

ORIGINAL ARTICLE

Association between preschool eczema and medication for attention-deficit/hyperactivity disorder in school age

Emma Kristin Johansson^{1,2}, Natalia Ballardini^{3,4,5}, Inger Kull^{5,6}, Anna Bergström⁵ & Carl-Fredrik Wahlgren^{1,7}

¹Dermatology and Venereology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; ²Dermatological and Venereal Clinic, Södersjukhuset Stockholm, Sweden; ³Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm, Sweden; ⁴St John's Institute of Dermatology, King's College London, London, UK; ⁵Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden;

⁶Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; ⁷Department of Dermatology, Karolinska University Hospital Solna, Stockholm, Sweden

To cite this article: Johansson EK, Ballardini N, Kull I, Bergström A, Wahlgren C-F. Association between preschool eczema and medication for attention-deficit/hyperactivity disorder in school age. *Pediatr Allergy Immunol* 2016; **00**.

Keywords

attention-deficit/hyperactivity disorder; adolescent; atopic dermatitis; child; depression; epilepsy; migraine

Correspondence

Emma Kristin Johansson, Department of Dermatology and Venereology, Södersjukhuset, Sjukhusbacken 10, SE-118 83 Stockholm, Sweden
Tel.: +46-739966540
Fax: +46-86162564
E-mail: emma.k.johansson@sl.se

Accepted for publication 14 September 2016

DOI:10.1111/pai.12657

Abstract

Background: Several studies show an association between eczema and attention-deficit/hyperactivity disorder (ADHD) in childhood, but the mechanisms and time sequence remain unclear. Information on the association between eczema and other disorders involving the central nervous system (CNS) is limited. The aim was to explore whether preschool eczema was associated with ADHD or other CNS-associated disorders requiring pharmacotherapy at school age and to analyze whether eczema at other ages of childhood was associated with medication for ADHD.

Methods: From a Swedish birth cohort, 3606 children were included in the analyses. At 1, 2, 4, 8, 12, and 16 years of age, their parents answered questionnaires regarding eczema the last year. Information on prescribed medications during school age (10–18 years of age) was derived by record linkage to the Swedish Prescribed Drug Register.

Results: A total of 1178 (32.7%) of the children had preschool eczema (eczema at 1, 2, and/or 4 years), and 162 (4.5%) of the children had dispensed ADHD medication at school age. Preschool eczema was not associated with ADHD medication at school age (crude odds ratio 1.16; 95% Confidence Intervals: 0.83–1.61). There was no significant association between preschool eczema and use of antidepressants, migraine drugs, or anti-epileptics at school age. Infantile eczema, school-age eczema, and eczema ever up to 16 years of age were not associated with ADHD medication at school age.

Conclusions: In this large birth cohort, there were no significant associations between preschool eczema and medications for ADHD, depression/anxiety/phobia, migraine, or epilepsy at school age.

Eczema (atopic dermatitis (1)) is a common skin disease that affects many children with a high negative impact on their quality of life (2). Eczema often starts in early childhood (3), and the prevalence in children is 15–30% (2). Eczema is associated with asthma and rhinitis (4–6). In recent years, studies have shown association between eczema and disorders involving the central nervous system (CNS), such as attention-deficit/hyperactivity disorder (ADHD) (7–11), depression and anxiety disorders (8, 12), and epilepsy (13, 14).

The most well-studied association is between eczema and ADHD, and in a systematic review, the odds ratios (OR) range from 1.47 to 7.75 (7). The underlying mechanisms and temporal relationship remain unclear. However, several

possible explanations have been suggested. One is through inflammatory-released cytokines that penetrate the blood–brain barrier during eczema episodes and interfere with maturation of the cortex and the transmitter systems involved in development of ADHD and other CNS-associated disorders (15). Studies have also shown association between asthma and/or rhinitis and ADHD (9, 16, 17). Another possible pathomechanism is shared risk factors between atopic diseases and ADHD. For example, low socioeconomic status, low birthweight, impaired fetal growth, and parental smoking are all risk factors for both asthma and ADHD (18). A third explanation could be that children with eczema are more prone to develop mental and behavioral symptoms due to their

illness (17). Children with chronic diseases, such as arthritis, migraine, heart, or blood disorder, more often have emotional and behavioral problems compared with the general population (19). CNS-associated disorders could be a result of chronic diseases in childhood, with eczema being one of them (8). Furthermore, ADHD might be a trigger for eczema. Children with ADHD have psychosocial impairment and increased risk for depression, anxiety, and sleep disturbance. Psychosocial stress affects the severity of eczema (20).

