Ballardini, N., Kramer, M. S., Oken, E., Henderson, J., Bogdanovich, N., Dahhou, M., Patel, R., Thompson, J., Vilchuck, C., Yang, S., Martin, R., & Flohr, C. (2019). Associations of atopic dermatitis and asthma with child behaviour: Results from the PROBIT cohort. *Clinical and Experimental Allergy*. https://doi.org/10.1111/cea.13417

TITLE PAGE

Title: Associations of atopic dermatitis and asthma with child behaviour: results from the PROBIT cohort

Running title: atopic dermatitis, asthma and child behaviour

Word count: 4,180

Table count: 4 (+ 2 supplementary tables)

Figure count: 1

Author listing: Natalia Ballardini, MD, PhD, [a, b, c] Michael S Kramer, MD, [d] Emily Oken, MD, MPH, [e] A. John Henderson, MD, [f] Natalia Bogdanovich, MD, [g] Mourad Dahhou, [h] Rita Patel, BSc, MSc, PhD, [f] Jennifer Thompson, MPH, [e] Konstantin Vilchuck, MD, [g] Seungmi Yang, PhD, [h] Richard M Martin, BMBS, PhD, [f, i, j]* and Carsten Flohr, MD, PhD, [k]*

Affiliations

[a]Institute of Environmental Medicine, Karolinska Institutet, SE-17177 Stockholm, Sweden

[b]Sachs' Children and Youth Hospital, Södersjukhuset, SE-11883 Stockholm, Sweden

[c]St John's Institute of Dermatology, King's College London, London, UK

[d]Department of Epidemiology, Biostatistics and Occupational Health, McGill University Faculty of Medicine, Montreal, Quebec, Canada

[e]Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Drive Suite 401E, Boston MA, US

[f]Department of Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

[g]National Research and Applied Medicine Mother and Child Centre, Minsk, Republic of Belarus

[h] Departments of Pediatrics and of Epidemiology, Biostatistics and Occupational Health, McGill University Faculty of Medicine, Montreal, Quebec, Canada

[i]University Hospitals Bristol NHS Foundation Trust National Institute for Health Research Bristol Biomedical Research Centre, University of Bristol, Bristol, UK

[j]Medical Research Council Integrative Epidemiology Unit at the University of Bristol, Bristol, UK

[k]St John's Institute of Dermatology, Guy's and St Thomas' Hospital NHS Foundation Trust and King's College London, London, UK

*These authors should be considered joint senior author.

Corresponding author: Natalia Ballardini

Postal address: Institute of Environmental Medicine, Karolinska Institutet, SE-171 77 Stockholm, Sweden

E-mail: natalia.ballardini@ki.se Telephone: +46708187745 Fax: +468304571

Conflicts of interest: Included authors declare no conflicts of interest.

ABSTRACT (280/300)

Background: Conflicting findings from studies evaluating associations of allergic disease with child behaviour require longitudinal studies to resolve.

Objective: To estimate the magnitude of associations of atopic dermatitis (AD) in infancy, and symptoms of asthma and AD at 6.5 years, with child behaviour at 6.5 years.

Methods: Secondary cohort analysis of the PROmotion of Breastfeeding Intervention Trial (PROBIT). PROBIT enrolled 17,046 infants at birth and followed them up at 6.5 years (n=13,889). Study paediatricians collected data on infantile AD at repeated follow-up examinations during the first year of life. At 6.5 years paediatricians performed skin prick tests and parents reported asthma and AD symptoms during the prior year. In addition, parents and teachers completed the Strength and Difficulties Questionnaire, which includes scales on hyperactivity/inattention, emotional problems, conduct problems, peer problems and prosocial behaviours.

Results: Physician-diagnosed AD in the first year of life was not associated with increased risk for behavioural problems at 6.5 years. Emotional problems at 6.5 years were more common among children with AD symptoms (OR: 2.24, 95% CI 1.62-3.12) and asthma symptoms (OR: 1.45; 95% CI, 1.07-1.96) during the past year at 6.5 years and ORs for children with symptoms of more severe AD and asthma were also higher. AD in the past year was also associated with probable hyperactivity/inattention disorder at 6.5 years (OR: 2.05; 95% CI, 1.09-3.84). Other subscales of the SDQ were not related to asthma or AD symptoms during the past year.

Conclusions and clinical relevance: Children with AD symptoms were at higher risk for concomitant hyperactivity/inattention and emotional disorder and children with asthma

symptoms were at higher risk of having concomitant emotional problems. However, AD during infancy did not predict childhood behaviours.

