited for examination of the long-term effects of prenatal and early-life exposures on child health outcomes.[8] The Finnish families were recruited by study nurses between December 2011 and April 2015 in connection with routine free-of-charge ultrasound examinations offered to all pregnant women at pregnancy week 12. Recruitment took place in three maternity welfare clinics in the Hospital District of Southwest Finland and the Åland Islands. The present study included father–child dyads successfully followed-up until the child was 5.5 years and where data for outcomes, exposure to paternal ACE and selected covariates were available. The covariates were parental level of education, maternal depressive symptoms during gestation and maternal and/or parental atopic disease, which included allergic rhinitis and/or atopic eczema (Figure 1 and Table 1). Father–child dyads without these data were excluded.

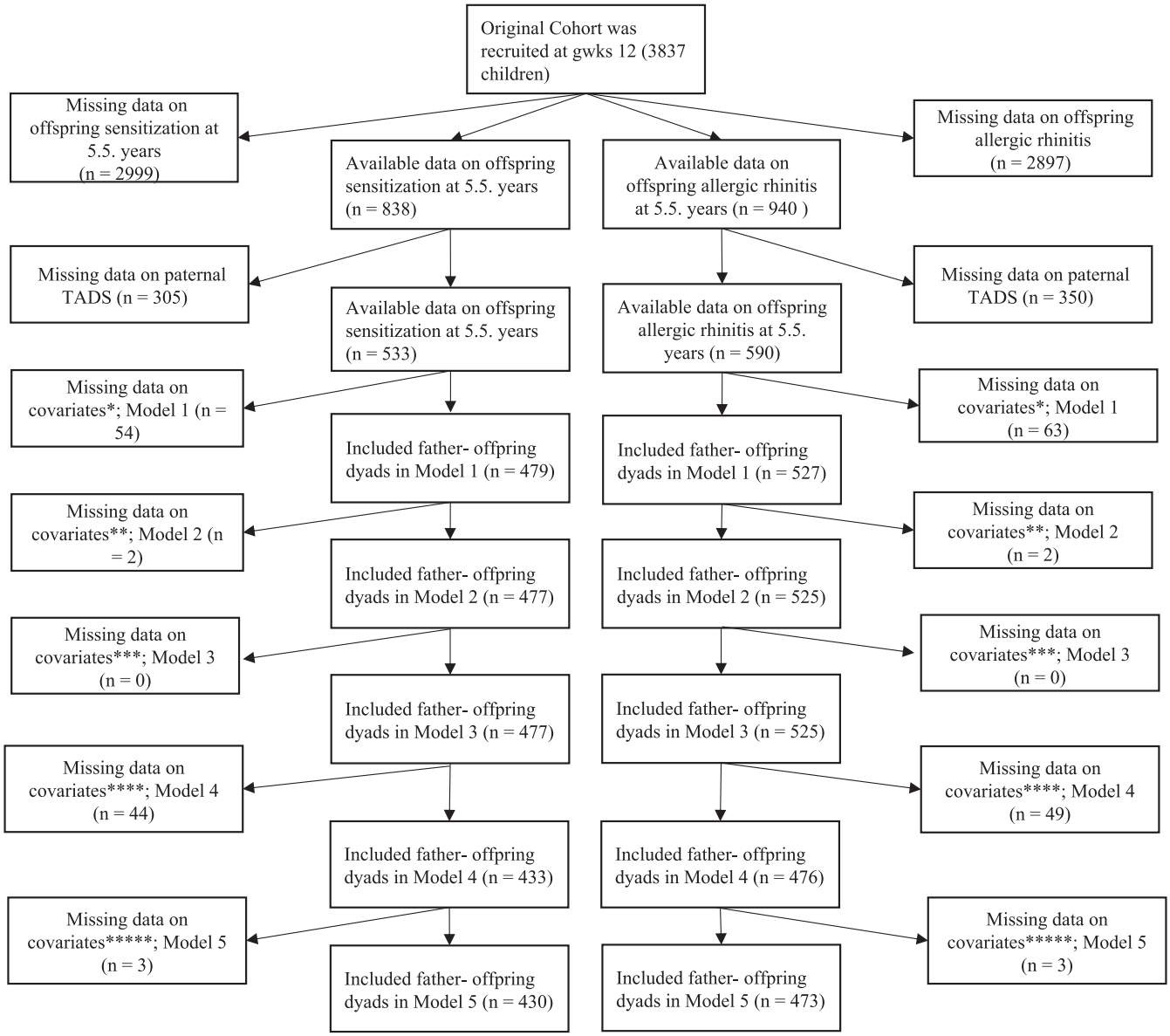

FIGURE 1 Flow chart. EPDS, Edinburgh Postnatal Distress Scale; gwks, gestational weeks; TADS, Trauma and Distress Scale. *Maternal EPDS at gwks 34, maternal atopic diseases; **Maternal EPDS at gwks 34, parental atopic diseases; ***Maternal EPDS at gwks 34, maternal atopic diseases, parental educational level; ****Maternal EPDS at gwks 34, maternal atopic diseases, number of siblings; *****Maternal EPDS at gwks 34, parental atopic diseases, number of siblings.

2.2 | Outcomes

The primary outcome was any objectively measured, laboratory-verified sensitisation of the offspring at age 5.5 years. This was defined as positive findings of serum IgE antibodies (0/1) against at least one common allergen measured with fluorescent enzyme immunoassay using Phadiatop Combi (Phadia, Uppsala, Sweden). The allergens that were included in the immunoassay were codfish, cows' milk, eggs, peanuts, soybeans, wheat, cat, dog, horse, birch, mugwort (*Artemisia*), timothy (*Phleum pratense*), *Cladosporium herbarium* and *Dermatophagoides pteronyssinus* which were assessed routinely by the Central Laboratory of the Turku University Hospital. The cut-off level 0.35 kU/L was considered moderate sensitisation and 0.70 kU/L significant sensitisation. The secondary outcome was a clinical diagnosis of AR. The symptoms of AR, based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, were reported by the parents and recorded after an interview by the study paediatricians.[19,20] We further divided the sensitisation (cut-off 0.70 IU/L) into aeroallergens (cat, dog, horse, birch, mugwort, timothy, *Cladosporium herbarum* and *Dermatophagoides pteronyssinus*) and into food allergens (codfish, cows' milk, eggs, peanuts, soybeans and wheat).