The reported prevalence of ADHD has increased during recent decades and is estimated to 6.7–7.8% (21). Psychostimulant medication is used as treatment for ADHD. In a Swedish study performed in 2006–2011, 83.1–84.7% of children (6–17 years of age) with ADHD had used ADHD medication (22).

The primary aim of this study was to explore whether preschool eczema is associated with medication for ADHD, depression/anxiety/phobia, migraine, or epilepsy at school age using longitudinal data from a population-based setting and information on prescribed drugs from a register with national coverage. In addition, we wanted to investigate whether eczema at other ages during childhood was associated with ADHD medication, because any temporal relationship between eczema and ADHD remains unclear.

Methods

Study design and setting

The BAMSE project is a longitudinal birth cohort study recruited from the general population in which children were included at birth and followed during childhood. Parents of all children ($n = 7221$) born between February 1994 and November 1996 living in predefined areas of Stockholm County were asked to participate. The final study cohort of 4089 children constituted 75% of the eligible children (23). Detailed data on residential characteristics, environmental factors, and parental allergy were obtained when the child was around 2 months old from a baseline parental questionnaire (23). When the children

were 1, 2, 4, 8, 12, and 16 years, the parents completed questionnaires about manifestations of eczema, asthma, and rhinitis during the preceding 12 months. At the 16-year follow-up, 3181 (78%) still remained in the cohort.

Study population

The study population consisted of children whose parents completed the questionnaires and provided information regarding eczema at 1, 2, and 4 years of age ($n = 3606$; 88.2% of the original cohort). A subpopulation ($n = 2736$; 66.9% of the original cohort) consisting of children with complete data on eczema in all parental questionnaires (at 1, 2, 4, 8, 12, and 16 years of age) was used when analyzing eczema at other ages (Fig. 1).

Definition of exposures and background factors

The definitions of eczema are based on parental questionnaires and include report of dry skin in combination with itchy skin lesions on age-specific locations and/or reported doctor's diagnosis of eczema in the latest 12 months (Table 1). Eczema phenotypes used as exposures in the current study are presented in Fig. 2. Definitions of background variables and potential confounders are shown in Table S1.

Definition of outcomes

Definition of ADHD and the other CNS-associated disorders was based on prescribed drugs for that particular disease. Information on prescribed medications during school age (10–18 years) was derived by record linkage to the Swedish Prescribed Drug Register (SPDR). Linkage was performed using the Swedish personal identity number (24). When SPDR was started in 2005, the children in the BAMSE cohort were 10 years of age (range 8.6–11.4); the register contains data on all dispensed drug prescriptions in Sweden (25). Data from SPDR were collected through Dec 31, 2013, when the participants in the BAMSE cohort were 18 years of age (range

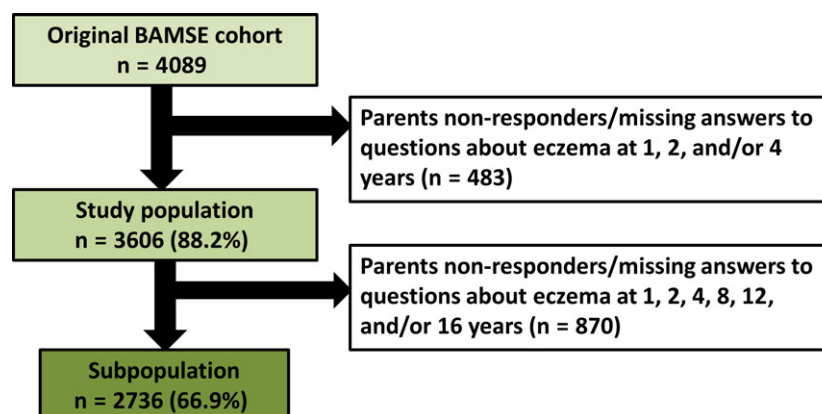


Figure 1 Flowchart of the study population.