Abbreviations

AD: atopic dermatitis

ADHD: attention deficit/hyperactivity disorder

CI: confidence intervals

OR: odds ratio

SPT: skin prick test

INTRODUCTION

Atopic dermatitis (AD, syn. 'atopic eczema'(1)) and asthma are common chronic diseases in childhood. A number of studies have reported associations of allergic diseases with attention deficit hyperactivity disorder (ADHD) and other behavioural problems in childhood.(2-22)However, many of these studies were retrospective in design (2-8, 11, 13, 18, 19), with recalled ascertainment of exposure data after diagnosis, and so are inherently vulnerable to recall and reverse causation biases.(23) Other cross-sectional studies have not observed an association between allergic diseases and behaviour.(24-26)

Longitudinal cohorts include prospectively collected data on background factors and potential confounders and allow stronger causal inference, based on the temporal sequence between exposure and outcome. Findings from longitudinal studies evaluating allergic diseases in relation to child behaviour are inconsistent.(27-31) In longitudinal studies from Germany, AD early in life was associated with conduct problems, emotional problems, and ADHD at school age(28, 29), while no association was found between AD and ADHD in a larger birth cohort including 3,000 Swedish children.(30) In the British ALSPAC birth cohort, child behaviour was reported by teachers for a subpopulation (n=4,366) at age 8 years; late-onset AD was associated with a higher risk of internalizing behaviours (emotional problems and peer problems), persistent rash increased the risk for externalizing behaviours (conduct problems and hyperactivity/inattention), while no association was observed between wheeze and behaviour.(31) In contrast, a birth cohort study from the US in 546 newborns at risk of developing allergic diseases found that wheezing at age 4 years was associated with internalizing behaviour at age 7 years, while no association was found between AD and behaviour.(27)

Several potential pathways have been suggested to explain the associations between atopic diseases and child behaviour, including: i) shared genetic vulnerability; ii) behavioural consequences of chronic symptoms; iii) a neuro-immunologic pathway in which the release of pro-inflammatory mediators early in life (due to an atopic disease) affects brain maturation and leads to behaviour problems; and iv) disturbed sleep due to atopic diseases, in particular the intense itching associated with AD, may cause subsequent behavioural problems.(23, 27)

The PROBIT cohort (n=17,046) provides an opportunity to prospectively study the relationship of physician diagnosed infantile AD with behavioural problems at 6.5 years and the cross-sectional relationship between AD and asthma symptoms with behavioural problems at 6.5 years. We undertook a secondary (observational) analysis to estimate the magnitude of these associations. We hypothesized that AD in infancy and also AD or asthma symptoms during childhood would be associated with behavioural problems assessed at 6.5 years.

MATERIAL AND METHODS

Study design and study subjects

PROBIT is a cluster-randomized controlled trial (ISRCTN37687716) of a breastfeeding promotion intervention set in the Republic of Belarus.(32) Maternity hospitals and one each of their affiliated polyclinics were randomly assigned to receive the intervention based on the Baby-Friendly Hospital Initiative (intervention group) or to continue the prevailing maternity hospital and polyclinic practices at the time of randomization (control group). A total of 17,046 mothers and their healthy, full-term singleton infants born between June 1996 and December 1997 were recruited during their post-partum stay in 31 maternity hospitals and followed-up in infancy and childhood at affiliated polyclinics. At recruitment, information on background characteristics was collected.

Mother-infant pairs were followed up at 1, 2, 3, 6, 9 and 12 months of age, including regular paediatrician-conducted skin examinations of all participants. Additional follow-up was carried out 2002-2005, when the children were aged 6.5 years. The accompanying parent (usually the mother) answered questions on allergic symptoms contained in the International Study for Asthma and Allergies in Childhood (ISAAC) questionnaire(33), as well as other questions. In addition, both a parent and the child's teacher evaluated the child's behaviour using the Strength and Difficulties Questionnaire (SDQ).(34) Finally, study paediatricians administered skin prick tests (SPTs) for five inhalant allergens at the 6.5-year visit.(35) PROBIT was approved by the Belarusian Ministry of Health and received ethical approval from the McGill University Health Centre research ethics board, the institutional review board at Harvard Pilgrim Health Care, and the Avon Longitudinal Study of Parents and Children Law and Ethics Committee. A parent or legal guardian provided written informed consent in Russian at enrollment and at the 6.5-year follow-up.