2.3 | Exposures

Paternal ACE were assessed using the TADS questionnaire (Trauma And Distress Scale) at week 14 of the index pregnancy.[21] The TADS

TABLE 1 Cohort population characteristics and the attrition analysis.

Exposures	Cohort *N* = 3837	Included *N* = 590	Excluded *N* = 3247	*p*[a]
Parental characteristics				
Paternal age at birth, years, mean (SD)	32 (5.4) *n* = 2630	33 (5.2) *n* = 589	32 (5.5) *n* = 2041	**<0.010**
Maternal age at birth, years, mean (SD)	31 (4.7) *n* = 3837	31 (4.4) *n* = 590	30 (4.8) *n* = 3247	**0.011**
Maternal pre-pregnancy body-mass index, kg/m^2, median (IQR)	23 (21:27) *n* = 3684	23 (21:26) *n* = 587	24 (21:27) *n* = 3097	0.82
Maternal smoking, no. (%)				
Quit in early pregnancy	274/3690 (7.4)	25/87 (4.3)	249/3101 (6.3)	**<0.001**
Through pregnancy	207/3690 (5.6)	13/587 (2.2)	194/3103 (6.3)	
Paternal smoking, no. (%)	1095/3317 (33)	166/579 (29)	455/1338 (34)	**0.022**
Maternal atopic eczema and/or allergic rhinitis, no. (%)	1299/3096 (42)	234/580 (40)	1065/2516 (42)	0.38
Paternal atopic eczema and/or allergic rhinitis, no. (%)	694/2012 (35)	213/587 (36)	481/1425 (34)	0.28
Paternal level of education, no. (%)				
Up to 12 years	996/2911 (49)	262/533 (43)	766/1478 (52)	**0.003**
13–15 years	593/2911 (30)	177/533 (33)	416/1478 (28)	
Over 15 years	422/2011 (21)	126/533 (24)	296/1478 (20)	
Parental level of education, no. (%)				
Up to 12 years	1070/3163 (34)	262/589 (45)	734/1422 (52)	**0.014**
13–15 years	1077/3163 (34)	191/589 (32)	402/1422 (28)	
Over 15 years	1016/3163 (32)	422/2011 (23)	289/1422 (20)	
Maternal EPDS score (range 0–30), median at gwks 34 (IQR)	2.0 (1.0:5.0) *n* = 1491	3.0 (1.0:7.0) *n* = 536	4.0 (2.0:7.0) *n* = 2066	**0.002**
Paternal EPDS score (range 0–30), median at gwks 34 (IQR)	4.0 (2.0:7.0) *n* = 2602	2.0 (1.0:5.0) *n* = 454	2.0 (1.0:5.0) *n* = 1037	0.82
Paternal TADS between 0 and 18 years, median (IQR)	18 (11:27) *n* = 1952	17 (11:27) *n* = 590	18 (11:27) *n* = 1362	0.45
Paternal TADS between 0 and 6 years, median (IQR)	10 (5.0:17) *n* = 1944	10 (5.0:17) *n* = 588	10 (5.0:17) *n* = 1356	0.59
Paternal TADS between 7 and 12 years, median (IQR)	14 (8.0:22) *n* = 1946	14 (8.0:22) *n* = 589	15 (8.0:22) *n* = 1357	0.48
Paternal TADS between 13 and 18 years, median (IQR)	17 (10:26) *n* = 1946	17 (10:26) *n* = 589	17 (10:26) *n* = 1357	0.26
Child characteristics				
Gestational age, weeks, mean (SD)	40 (1.8) *n* = 3758	38 (1.7) *n* = 590	40 (1.8) *n* = 3172	0.054
Birth weight, g, mean (SD)/length, cm, mean (SD)	3500 (550) *n* = 3696/50 (2.5) *n* = 3676	3500 (550) *n* = 587/51 (2.4) *n* = 587	3500 (550) *n* = 3097/50 (2.5) *n* = 3097	0.076/0.070
Male sex, no. (%)	1964/3760 (52)	317/590 (54)	1647/3170 (52)	0.43
Number of older siblings, no. (%)				
One	1216/3811 (32)	149/500 (30)	576/1754 (33)	0.10
Two or more	413/3811 (11)	47/500 (10)	203/1754 (12)	
Older siblings with mother-reported atopic diseases, no. (%)	444/3096 (12)	80/580 (14)	364/2516 (15)	0.68
Physician-diagnosed allergic rhinitis ever, no. (%)	122/940 (41)	77/590 (13)	45/350 (13)	0.93

TABLE 1 (Continued)

Exposures	Cohort N = 3837	Included N = 590	Excluded N = 3247	p[a]
Current allergic rhinitis during preceding 12 months, *n* (%)	192/940 (20)	117/590 (20)	75/350 (21)	0.56
Allergic rhinitis[b], *n* (%)	201/940 (22)	122/590 (21)	79/350 (23)	0.49

Abbreviations: CI, Confidence interval; EPDS, Edinburgh Postnatal Depression Scale; gwks, Gestational weeks; IQR, Interquartile range; OR, Odds ratio; SD, Standard deviation; TADS, Trauma and Distress Scale.

[a]Indicates the comparisons between included and excluded.

[b]Defined as physician-diagnosed allergic rhinitis ever and/or current allergic rhinitis symptoms during the preceding 12 months at offspring age 5.5 years.

Bold indicating *p* values below 0.05.

ranges from 0 to 172 points and provides an assessment of the respondent's trauma experiences at 0–18 years of age. It includes 43 items divided into five core domains: neglect (physical and emotional) and abuse (physical, emotional and sexual), each scores 0–4 points.[21] In our study, two statements, used for recognition of exaggerated positive responses to validation, were excluded: 'My family was the greatest ever' and 'My childhood was perfect'. Thus, the final total TADS-range was 0–164 points after exclusion of these two statements.