Table 1 Definition of exposure variables based on parental questionnaires

Variable	Definition
Eczema at 1 year of age	Dry skin and itchy skin rash for ≥ 2 weeks on specific location (face or arms/legs extension surfaces or arms/legs flexures or wrists/ankles flexures) and/or doctor's diagnosis of eczema after 3 months of age up to 1 year of age
Eczema at 2 years of age	Dry skin and itchy skin rash for ≥ 2 weeks on specific location (face or arms/legs extension surfaces or arms/legs flexures or wrists/ankles flexures) and/or doctor's diagnosis of eczema after 1 year of age up to 2 years of age
Eczema at 4 years of age	Dry skin and itchy skin rash for ≥ 2 weeks on specific location (face or arms/legs extension surfaces or arms/legs flexures or wrists/ankles flexures) over the last 12 months and/or doctor's diagnosis of eczema after 2 years of age up to 4 years of age
Eczema at 8 years of age	Dry skin and itchy skin rash for ≥ 2 weeks on specific location (face or arms/legs flexures or wrists/ankles or neck) over the last 12 months and/or doctor's diagnosis of eczema after 4 years of age up to 8 years of age
Eczema at 12 years of age	Dry skin and itchy skin rash on specific location (arms/legs flexures or wrists/ankles or neck) over the last 12 months and/or doctor's diagnosis of eczema after 10 years of age up to 12 years of age
Eczema at 16 years of age	Dry skin and itchy skin rash on specific location (arms/legs flexures or wrists/ankles or neck/throat) over the last 12 months and/or doctor's diagnosis of eczema after 12 years of age up to 16 years of age
Doctor's diagnosis of infantile eczema	Reported doctor's diagnosis of eczema at 1 and/or 2 years of age. Children without infantile eczema and children with reported symptoms of infantile eczema (without doctor's diagnosis) were classified as control group
Doctor's diagnosis of preschool eczema	Reported doctor's diagnosis of eczema at 1, 2, and/or 4 years of age. Children without preschool eczema and children with reported symptoms of preschool eczema (without doctor's diagnosis) were classified as control group
Preschool eczema with sleep disturbance	Eczema (reported symptoms and/or doctor's diagnosis) in combination with reported sleep disturbance due to itch at least once a week at 1, 2, and/or 4 years of age. Children without preschool eczema were classified as reference

17.1–19.9). CNS-associated disorders with disease-specific medication were chosen for analysis: antimigraine medications (N02C), anti-epileptics (N03A), antidepressants (N06A), and psychostimulants (N06BA). The drugs had to be registered at least once between July 1, 2005, and Dec 31, 2013, and were assumed to be a proxy for the diagnoses migraine, epilepsy, depression/anxiety/phobia, and ADHD, respectively.

Statistics

Background characteristics were expressed as percentage of the total number of individuals observed, and 95% confidence intervals (95% CI) were calculated by applying one sample *t*-test with finite population correction. The prevalence of eczema, asthma, and rhinitis was assessed over a 12-month period. Chi-square tests were used for dichotomous variables. *p*-values <0.05 were considered statistically significant. Logistic regression was used for evaluation of the association between eczema and CNS-associated disorders. Different potential confounder models were tested. All tested confounders changed the OR <10%. The final model included adjustment for sex, socioeconomic status, breastfeeding, and parental smoking, based on prior knowledge. In addition, adjustments were made for asthma and rhinitis. Potential significant interaction was explored for the same covariates, but not

observed. Assuming an ADHD prevalence of 5% among children without preschool eczema and a two-sided significance level of 0.05, the study had 80% power to detect an odds ratio (OR) of 1.51. Statistical calculations were performed with STATA Statistical Software (Stata-Corp, College Station, TX, USA).

Ethics

This study was approved by the Regional Ethical Review Board at Karolinska Institutet, Stockholm. Informed consent was provided by teenagers and guardians.

Results

There were minor significant differences between the study participants (*n* = 3606) and the original cohort (*n* = 4089) concerning background characteristics (Table S2).

In the study population, 6.6% of the children had dispensed antidepressants, 4.5% ADHD medication, 2.1% migraine drugs, and 1.6% antiepileptics. The group that used ADHD medication differed somewhat from non-users and was characterized by male sex (69.8% vs. 49.7%, *p* < 0.001), low socioeconomic (28.0% vs. 15.9%, *p* < 0.001), parental smoking (28.8% vs. 20.1%, *p* = 0.008), and young mothers (15.4% vs.