Exposures and outcomes

AD assessments based on skin examinations in infancy (PROBIT Phase I)

Participants were categorized as having infantile AD if they had rashes that lasted at least two weeks or recurred after clearing for at least one week, were itchy and occurred on the face and/or the extensor surfaces of the arms and/or on the extensor surfaces of the legs. Participants with infantile AD that was present at two or more follow-up visits and that affected two or more body sites were categorized as having 'severe' infantile AD.

SPTs, AD and asthma symptoms in the past year at 6.5 (PROBIT Phase II)

Skin-prick tests were performed with inhalant allergens (Allergy Canada) to house dust mite, cat dander, birch pollen, mixed northern grasses, and Alternaria.(35) The accompanying parent completed the International Study for Asthma and Allergies in Childhood (ISAAC) questionnaire which included a series of yes or no questions about asthma and AD symptoms.(36) The question on asthma symptoms in the previous year was: "Has your child had wheezing or whistling in your chest at any time in the last 12 months?" ('wheeze past year'). For assessment of severe asthma the questionnaire asked: "How many attacks of wheezing has your child had in the last 12 months?", "In the past 12 months, on average, has your child's sleep been disturbed due to wheezing?" and "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?" We used the ISAAC definition of severe asthma: 4 or more attacks of wheeze or 1 or more nights per week sleep disturbance from wheeze or wheeze affecting speech in the past 12 months.(37) For AD symptoms, the questionnaire asked: "Has your child ever had an itchy rash which was coming and going for at least six months?", "Has your child had this itchy rash at any time in the past 12 months?" ('AD symptoms past year'), and "Has this itchy rash at any time affected any of the following places: folds of the elbows,

behind the knees, in front of the ankles, around the neck, or eyes?" ('flexural AD past year'). AD severity was assessed by the questions "Has this rash cleared completely at any time during the past 12 months?" and "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').

Behaviour assessments at 6.5 years (PROBIT Phase II)

We used the Strength and Difficulties Questionnaire (SDQ), a validated screening tool, designed to detect behavioural strengths and difficulties of children 4 to16 years of age.(34) The SDQ evaluates child behaviour over the last six months and consists of 5 subscales; emotional problems, conduct problems, hyperactivity/inattention, peer problems and prosocial behaviour. The questionnaire also contains an impact supplement, which includes questions evaluating whether the respondent thinks the child has a problem, and if so, inquires further about chronicity, distress, social impairment and burden to others. Both parents and teachers of the children were asked to complete the SDQ questionnaire and the impact supplement. In accordance with international recommendations we combined teacher and parent SDQ assessments(34), and we used the result from one respondent in cases where only one was available. Using a computerized algorithm for predicting disorders from multi-informant SDQ and impact scores, children were classified into three categories: "unlikely", "possible" or "probable" for emotional disorder, conduct disorder and hyperactivity disorder.(38, 39) We subsequently dichotomized each scale into "possible/probable" versus "unlikely, as has been done by others investigating the relationship between AD and child behaviour using the SDQ.(29) For the SDQ subscales on peer problems and prosocial behaviour, algorithms for disorder prediction are not available, so we dichotomized these outcomes, with the 15% assessed as having most problems in each scale compared to the remaining 85%, as has been reported previously.(29)

Statistical analysis

Logistic regression with calculation of robust standard errors using the "vce"-cluster command in STATA was used to assess associations of infantile AD, severe infantile AD, asthma symptoms, severe asthma and AD symptoms in the prior year at 6.5 years (the exposures) with the behaviour outcomes. We present results for: (1) a univariable cluster-adjusted model; (2) a simple cluster- and sex-adjusted model; and (3) a fully-adjusted model, including trial arm and covariables selected based on current knowledge about the causes of the exposures and outcomes and previously published evidence of factors associated with the exposures and outcomes: maternal age at delivery, trial arm, exclusive breastfeeding≥3 months, birth weight (weight-for-length z-score at birth), maternal and paternal occupation (non-manual, manual, unemployed and unknown), parental alcohol consumption at 6.5 years (one or two parents with weekly or more frequent heavy drinking, one or two parents with weekly or more frequent moderate drinking and two parents with light or infrequent drinking),(40) maternal and paternal education (completed university, advanced secondary or partial university, common secondary and incomplete secondary or unknown), parental allergy (asthma, AD and/or hay fever present in mother and/or father at enrolment) and family situation at 6.5 years (stable two-parent family since birth, new two parent family and single parent). Revision of the covariates showed that sex was a confounder for many of the associations and we therefore present a sex and cluster-adjusted model. Otherwise, there was limited confounding. The addition of maternal education to the models increased the OR for the association between AD at 6.5 years with peer problems at 6.5 years by 6 %, ORs; 0.92; 95% CI, 0.60-1.43 and 0.98; 95% CI, 0.62-1.53, respectively. Otherwise, included covariates did not impact risk estimates in the range outside +/- 5% for the exposures infantile AD or AD and asthma at 6.5 years. Participants with complete information on exposures, outcomes and variables included in the fully adjusted model were selected for the current study. The