The data for maternal pre-pregnancy body mass index, maternal smoking and delivery type were derived from the Finnish Medical Birth Register, while other background information was obtained from the parental questionnaires separately for mothers and fathers when the mother was 14 weeks pregnant. The parents were asked whether they had allergies, allergic rhinitis and/or eczema, and parental atopic diseases were identified if the reply was 'yes'.[20,22] Maternal prenatal depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS, range 0–30 points) at 34 weeks of pregnancy.[23] The highest parental (either mother or father) level of education was used as a proxy for family socioeconomic status, since low socioeconomic status is a known risk factor for atopic diseases.[2] The number of older siblings was categorised into three classes: no siblings, one sibling and two or more siblings.

2.4 | Statistical analyses

The risk of sensitisation and AR was assessed using binary logistic regression, first unadjusted and then adjusted. The TADS was used as a four-class categorical variable divided into quarters based on the quartiles with the lowest quarter as the reference. The analyses were adjusted for known risk factors: parental atopic diseases, parental level of education, maternal depressive symptoms at 34 weeks of pregnancy and number of older siblings (models one to five).[4,5] The models were formed to test possible residual confounding and consisted of different combinations of significant covariables. The genetic inheritance of atopic diseases was tested by adjusting for parental atopic diseases: only maternal atopic diseases in models one, three and four and parental (both maternal and paternal) atopic diseases in model two. Model three was also adjusted for parental level of education and model four for the number of older siblings. Model five was adjusted for all covariates mentioned. Separate supplementary analyses were run to examine sensitisation to aeroallergens and food allergens. Additionally, a combined variable was formed which included sensitisation to aeroallergens (cut-off over 0.70 kU/L) and AR. To test for residual confounding factors, models six to eight were expanded to include all covariates from model five plus the maternal TADS score (model six), area of living (rural/city; model seven) and population density (more than or less than 100 people/250 m × 250 m grid; model eight). A p value < 0.05 was regarded as significant. Analyses were performed using the IBM SPSS 29.0 software (IBM Corp, New York, USA).

2.5 | Ethics

The study conforms to the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital District of Southwest Finland (ETMK: 57/180/2011). The study started only after written informed consent had been obtained from the guardians.

3 | RESULTS

3.1 | Study population and characteristics

Originally, the FinnBrain Birth Cohort comprised of 3808 mothers, 2623 fathers and 3837 children. At offspring age 5.5 years, the study paediatricians carried out the ISAAC-based interview of 940 parents regarding the atopic outcomes of the offspring. Of these 838 children, blood tests for allergic sensitisation were drawn (Figure 1). Data for the outcomes concerning sensitisation, exposures and covariates were available of 479 dyads for model one, 477 for models two and three, 433 for model four and 430 for model five (Figure 1). For the outcome of AR, the data was available from 527 dyads for model one, 525 for model two and three, 476 for model four and 473 for model five. The prevalence of moderate sensitisation of the offspring was 206/533 (38%) and of significant sensitisation 162/533 (30%) and AR 122/590 (21%) (Tables 1 and 2).

The median paternal TADS value was 17 points and the interquartile range (IQR) was 11–27 for all included dyads. The corresponding values for dyads with significant sensitisation of the offspring were 15 and 9.0–23 and for dyads with offspring with AR 16 and 10–23 (Tables 1 and 2). Maternal atopic diseases were more common among the children with sensitisation and AR than without, whereas paternal atopic diseases were more common only among the children with AR (Table 2). The correlation between paternal ACE and paternal level of education and between parental ACE and parental level of education was mild (beta coefficient −0.144; $p < 0.001$ and −0.114; <0.001, respectively).

3.2 | Risk of sensitisation at age 5.5 years

Unadjusted analyses showed that the two highest scoring quarters of paternal TADS were dose-dependently associated with a reduced risk of offspring sensitisation; the risk was lowest among the children whose fathers scored the highest quarter and the risk was second lowest among the children whose fathers scored the second highest quarter (Table 3). Paternal or parental level of education, number of siblings or paternal smoking was not associated with offspring sensitisation (Table 3).

Adjusted analyses of models one and two showed that the two highest scoring quarters were dose-dependently associated with a reduced risk of offspring sensitisation (Table 3). Analyses of models three, four and five showed that the highest quarter of paternal TADS was associated with a reduced risk of significant sensitisation.

The separate analyses of sensitisation to aeroallergens and food allergens showed that the two highest quartiles of TADS were negatively associated with sensitisation of the offspring to food allergens, while the highest quartile of paternal TADS was negatively associated with sensitisation of the offspring to aeroallergens (Table S1). When testing for residual confounding, the highest quartile of paternal TADS was associated with a reduced risk for sensitisation of the offspring in models six to eight (Table S2).

3.3 | Risk of allergic rhinitis at age 5.5 years

Unadjusted analyses did not show statistical significance between paternal TADS and AR. Adjusted analyses of models one, two, four and five showed, on the other hand, an association between the highest scoring quarter of paternal TADS and a reduced risk of AR (Table 3). When testing for residual confounding, the highest quartile of paternal TADS was associated with a reduced risk for AR of the offspring in models six to eight (Table S2). The supplementary analyses of the association between the combined variable AR plus sensitisation to aeroallergens showed that the highest quartile of paternal TADS was inversely associated only with the group of aeroallergen sensitisations (Table S3).

4 | DISCUSSION

Little is known about the effects of paternal ACE on offspring atopic diseases. Studies on this large birth cohort show that paternal ACE were associated with a lowered risk of offspring sensitisation and allergic rhinitis when the child was 5.5 years of age. There was a dose response: the risk was lowest for the offspring whose fathers scored the highest quarter in the Trauma and Distress Scale (TADS). This suggests that paternal ACE might induce alterations in the immune system of the offspring and reduce the risk of atopic diseases.