Eczema at 1 year	Eczema at 2 year	Eczema at 4 year	Eczema at 8 year	Eczema at 12 year	Eczema at 16 year
Infantile eczema* (eczema at 1, and/or 2 year)					
Preschool eczema* (eczema at 1, 2, and/or 4 year)					
			Eczema at school age* (eczema at 8, 12, and/or 16 year)		
Eczema ever up to 16 year [†] (eczema at 1, 2, 4, 8, 12, and/or 16 year)					
Transient eczema [†] (eczema at 1, 2, and 4 year and no eczema at 8, 12, and 16 year)			Eczema with onset at school age [†] (eczema at 8, 12, and 16 year and no eczema at 1, 2, and 4 year)		
Persistent eczema [†] (eczema at 1, 2, and/or 4 year AND eczema at 8, 12, and/or 16)					

*Children without eczema at that particular age (infancy, preschool age, or school age) but possibly eczema at other ages were classified as non-exposed.

[†]Children without eczema at 1, 2, 4, 8, 12 and 16 years were classified as non-exposed

Figure 2 Eczema phenotypes used as exposures in the current study. Children with or without infantile and/or preschool eczema could have had eczema later in life, and children with or without school-age eczema could have had eczema earlier in life. Only children with complete data regarding eczema were included in both eczema and non-eczema groups (no missing).

Table 2 Association between preschool eczema and use of drugs for central nervous system-associated disorders at school age (10–18 years of age)

	Children with preschool eczema N = 1178		Children without preschool eczema [†] N = 2428		Crude OR OR (95% CI)	Adjusted OR ^{‡,§} OR (95% CI)
	n	%	n	%		
Prescribed medication						
Antidepressants	69	5.9	168	6.9	0.84 (0.63–1.12)	0.83 (0.62–1.11)
ADHD drugs	58	4.9	104	4.3	1.16 (0.83–1.61)	1.12 (0.80–1.56)
Migraine drugs	27	2.3	48	2.0	1.16 (0.72–1.87)	1.05 (0.64–1.72)
Anti-epileptics	20	1.7	38	1.6	1.09 (0.63–1.88)	1.05 (0.60–1.84)

Children in the BAMSE cohort whose parents participated in the follow-up and provided information on eczema at 1, 2, and 4 years of age, constituted the study population, N = 3606.

[†]The reference group were children without preschool eczema including children who have had eczema later in life.

[‡]Adjusted for background variables; sex, exclusive breastfeeding >4 months, parental smoking, socioeconomic.

[§]There was 0–19 missing values among background variables, N = 3573.

7.0%, $p < 0.001$). Exclusive breastfeeding was less common among those with ADHD medication (72.8% vs. 80.3%, $p = 0.02$). Preschool eczema was reported among 32.7% of the children, and 25.2% had infantile eczema (Fig. 2).

In the subpopulation of children who participated in all follow-ups, 41.2% (1126 of 2736) had eczema ever up to 16 years. Of these children, 434 had transient eczema, 440 had persistent eczema, and 252 had eczema with onset during school age. The prevalence of ADHD medication was significantly lower among children in the subpopulation (3.7%; Table S2).

Preschool eczema in relation to ADHD medication at school age

Preschool eczema was not significantly associated with ADHD medication (crude OR 1.16; 95% CI: 0.83–1.61; Table 2). Furthermore, preschool eczema in combination with sleep disturbances due to itching was not statistically associated with ADHD medication at school age (crude OR 1.36; 95% CI: 0.85–2.16). Reported doctor's diagnosis of preschool eczema (817 of 3604, 22.7%) was not associated with ADHD

Table 3 Association between eczema ever up to 16 years, and ADHD medication (any time at 10–18 years of age)

Eczema ever up to 16 years†	ADHD medication at school age			Crude OR OR (95% CI)	Adjusted OR‡§ OR (95% CI)
	Total N = 2736	Cases N = 101	%		
No eczema ever (ref)	1610	57	3.5	1	1
Eczema ever up to 16 years	1126	44	3.9	1.11 (0.74–1.65)	1.09 (0.72–1.64)
Transient eczema¶	434	15	3.5	0.98 (0.55–1.74)	0.99 (0.55–1.78)
Eczema with onset at school age††	252	7	2.8	0.78 (0.35–1.73)	0.87 (0.39–1.93)
Persistent eczema‡‡	440	22	5.0	1.43 (0.87–2.37)	1.28 (0.75–2.16)

The analysis was performed among children in the BAMSE cohort who participated in all follow-ups, N = 2736.