same study population including 11,668 individuals were used in all models. We compared these with those who were not included using chi-2 tests and found no significant differences regarding main exposures and outcomes, all p>0.19. Previous studies indicate that AD might be a confounder for the association between asthma and behaviour.(23) In models where asthma symptoms were the predictor, we therefore adjusted for concomitant and infantile AD. We fitted interaction terms to test whether the associations differed by sex, but sex did not modify the association between AD or asthma and child behaviour (all interaction p values >0.06) and so we present all results for both sexes combined. To evaluate whether another dichotomization of behaviour outcomes affected our results we performed sensitivity analyses for all AD and asthma exposures calculating ORs for 'probable' as compared to' unlikely' behavioural problems for the outcomes emotional disorder, conduct disorder and hyperactivity disorder. In addition, stratified analyses for children with and without any positive SPT and symptoms of AD and asthma at 6.5 years were undertaken. All statistical analyses were performed with STATA Statistical Software (release 14.2; Stata-Corp, College Station, TX, USA).

RESULTS

Study population and follow-up

Fig 1 shows the flow of the study population from recruitment. For the current study, children with data available for either parent or teacher SDQ and complete data for AD, asthma and for covariables used in the fully adjusted model were included (n=11,668). Characteristics for included children and the original cohort were similar with the exception of family situation, Table I. Missing data was more common for children with separated parents and since complete data was required for inclusion more children in the study population compared to the original cohort lived in stable two-parent families since birth. SDQ assessments from just teacher, just parent and both teacher and parent were available for 27, 1,561 and 10,080 participants, respectively. In Belarus children start school at 6 years of age and most missing teacher-completed SDQ forms were because the child had not yet started regular school.

AD, asthma, SPT and behaviour problems in the study population

The prevalence of AD decreased from 5.0% in infancy to 1.3% at 6.5 years (Table II). Wheeze in the past year was reported for 3.0%, and severe asthma symptoms for 0.7%, of children at 6.5 years. Of the 9,388 children who had SPTs, 22.6% had at least one positive result. The corresponding proportions among children with AD symptoms, asthma symptoms or severe asthma symptoms in the previous year were 35.7%, 49.5% and 66.1% respectively. Table II shows the number of girls and boys classified as having ‘probable’, ‘possible’ and ‘unlikely’ problems based on the SDQ disease prediction for the behaviour outcomes hyperactivity/inattention, emotional and conduct problems. Corresponding numbers for the SDQ-scales peer problems and prosocial behaviour as well as cut-offs used for dichotomisation are also shown in Table II.

Infantile AD in relation to child behaviour at 6.5 years

AD in infancy was not associated with 'possible/probable' hyperactivity/inattention disorder (fully-adjusted OR, 0.91; 95% CI, 0.77 - 1.08), emotional disorder (fully-adjusted OR, 1.04; 95% CI, 0.86 - 1.25) or conduct disorder (fully-adjusted OR, 1.12; 95% CI, 0.95 - 1.31). However, severe AD (versus no AD) in infancy was associated with lower odds for possible/probable hyperactivity/inattention disorder (fully-adjusted OR, 0.65; 95% CI, 0.44 - 0.98) at 6.5 years (Table III). We excluded children with possible behaviour disorder in a sensitivity analysis and evaluated ORs for 'probable' behaviour versus 'unlikely' behaviour problems. In the sensitivity analysis, the negative association for severe infantile AD with probable hyperactivity/inattention was non-significant. However, in the sensitivity analysis infantile AD was associated with lower odds for probable hyperactivity/inattention (fully-adjusted OR, 0.72; 95% CI, 0.53-0.99) at 6.5 years (Table E1).

Infantile AD was not associated with peer problems (fully-adjusted OR, 0.87; 95% CI, 0.70 - 1.08) or prosocial behaviour (fully-adjusted OR, 1.01; 95% CI, 0.82 - 1.26) at 6.5 years, (Table III).