To our knowledge, this is the first study on paternal ACE and offspring atopic traits. The study showed a lowered risk of laboratory-verified sensitisation and AR in the offspring of fathers who in their childhood had experienced neglect and/or abuse. This finding was contradictory our hypothesis. Studies in the novel field of paternal ACE and offspring health outcomes and, especially, atopic diseases are limited. A publication by Brew et al. reported an elevated risk of offspring inflammatory diseases in children whose fathers had experienced bereavement of a parent in their childhood.[9] These autoimmune diseases included insulin-dependent diabetes mellitus, coeliac disease and autoimmune thyroid disease.[9] Autoimmune diseases constitute a heterogenous group with significant variation in aberrant immune responses. Several of these diseases express predominantly a shift towards Th1-driven immune responses, while Th2-responses are especially associated with allergic diseases.[9] Interestingly, also Brew et al. reported a tendency for a lowered risk of atopic diseases and asthma among the offspring to fathers who had been exposed to ACE, but they did not highlight this finding.[9]

We showed that particularly paternal ACE was associated with a lowered risk of offspring sensitisation to food, aeroallergens and AR. In small children, AR does not always coexist with elevated serum IgE antibody levels and AR without elevated serum IgE levels is, in fact, common.[24,25] Therefore, we chose not to define AR based solely on elevated serum IgE antibody levels against aeroallergens. As we tested the association between paternal ACE and the combination of AR with sensitisation exclusively to aeroallergens, statistical power declined, but the clinically intriguing perspective remained. Parental atopic diseases are a known risk factor for offspring atopic diseases.[26] This could also be seen in our study, as maternal atopic diseases were a risk factor for offspring sensitisation and AR, while paternal atopic diseases were only associated with AR in the offspring.

Only a few previous studies have considered the possibility that maternal and paternal ACE may exert different effects on offspring atopy. Studies on exclusively paternal ACE are scarce.[9] Parental ACE exposure has mostly been examined either as one entity of maternal and paternal ACE combined or parental sex has been used as a confounder or the studies have only reported the effects of maternal ACE.[6,8,18,27] Some studies have reported an elevated risk of asthma and allergy symptoms in the offspring when mothers were exposed to ACE or when parental sex was used as a confounder.[8,9] Interestingly, animal and human studies have suggested that maternal and paternal ACE could induce different epigenetic effects,

TABLE 2 Characteristics of study population.

Exposures	No sensitisation ($n=327$)	Sensitisation cut-off 0.35 kU/L ($n=206$)	p[a]	No sensitisation ($n=371$)	Sensitisation cut-off 0.70 kU/L ($n=162$)	p[a]	No rhinitis ($n=468$)	Allergic rhinitis ($n=122$)	p[a]
Parental characteristics									
Paternal age at birth, years, mean (SD)	33 (5.0) $n=327$	32 (5.3) $n=205$	0.89	32 (5.2) $n=371$	33 (5.0) $n=161$	0.93	33 (5.3) $n=468$	32 (5.1) $n=121$	0.80
Maternal age at birth, years, mean (SD)	31 (4.4) $n=325$	30 (4.3) $n=205$	0.29	31 (4.5) $n=369$	31 (4.1) $n=161$	0.78	31 (4.4) $n=465$	31 (4.3) $n=122$	0.72
Maternal pre-pregnancy body-mass index, kg/m^2, median (IQR)	23 (21:26) $n=325$	24 (21:27) $n=205$	0.22	24 (21:27) $n=369$	23 (21:26) $n=161$	0.94	24 (21:27) $n=465$	23 (21:26) $n=122$	0.13
Maternal smoking, no. (%)									
Quit in early pregnancy	17/325 (5.2)	6/205 (2.9)	0.41	17/369 (4.6)	6/161 (3.7)	0.82	22/465 (4.7)	3/122 (2.5)	0.091
Through pregnancy	8/325 (2.5)	4/325 (2.0)		9/369 (2.4)	3/161 (1.9)		10/465 (2.2)	3/122 (2.5)	
Paternal smoking, no. (%)	84/276 (30)	43/173 (25)	0.20	93/313 (30)	34/136 (25)	0.31	133/460 (29)	33/119 (28)	0.80
Maternal atopic diseases, no. (%)	111/325 (34)	97/199 (49)	**<0.001**	135/368 (37)	73/156 (47)	**0.032**	170/461 (37)	64/119 (54)	**<0.001**
Paternal atopic diseases, no. (%)	116/326 (36)	79/205 (39)	0.52	131/370 (35)	64/161 (40)	0.38	152/465 (33)	61/122 (50)	**<0.001**
Paternal level of education, no. (%)									
Up to 12 years	139/327 (43)	91/206 (44)	0.81	160/371 (43)	70/162 (43)	0.64	209/467 (45)	53/122 (44)	0.96
13–15 years	112/327 (34)	65/206 (32)		127/371 (34)	50/162 (31)		151/467 (32)	40/122 (33)	
Over 15 years	76/327 (23)	50/206 (24)		84/371 (23)	42/162 (26)		107/467 (23)	29/122 (24)	
Parental level of education, no. (%)									
Up to 12 years	67/327 (20)	42/204 (21)	0.71	79/371 (21)	30/160 (19)	0.16	101/468 (22)	21/120 (18)	0.56
13–15 years	123/327 (38)	70/204 (34)		142/371 (38)	51/160 (32)		168/468 (36)	43/120 (36)	
Over 15 years	137/327 (42)	92/204 (45)		150/371 (40)	79/160 (49)		199/468 (43)	56/120 (47)	
Maternal EPDS score (range 0–30), median at gwks 34 (IQR)	3.0 (1.0:7.0) $n=303$	3.0 (1.0:7.0) $n=184$	0.64	3.0 (1.0:7.0) $n=341$	3.0 (1.0:7.0) $n=146$	0.36	4.0 (1.0:7.0) $n=423$	4.0 (2.0:8.0) $n=113$	0.074

(Continues)

TABLE 2 (Continued)