†Eczema at 1, 2, 4, 8, 12, and/or 16 years.

‡Adjusted for background variables; sex, breastfeeding, parental smoking, socioeconomic.

§There were 0–15 missing values among background variables, N = 2714.

¶Eczema at 1, 2, and/or 4 years AND no eczema at 8, 12, and 16.

††Eczema at 8, 12, and/or 16 years AND no eczema at 1, 2, and 4 years.

‡‡Eczema at 1, 2, and/or 4 years AND eczema at 8, 12, and/or 16 years.

medication (crude OR 1.09; 95% CI: 0.75–1.57). Stratification by sex showed no differences between males and females. The analyses were adjusted for asthma and for rhinitis ever up to 16 years of age, with no major changes to the OR (data not shown).

Preschool eczema in relation to medication for depression/anxiety/phobia, migraine, and epilepsy at school age

There were no significant associations between preschool eczema and use of antidepressants, migraine drugs, or anti-epileptics at school age (Table 2).

Eczema in other ages in relation to ADHD at school age

Infantile eczema (crude OR 1.30; 95% CI: 0.92–1.84) and eczema at school age (crude OR 1.20; 95% CI: 0.77–1.86) were not associated with ADHD medication at school age. Neither reported doctor's diagnosis of infantile eczema (656 of 3606, 18.2%; crude OR 1.16; 95% CI 0.78–1.71) nor eczema ever up to 16 years of age was associated with ADHD medication (Table 3). Adjustment for asthma and for rhinitis ever up to 16 years of age did not change the association between eczema ever and ADHD medication (data not shown).

Discussion

In this large birth cohort (n = 3606) recruited from the general population, there were no significant associations between preschool eczema and medication for ADHD, depression/anxiety/phobia, migraine, or epilepsy at school age. Thus, the previously described association between eczema and ADHD could not be confirmed.

This study has several strengths, especially the large number of participants with prospective follow-up from birth to 16 years. In this study, the exposure variable, eczema, was derived from a combination of parental reports of symptoms and doctor's diagnosis. Thus, individuals with eczema that had

not been diagnosed within the healthcare system were included. According to a Danish study, about 30% of school children with allergic symptoms never visited a doctor (26), and it is a major strength to include those when looking at associations in the general population. Another strength is that we were able to adjust for various confounders. In addition to background factors, such as socioeconomic and mother's age, we could also adjust for asthma and rhinitis at various ages based on prospectively collected data, which minimizes the risk of misclassification. The reliability and completeness of the SPDR, and the open access and low fares in health care, are also strengths when measuring the outcome variables. Every dispensed prescribed drug in Sweden was recorded during the follow-up (25). This measure will miss children with ADHD who have not been dispensed ADHD medication. Thus, underestimation of ADHD is probably a limitation of our study. As mentioned before, more than 80% of Swedish children and teenagers diagnosed with ADHD had reportedly used medication at some point (22). There is also a risk of misclassification if the studied medications were prescribed for some other condition (e.g., psychostimulants for rare disorders such as narcolepsy). Another limitation is that data on ADHD medication were only available after 8 years of age. Therefore, we were unable to determine age at onset for the outcomes. Concerning unusual outcomes, such as epilepsy, the sample size is a weakness resulting in limited power to detect weaker associations. The sample size was neither sufficient to restrict the cases with ADHD medication by age which ruled out the possibility to analyze early vs. late ADHD medication.

The prevalence of ADHD medication (4.5%) in our study is comparable with a large American cross-sectional study (8), which reported an association between eczema the last 12 months and use of ADHD drugs ever (OR 1.49; 95% CI, 1.17–1.88) (8). In contrast, we observed no significant association between any of the studied eczema phenotypes and ADHD medication. In an overview of systematic reviews from 2014, there was as positive association between eczema and ADHD (OR 1.47–7.75) and the authors stated that 'studies

consistently suggest a positive association between eczema and ADHD' (27). Later studies have also shown an association between childhood eczema and ADHD. For example, a large case-control study (4692 cases and 18,768 controls, OR 1.40; 95% CI, 1.22–1.61) (17), and a smaller population-based birth cohort study ($n = 770$) found an association between eczema at 0–4 years of age and ADHD (relative risk 1.92; 95% CI, 1.03–3.57) (10).