Exposures	No sensitisation ($n=327$)	Sensitisation cut-off 0.35 kU/L ($n=206$)	p[a]	No sensitisation ($n=371$)	Sensitisation cut-off 0.70 kU/L ($n=162$)	p[a]	No rhinitis ($n=468$)	Allergic rhinitis ($n=122$)	p[a]
Paternal EPDS score (range 0–30), median at gwks 34 (IQR)	2.0 (1.0:5.0) $n=251$	2.0 (1.0:5.0) $n=161$	0.76	2.0 (1.0:5.0) $n=286$	2.0 (1.0:5.0) $n=126$	0.96	2.0 (1.0:4.6) $n=358$	2.0 (1.0:5.0) $n=96$	0.76
Paternal TADS (range 0–164) between 0 and 18 years, median (IQR)	18 (11:27) $n=327$	16 (10:24) $n=206$	**0.044**	18 (12:27) $n=371$	15 (9.0:23) $n=162$	**0.003**	18 (11:27) $n=468$	16 (10:23) $n=122$	0.078
Paternal TADS (between 0 and 18 years)									
<11 points	84/327 (26)	66/206 (32)	**0.31**	92/371 (25)	58/162 (36)	**0.055**	128/468 (27)	39/122 (29)	0.17
11–17 points	75/327 (23)	44/206 (21)		83/371 (22)	36/162 (22)		98/468 (21)	33/122 (27)	
18–27 points	80/327 (24)	52/206 (25)		97/371 (26)	35/162 (22)		117/468 (25)	27/122 (22)	
>27 points	88/327 (27)	44/206 (21)		99/371 (27)	33/162 (20)		125/468 (27)	23/122 (19)	
Father-experienced bereavement of a parent during own childhood, no. (%)	13/309 (4.2)	4/201 (2.0)	0.17	14/352 (4.0)	3/158 (1.9)	0.23	12/442 (2.7)	6/119 (5.0)	0.20
Child characteristics									
Gestational age, weeks, mean (SD)	40 (1.6) $n=327$	40 (1.6) $n=206$	0.32	40 (1.7) $n=371$	40 (1.6) $n=162$	0.56	39 (1.9) $n=468$	40 (1.7) $n=122$	0.82
Birth weight, g, mean (SD)/ length, cm, mean (SD)	3600 (550) $n=325$/51 (2.4) $n=325$	3600 (520) $n=205$/51 (2.3) $n=205$	0.63/0.83	3600 (540) $n=369$/51 (2.4) $n=369$	3600 (540) $n=161$/51 (2.4) $n=161$	0.75/0.63	3500 (550) $n=465$/51 (2.5) $n=465$	3600 (560) $n=122$/51 (2.4) $n=122$	0.88/0.86
Male sex, no. (%)	175/327 (54)	113/206 (55)	0.42	193/371 (52)	95/162 (59)	0.19	246/468 (53)	71/122 (58)	0.27
Number of older siblings, no. (%)									
One	153/445 (34)	85/264 (32)	0.63	172/505 (53)	115/204 (56)	0.74	120/404 (30)	29/96 (30)	0.73
Two or more	57/445 (13)	30/264 (11)		64/505 (13)	23/204 (11)		40/404 (9.9)	7/96 (7.3)	
Older siblings with mother-reported atopic diseases, no. (%)	43/325 (13)	31/199 (16)	0.27	48/368 (13)	26/156 (17)	0.28	60/461 (13)	20/119 (17)	0.29

Abbreviations: CI, Confidence interval; EPDS, Edinburgh Postnatal Depression Scale; gwks, Gestational weeks; IQR, Interquartile range; OR, Odds ratio; SD, Standard deviation; TADS, Trauma and Distress Scale.

[a]Indicates group comparisons.

Bold indicating p values below 0.05.

TABLE 3 Risk of sensitisation and allergic rhinitis.

	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^a**	**OR**	**95% CI**	**p^a**	**OR**	**95% CI**	**p^a**
Unadjusted analyses									
Maternal atopic diseases	1.8	1.3–2.6	<0.001	1.5	1.0–2.2	0.031	2.0	1.3–2.0	<0.001
Paternal atopic diseases	1.1	0.79–1.6	0.49	1.2	0.81–1.8	0.34	2.1	1.4–3.1	<0.001
Maternal smoking during pregnancy									
Quit in early pregnancy	0.54	0.21–1.4	0.21	0.80	0.31–2.1	0.64	0.51	0.15–1.7	0.28
Through pregnancy	0.77	0.22–2.6	0.67	0.75	0.20–2.8	0.75	1.1	0.30–4.1	0.87
Paternal smoking	0.67	0.45–1.0	0.049	0.66	0.43–1.0	0.054	0.94	0.60–1.5	0.80
Older children with mother-reported atopic diseases	1.2	0.73–2.0	0.45	1.3	0.74–2.2	0.28	1.4	0.78–2.3	0.29
Male vs. female sex	1.1	0.74–1.5	0.76	1.3	0.90–1.9	0.16	1.3	0.84–10.9	0.27
Paternal level of education									
Up to 12 years	1.0	0.64–1.6	0.98	0.88	0.55–1.4	0.88	0.94	0.56–1.6	0.80
13–15 years	0.88	0.55–1.4	0.60	0.79	0.48–1.3	0.34	0.98	0.57–1.7	0.93
Over 15 years	ref			ref			ref		
Parental level of education									
Up to 12 years	0.93	0.59–1.5	0.77	0.72	0.44–1.2	0.20	0.74	0.42–1.3	0.29
Between 13 and 15 years	0.85	0.57–1.3	0.41	0.68	0.45–1.0	0.074	0.91	0.58–1.4	0.68
Over 15 years	ref			ref			ref		
Maternal EPDS score at gwks 34	0.99	0.95–1.0	0.73	0.97	0.92–1.0	0.20	1.0	0.99–1.1	0.11
Paternal EPDS score at gwks 34	1.0	0.96–10.1	0.52	10.0	0.95–1.1	0.72	1.0	0.93–1.1	0.87
Paternal TADS between 0 and 18 years of life per point (range 0–164 continuous)	0.99	0.97–1.0	0.069	0.98	0.968–0.998	0.023	0.99	0.97–1.0	0.081
Paternal TADS between 0 and 18 years of life, quartiles									
<11 points	ref			ref			ref		
11–17 points	0.75	0.46–1.2	0.25	0.67	0.41–1.1	0.69	1.1	0.65–1.9	0.71
18–27 points	0.83	0.51–1.3	0.83	0.57	0.35–0.95	0.031	0.76	0.44–1.3	0.32
>27 points	0.64	0.39–1.0	0.068	0.53	0.32–0.88	0.015	0.60	0.34–1.1	0.084
Number of older siblings									
None	1.2	0.74–2.0	0.44	1.2	0.71–2.0	0.51	0.98	0.60–1.6	0.95
One	1.1	0.64–1.8	0.80	1.1	0.62–1.9	0.79	0.71	0.30–1.7	0.43
Two or more	ref			ref			ref		
Adjusted analyses									
Model one									
Paternal TADS between 0 and 18 years of life, quartiles									

(Continues)

TABLE 3 (Continued)

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^a	OR	95% CI	p^a	OR	95% CI	p^a
<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
Maternal EPDS score at gwks 34	1.0	0.95–1.0	0.094	0.98	0.93–1.0	0.44	1.1	1.0–1.1	0.048
Maternal atopic diseases	2.0	1.3–2.9	<0.001	1.5	1.0–2.3	0.049	1.8	1.2–2.7	0.008
Model two									
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
Maternal EPDS score at gwks 34	1.0	0.95–1.1	1.0	0.98	0.93–1.0	0.52	1.1	1.0–1.1	0.018
Maternal atopic diseases	2.0	1.3–2.9	<0.001	1.5	1.0–2.3	0.048	1.9	1.2–2.9	0.004
Paternal atopic diseases	1.1	0.75–1.7	0.60	1.2	0.82–1.9	0.31	2.2	1.4–3.5	<0.001
Model three									
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
Maternal EPDS score at gwks 34	1.0	0.95–1.0	0.87	0.98	0.92–1.0	0.36	1.1	1.0–1.1	0.054
Maternal atopic diseases	2.0	1.3–2.9	<0.001	1.5	1.0–2.3	0.041	1.8	1.2–2.8	0.007
Parental level of education									
Up to 12 years	0.089	0.52–1.5	0.65	00.77	0.44–1.3	0.36	0.77	0.42–1.4	0.41
Between 13 and 15 years	0.82	0.54–1.3	0.36	0.68	0.43–1.1	0.092	0.94	0.58–1.5	0.80
Over 15 years	ref			ref			ref		
Model four									
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

TABLE 3 (Continued)

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^a	OR	95% CI	p^a	OR	95% CI	p^a
18–27 points	0.88	0.50–1.5	0.65	0.57	0.31–1.0	0.060	0.76	0.040–1.4	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
Maternal EPDS score at gwks 34	0.99	0.94–1.0	0.74	0.98	0.92–1.0	0.50	1.1	1.0–1.1	0.070
Maternal atopic diseases	2.1	1.4–3.2	<0.001	1.7	1.1–2.7	0.013	1.8	1.1–2.9	0.012
Number of older siblings									
None	2.0	0.90–4.5	0.087	1.8	0.77–4.4	0.17	1.4	0.54–3.5	0.50
One	1.5	0.64–3.5	0.35	1.5	0.59–3.7	0.40	0.56	0.56–3.9	0.42
Two or more	ref			ref			ref		
Model five									
Paternal TADS between 0 and 18 years of life, quartiles									
<11 points	ref			ref			ref		
11–17 points	0.66	0.038–1.2	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
Maternal EPDS score at gwks 34	0.99	0.94–1.0	0.72	0.98	0.92–1.0	0.41	1.1	1.0–1.1	0.034
Paternal atopic diseases	1.2	0.81–1.9	0.34	1.4	0.87–2.1	0.18	2.2	1.4–3.6	0.001
Maternal atopic diseases	2.2	1.5–3.4	<0.001	1.8	1.2–2.8	0.009	2.0	1.2–3.3	0.004
Parental level of education									
Up to 12 years	0.83	0.47–1.5	0.51	0.72	0.39–1.3	0.72	0.69	0.34–1.4	0.30
Between 13 and 15 years	0.83	0.53–1.3	0.43	0.71	0.44–1.1	0.71	0.99	0.59–1.7	0.96
Over 15 years	ref			ref			ref		
Number of older siblings									
None	1.9	0.84–4.2	0.12	1.7	0.70–4.1	0.24	1.2	0.48–3.2	0.65
One	1.4	0.61–3.4	0.40	1.4	0.56–3.6	0.45	1.5	0.56–4.1	0.41
Two or more	ref			ref			ref		

Abbreviations: CI, Confidence interval; EPDS, Edinburgh Postnatal Depression Scale; gwks, Gestational weeks; IQR, Interquartile range; OR, Odds ratio; TADS, Trauma and Distress Scale.

behavioural outcomes and health outcomes in the offspring, and this highlights the significance of separating the effect of parental sex.[7,9,11]

Therefore, the pathways explaining the link between paternal ACE and lowered risk of offspring atopic traits might involve parental sex differences depending upon whether it has been the mother or the father who has been exposed to ACE. This gains support from studies showing that the function of the hypothalamic–pituitary–adrenal axis and the status of glucocorticoid receptors were dissimilarly altered among the offspring of Holocaust survivors, depending on the sex of the parent who survived the Holocaust and developed the post-traumatic stress disorder.[10,11] Interestingly, paternal exposure to the post-traumatic stress disorder decreased the sensitivity of the dexamethasone suppression test of the offspring, increased the 24-h cortisol excretion[11,12] and induced methylation of the 1F promoter gene of the glucocorticoid receptor which affects glucocorticoid metabolism.[10] These findings were opposite to what maternal exposure to the

post-traumatic stress disorder caused in the offspring.[10,11] Several animal studies and a few human studies have similarly reported sex-specific alterations of glucocorticoid metabolism and various epigenetic factors, as described in a review by Condon et al.[7] Maternal prenatal psychological distress symptoms have been linked to atopic diseases in the offspring and our results suggest that paternal ACE influences atopy in the offspring independently of maternal prenatal psychological distress symptoms.[8,9,27]

This observational study can report associations but cannot establish causality. Intergenerational pathways could be mediated by epigenetic changes in paternal germ cells or by interactions between genes and the environment. Animal studies have shown that transgenerational epigenetic changes occur in the paternal germline after exposure to stressful situations postnatally.[7,28] The epigenetic changes are then passed on to the offspring, and as mentioned above, result in functional changes in the hypothalamic–pituitary–adrenal axis and stress responses in the offspring.[28] This mechanism could lead to blunted Th2 immune responses evidenced as lowered levels of IgE antibodies and AR, as was also evidenced by our study. Obviously, the mechanisms of the somewhat surprising associations, not reported previously, need to be addressed in further studies. At this stage, they are hypothetical.