Our study is the largest with longitudinal data on eczema and ADHD medication, and the association was, in contrast with previous studies, non-significant. One explanation could be that our eczema definition includes milder cases. In one earlier study, the prevalence of ADHD was strongly associated with eczema severity. The association between mild eczema and reported doctor's diagnosis of ADHD was significant (OR 1.66; 95% CI: 1.28–2.15), and for moderate and severe eczema, the associations were even stronger (OR 1.76; 95% CI: 1.30–2.38 and OR 4.35; 95% CI: 2.73–6.93) (8). Current eczema with sleep disturbance is often used as a proxy for severe eczema (28). However, neither preschool eczema with sleep disturbances due to itching nor reported doctor's diagnosis of eczema (presumably more severe cases) was associated with ADHD medication in our study.

In recent years, a large number of studies have been published regarding the association between eczema and both allergy-related diseases and non-allergic diseases (27, 29). For example, in a cross-sectional study among children 0–17 years of age, the 12-month prevalence of eczema based on reported doctor's diagnosis was associated with being diagnosed with epilepsy ever (OR 1.73; 95% CI, 1.17–2.56) (13). In a similar cross-sectional study, reports of doctor's diagnosis of eczema the last year were associated with depression (OR 1.81; 95% CI 1.33–2.46) (8). In our study, we did not find any significant association between preschool eczema and medications for treating epilepsy or depression at school age. Explanations for this could be related to insufficient power due to smaller study population and/or the definition of eczema. In our study, we

were able to include not only persons with reports of doctor's diagnosis of eczema, but also persons with reports of eczema symptoms. This probably minimizes the risk of ascertainment bias.

Most studies evaluating comorbidities of eczema have a cross-sectional design and are based on doctor's diagnosis. Patients with severe eczema are more likely to visit a doctor, making it more likely that symptoms from other diseases would be recognized and handled by the doctor. Similarly, when patients meet a doctor for diseases like cancer, epilepsy or diabetes they might mention their itchy dermatitis and get eczema diagnosed at the same visit. Therefore, a person having one diagnosis is more likely to get a second one. This phenomenon, known as ascertainment bias, has been discussed to influence the association found between eczema and cancer (30). Ascertainment bias is a differential misclassification and will remain regardless of study size. To minimize the risk of ascertainment bias, population-based studies are preferable and for exposures and outcomes with symptoms that do not always require medical care (e.g., allergy-related diseases), other measures than doctor's diagnosis should be considered. Even though the outcomes in our study are defined by medical treatment, we did not find a positive association between eczema and ADHD medication.

In conclusion, in this birth cohort, we did not find any significant associations between preschool eczema and medications for ADHD, depression/anxiety/phobia, migraine, or epilepsy at school age. Moreover, the previously described association between childhood eczema and ADHD could not be confirmed.

Acknowledgments

We would like to thank all the children and parents who have participated in the BAMSE project and all the staff involved in the project, especially Niklas Andersson, Eva Hallner, and Sara Nilsson.