4.1 | Strengths and limitations

Our study had several strengths. The study included data on the level of individuals of around 500 father-child dyads in the large FinnBrain Birth Cohort Study.[20] Outcomes were assessed validly – we used laboratory-verified sensitisation assessment, i.e., IgE antibody levels, and the clinical diagnosis of AR was based on the validated ISAAC questionnaire used by study paediatricians to diagnose or exclude AR when the child was 5.5 years of age.[19] AR in small children is a heterogenous condition and there is a potential for diagnostic errors, even when diagnosed by a physician or paediatrician or when the evaluation is based on a validated questionnaire. However, the prevalence of sensitisation (30%) and AR (21%) in our study was consistent with previous studies and this supports the supposition that our results are reliable and generalisable.[29]

Previous studies have used varying definitions of parental ACE, ranging from parental bereavement to major negative life events, such as divorce.[8,9] This lack of stringency could lead to heterogenous findings and to limited comparability between studies. We included both bereavement of the father's own parent during childhood and paternal ACE based on the TADS questionnaire to study different aspects of adverse childhood experiences. The number of fathers who had experienced parental bereavement was low in our population. A recent study by Karlsson et al. utilised the TADS questionnaire,[21] and found a positive association between cumulative paternal ACE and newborn brain white matter maturation, in terms of aberrantly high fractional anisotropy values in certain parts of the brain of newborn offsprings.[30] The TADS is clinically useful and reliable for evaluation of childhood traumatisation. The median TADS score in our study was in line with previous work on the psychometric properties of the TADS.[21]

Drop-out is inevitable in birth cohort studies, and only a proportion of the original study population was included in this study. In the included families the parental level of education was higher, psychiatric issues less frequent and the mothers older compared to the ones excluded due to missing data. However, as attrition analysis showed, the differences were not substantial. Despite the variation caused by drop-outs, the fact that the study data originated from a population-based cohort assures generalisability of the data from the study population. Any recall bias related to reporting paternal ACE with the TADS questionnaire is a common challenge in observational studies. Although we adjusted for multiple factors in several models, some residual confounding may have persisted. Some currently unknown mediators related, for example, to paternal lifestyle, could affect the epigenome of gametes and so influence the immune function of the offspring. Some covariates that affect allergic outcomes are probably not associated with paternal ACE but are still considerable risk factors and should therefore be included as covariates, such as maternal atopic diseases. The parental level of education was used as a proxy for the socioeconomic status of the family, since a low level of education is a known risk factor for atopic diseases.[2] Interestingly, the association between paternal TADS scores and the reduced risk of offspring sensitisation and AR persisted after adjustment for the parental level of education and other confounders, suggesting that paternal ACE is an independent factor affecting the development of atopic diseases in offspring.

5 | CONCLUSION

Paternal ACE were associated with a reduced risk of offspring sensitisation and AR. This might indicate that father-experienced childhood neglect and/or abuse affects the susceptibility of the offspring to atopic diseases through alterations in the immune balance between type 1 helper cells and type 2 helper cells. Although observational studies, similar to the present one, cannot prove causality, the mechanisms of the recently discovered and somewhat surprising associations need to be addressed in further studies.

AUTHOR CONTRIBUTIONS

Emma Puosi: Writing – review and editing; writing – original draft; funding acquisition; conceptualization; methodology; formal analysis; visualization; data curation. **Hasse Karlsson:** Writing – review and editing; funding acquisition; conceptualization; project administration; resources; data curation. **Heikki Lukkarinen:** Writing – review and editing; conceptualization; methodology; supervision. **Linnea Karlsson:** Writing – review and editing; funding acquisition; conceptualization; project administration; resources; data curation. **Minna Lukkarinen:** Writing – review and editing; writing – original

draft; funding acquisition; conceptualization; methodology; supervision; data curation.

ACKNOWLEDGEMENTS

We thank the families participating in the FinnBrain Birth Cohort Study and the study nurses and cohort staff for their assistance.

FUNDING INFORMATION

This work was supported by the Academy of Finland, the Allergy Research Foundation, the Finnish Medical Foundation, the Juho Vainio Foundation, the Maire Taposen Foundation, the Päivikki and Sakari Sohlberg Foundation, the Signe and Ane Gyllenberg Foundation, the Southwestern Finland Foundation of Allergy Research, and the TYKS Foundation – all in Finland. None of the funding sources were involved in study design, data collection, analyses, interpretation of data, writing of the report or decision to submit this manuscript for publication.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Emma Puosi https://orcid.org/0000-0002-6301-9353