References

- Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; **113**: 832–6.
- Bieber T. Atopic dermatitis. *N Engl J Med* 2008; **358**: 1483–94.
- Williams HC. Clinical practice Atopic dermatitis. *N Eng J Med* 2005; **352**: 2314–24.
- van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. *J Allergy Clin Immunol* 2007; **120**: 565–9.
- Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003; **112**: S118–27.
- Ballardini N, Bergstrom A, Bohme M, et al. Infantile eczema: prognosis and risk of asthma and rhinitis in preadolescence. *J Allergy Clin Immunol* 2014; **133**: 594–6.
- Schmitt J, Buske-Kirschbaum A, Roessner V. Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review *Allergy* 2010; **65**: 1506–24.
- Yaghmaie P, Koudelka CW, Simpson EL. Mental health comorbidity in patients with atopic dermatitis. *J Allergy Clin Immunol* 2013; **131**: 428–33.
- Chen MH, Su TP, Chen YS, et al. Is atopy in early childhood a risk factor for ADHD and ASD? a longitudinal study. *J Psychosom Res* 2014; **77**: 316–21.
- Genuneit J, Braig S, Brandt S, et al. Infant atopic eczema and subsequent attention-deficit/hyperactivity disorder—a prospective birth cohort study. *Pediatr Allergy Immunol* 2014; **25**: 51–6.
- Garg N, Silverberg JI. Association between childhood allergic disease, psychological comorbidity, and injury requiring medical attention. *Ann Allergy Asthma Immunol* 2014; **112**: 525–32.
- Yu SH, Silverberg JI. Association between Atopic Dermatitis and Depression in US Adults. *J Invest Dermatol* 2015; **135**: 3183–6.
- Silverberg JI, Joks R, Durkin HG. Allergic disease is associated with epilepsy in childhood: a US population-based study. *Allergy* 2014; **69**: 95–103.
- Chen MH, Wu YH, Su TP, et al. Risk of epilepsy among patients with atopic dermatitis: a nationwide longitudinal study. *Epilepsia* 2014; **55**: 1307–12.
- Buske-Kirschbaum A, Schmitt J, Plessow F, Romanos M, Weidinger S, Roessner V. Psychoendocrine and psychoneuroimmunological mechanisms in

- the comorbidity of atopic eczema and attention deficit/hyperactivity disorder. *Psychoneuroendocrinology* 2013; **38**: 12–23.
16. Holmberg K, Lundholm C, Anckarsater H, Larsson H, Almqvist C. Impact of asthma medication and familial factors on the association between childhood asthma and attention-deficit/hyperactivity disorder: a combined twin- and register-based study: epidemiology of allergic disease. *Clin Exp Allergy* 2015; **45**: 964–73.
 17. Tsai JD, Chang SN, Mou CH, Sung FC, Lue KH. Association between atopic diseases and attention-deficit/hyperactivity disorder in childhood: a population-based case-control study. *Ann Epidemiol* 2013; **23**: 185–8.
 18. Mogensen N, Larsson H, Lundholm C, Almqvist C. Association between childhood asthma and ADHD symptoms in adolescence—a prospective population-based twin study. *Allergy* 2011; **66**: 1224–30.
 19. Blackman JA, Gurka MJ, Gurka KK, Oliver MN. Emotional, developmental and behavioural co-morbidities of children with chronic health conditions. *J Paediatr Child Health* 2011; **47**: 742–7.
 20. Romanos M, Gerlach M, Warnke A, Schmitt J. Association of attention-deficit/hyperactivity disorder and atopic eczema modified by sleep disturbance in a large population-based sample. *J Epidemiol Community Health* 2010; **64**: 269–73.
 21. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics* 2015; **135**: e994–1001.
 22. Giacobini M, Medin E, Ahnemark E, Russo LJ, Carlqvist P. Prevalence, patient characteristics, and pharmacological treatment of children, adolescents, and adults diagnosed with ADHD in Sweden. *J Atten Disord* 2014; pii: 1087054714554617.
 23. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol* 2002; **13**(Suppl 15): 11–3.
 24. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009; **24**: 659–67.
 25. Wettermark B, Hammar N, Fored CM, et al. The new Swedish prescribed drug register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007; **16**: 726–35.
 26. Saval P, Fuglsang G, Madsen C, Osterballe O. Prevalence of atopic disease among Danish school children. *Pediatr Allergy Immunol* 1993; **4**: 117–22.
 27. Deckert S, Kopkow C, Schmitt J. Nonallergic comorbidities of atopic eczema: an overview of systematic reviews. *Allergy* 2014; **69**: 37–45.
 28. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009; **124**: 1251–8 e23.
 29. Simpson EL. Comorbidity in atopic dermatitis. *Curr Dermatol Rep* 2012; **1**: 29–38.
 30. Wedgeworth E, Powell AM, Flohr C. Incidence of cancer in the context of atopic dermatitis. *Br J Dermatol* 2011; **164**: 896–7; authors' reply 97–8.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Definition of background variables and potential confounders based on parental questionnaires.

Table S2. Background characteristics for children in the original cohort, the study population and the subpopulation.