REFERENCES

1. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. Nat Genet. 2017;49(12):1752-7. doi:10.1038/ng.3985
2. Schyllert C, Lindberg A, Hedman L, et al. Low socioeconomic status relates to asthma and wheeze, especially in women. ERJ Open Res. 2020;6(3):00258-02019. doi:10.1183/23120541.00258-2019
3. Flanigan C, Sheikh A, DunnGalvin A, Brew BK, Almqvist C, Nwaru BI. Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: a systematic review and meta-analysis. Clin Exp Allergy. 2018;48(4):403-14. doi:10.1111/cea.13091
4. Puosi E, Korhonen LS, Karlsson L, et al. Maternal prenatal psychological distress associates with offspring early-life wheezing – FinnBrain Birth Cohort. Pediatr Allergy Immunol. 2022;33(1):e13706. doi:10.1111/PAI.13706
5. Lukkarinen M, Puosi E, Kataja EL, et al. Maternal psychological distress during gestation is associated with infant food allergy. Pediatr Allergy Immunol. 2021;32(4):787-92. doi:10.1111/PAI.13449
6. Folger AT, Eismann EA, Stephenson NB, et al. Parental adverse childhood experiences and offspring development at 2 years of age. Pediatrics. 2018;141(4):e20172826. doi:10.1542/peds.2017-2826
7. Condon EM, Dettmer A, Baker E, McFaul C, Stover CS. Early life adversity and males: biology, behavior, and implications for fathers' parenting. Neurosci Biobehav Rev. 2022;135:104531. doi:10.1016/J.NEUBIOREV.2022.104531
8. Lê-Scherban F, Wang X, Kathryn HBS, Pachter LM. Intergenerational associations of parent adverse childhood experiences and child health outcomes. Pediatrics. 2018;141(6):e20174274. doi:10.1542/PEDS.2017-4274
9. Brew BK, Lundholm C, Caffrey Osvald E, et al. Early-life adversity due to bereavement and inflammatory diseases in the next generation: a population study in transgenerational stress exposure. Am J Epidemiol. 2021;191(1):38-48. doi:10.1093/AJE/KWAB236
10. Yehuda R, Daskalakis NP, Lehrner A, et al. Influences of maternal and paternal PTSD on epigenetic regulation of the glucocorticoid receptor gene in Holocaust survivor offspring. Am J Psychiatry. 2014;171(8):872-80. doi:10.1176/appi.ajp.2014.13121571
11. Lehrner A, Bierer LM, Passarelli V, et al. Maternal PTSD associates with greater glucocorticoid sensitivity in offspring of Holocaust survivors. Psychoneuroendocrinology. 2014;40(1):213-20. doi:10.1016/J.PSYNEUEN.2013.11.019
12. Van Steenwyk G, Roszkowski M, Manuella F, Franklin TB, Mansuy IM. Transgenerational inheritance of behavioral and metabolic effects of paternal exposure to traumatic stress in early postnatal life: evidence in the 4th generation. Environ Epigenet. 2018;4(2):1-8. doi:10.1093/EEP/DVY023
13. Demaestri C, Pan T, Critz M, Ofray D, Gallo M, Bath KG. Type of early life adversity confers differential, sex-dependent effects on early maturational milestones in mice. Horm Behav. 2020;124:104763. doi:10.1016/J.YHBEH.2020.104763
14. Mørkve Knudsen T, Rezwan FI, Jiang Y, Karmaus W, Svanes C, Holloway JW. Transgenerational and intergenerational epigenetic inheritance in allergic diseases. J Allergy Clin Immunol. 2018;142(3):765-72. doi:10.1016/J.JACI.2018.07.007
15. Liu J, Bowatte G, Pham J, et al. Pre-pubertal smoke exposure of fathers and increased risk of offspring asthma: a possible transgenerational effect. Eur Respir J. 2022;60(4):2200257. doi:10.1183/13993003.00257-2022
16. Merrill SM, Moore SR, Gladish N, et al. Paternal adverse childhood experiences: associations with infant DNA methylation. Dev Psychobiol. 2021;63(6):e22174. doi:10.1002/DEV.22174
17. Zheng X, Li Z, Wang G, et al. Sperm epigenetic alterations contribute to inter- and transgenerational effects of paternal exposure to long-term psychological stress via evading offspring embryonic reprogramming. Cell Discov. 2021;7(1):101. doi:10.1038/S41421-021-00343-5
18. Lacey RE, Bartley M, Kelly-Irving M, et al. Adverse childhood experiences and early life inflammation in the Avon longitudinal study of parents and children. Psychoneuroendocrinology. 2020;122:104914. doi:10.1016/J.PSYNEUEN.2020.104914
19. Asher MI, Keil U, Anderson HR, et al. International study of asthma and allergies in childhood (ISAAC): rationale and methods. Eur Respir J. 1995;8(3):483-91. doi:10.1183/09031936.95.08030483
20. Karlsson L, Tolvanen M, Scheinin NM, et al. Cohort profile: the FinnBrain Birth Cohort Study (FinnBrain). Int J Epidemiol. 2018;47(1):15-6. doi:10.1093/ije/dyx173
21. Salokangas RKR, Schultze-Lutter F, Patterson P, et al. Psychometric properties of the trauma and distress scale, TADS, in an adult community sample in Finland. Eur J Psychotraumatol. 2016;7(1):30062. doi:10.3402/EJPT.V7.30062/SUPPL_FILE/ZEPT_A_11820604_SM0002.PDF
22. Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733-43. doi:10.1016/S0140-6736(06)69283-0
23. Gibson J, McKenzie-Mcharg K, Shakespeare J, Price J, Gray R. A systematic review of studies validating the Edinburgh Postnatal Depression Scale in antepartum and postpartum women. Acta Psychiatr Scand. 2009;119(5):350-64. doi:10.1111/J.1600-0447.2009.01363.X
24. Incorvaia C, Fuiano N, Canonica GW. Seeking allergy when it hides: which are the best fitting tests? World Allergy Organ J. 2013;6(1):11. doi:10.1186/1939-4551-6-11
25. Colavita L, Catalano N, Sposito G, et al. Local allergic rhinitis in pediatric patients: is IgE dosage in nasal lavage fluid a useful diagnostic method in children? Int J Mol Cell Med. 2017;6(3):174-82. doi:10.22088/ACADPUB.BUMS.6.3.174

26. Alford SH, Zoratti E, Peterson EL, Maliarik M, Ownby DR, Johnson CC. Parental history of atopic disease: disease pattern and risk of pediatric atopy in offspring. J Allergy Clin Immunol. 2004;114(5):1046-50. doi:10.1016/j.jaci.2004.08.036
27. Tomfohr-Madsen LM, Bayrampour H, Tough S. Maternal history of childhood abuse and risk of asthma and allergy in 2-year-old children. Psychosom Med. 2016;78(9):1031-42. doi:10.1097/PSY.0000000000000419
28. Yehuda R, Lehrner A. Intergenerational transmission of trauma effects: putative role of epigenetic mechanisms. World Psychiatry. 2018;17(3):243-57. doi:10.1002/wps.20568
29. Schmidt F, Hose AJ, Mueller-Rompa S, et al. Development of atopic sensitization in Finnish and Estonian children: a latent class analysis in a multicenter cohort. J Allergy Clin Immunol. 2019;143(5):1904-13.e9. doi:10.1016/j.jaci.2018.12.1014
30. Karlsson H, Merisaari H, Karlsson L, et al. Association of cumulative paternal early life stress with white matter maturation in newborns. JAMA Netw Open. 2020;3(11):e2024832. doi:10.1001/jamanetworkopen.2020.24832

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: 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 Paediatr. 2024;00:1–14. https://doi.org/10.1111/apa.17345