AD and asthma symptoms in the past year at 6.5 years in relation to child behaviour at 6.5 years

We also evaluated the associations of the following questionnaire-derived binary ISAAC exposures in the past year: AD symptoms, persistent AD symptoms, sleep-disturbed AD symptoms, asthma symptoms and severe asthma symptoms with child behaviour at 6.5 years. We found a higher odds of 'possible/probable' emotional disorder at 6.5 years among children with AD symptoms in the previous year (fully-adjusted OR, 2.24, 95% CI 1.62-3.12), persistent AD in the previous year (fully-adjusted OR, 2.69; 95% CI, 1.38 - 5.22), wheeze in the previous year (fully-adjusted OR, 1.45; 95% CI, 1.07 - 1.96) and severe asthma symptoms in the previous year (fully-adjusted OR, 1.93; 95% CI, 1.13 – 3.32) (Table IV). The risk

estimate for possible/probable emotional disorder for the exposure asthma in the previous year without adjustment for AD in past year was similar (fully-adjusted OR, 1.51; 95% CI, 1.11 - 2.04). In a sensitivity analysis, we excluded children with 'possible' behaviour disorder and computed ORs for 'probable' versus 'unlikely' disorder. The risk estimates for 'probable' emotional disorder were similar but significant associations were only found for AD symptoms and persistent AD symptoms in the past year (Table E2). However, in the sensitivity analysis AD symptoms in the past year were significantly associated with 'probable' hyperactivity/inattention disorder (fully-adjusted OR, 2.05; 95% CI, 1.09-3.84). Also, severe asthma symptoms past year tended to be positively associated with probable hyperactivity/inattention but the association was non-significant in the fully-adjusted model (fully-adjusted OR, 1.93; 95% CI, 0.91 – 4.09). Out of children with AD at 6.5 years, 36 children also had AD in infancy. We evaluated the effects of AD at both time points using children with no history of AD at either time point as the reference and found an OR for emotional problems of 3.06 (95% CI 1.74- 5.37), but no other significant associations. AD or asthma symptoms in the previous year were not associated with any of the child behaviour outcomes: conduct problems, peer problems or prosocial behaviour at 6.5 years. We also assessed whether the SPT results affected child behaviour among children with AD and asthma (including severe phenotypes) the previous year, but effect sizes were similar for children with any positive SPTs versus those without (all interaction p values >0.10).

DISCUSSION

Physician-diagnosed AD during the first year of life did not increase the odds of behavioural problems at 6.5 years. However, at 6.5 years, emotional problems were more common among children with AD and with asthma symptoms in the past year. In addition, children with AD symptoms in the past year had increased odds for 'probable' hyperactivity/inattention disorder at 6.5 years. There was little evidence of important associations with other behaviours.

The strengths of our study include its prospective design, with collection of background data and repeated follow-up visits during the first year of life, thus reducing the risk of recall bias. We also adjusted for concomitant AD and AD recorded during the first year of life when exploring the association between asthma symptoms and behaviour. This is important, since positive associations between wheeze or asthma and ADHD might be explained by previous or concomitant AD(23), although this approach might infer overadjustment. Our large sample size and wide geographical spread in Belarus are additional strengths. Physician skin examination for AD during the first year of life and skin prick testing for several inhalant allergens at 6.5 years are also major strengths. Finally, behaviour assessments were made by both parent and teacher for most children. This is important since parental and teachers' SDQ assessment have been demonstrated to be complementary showing different informants sensitive to different domains of behaviours(38) and the SDQ prediction has been shown to work best when SDQs have been completed by both parents and teachers.(41)

Limitations of our study include that child behaviour was measured at one time point only and at an age (6.5 years) when behavioural problems might not be fully developed. We can also not fully exclude the possibility that behavioural problems might have preceded asthma and AD in some children. Another limitation is that we did not have information regarding parental psychopathology and therefore could not adjust for this possible confounder. Food allergy is more common among children with AD, especially during infancy and where

children have a more severe phenotype.(42) A recent study found an association between maternally reported emotional problems and food allergy among teenagers and young adults.(43) Sensitization to foods was not assessed in our study, however, food allergies are rare in Belarus, and severe AD was very uncommon in our study population (0.4%). Nevertheless, we cannot fully rule out that food allergies contributed to emotional problems in some study children with AD. We performed multiple testing which increase the risk for type 1 errors. We evaluate three independent exposures and five independent outcomes and if we had used a Bonferroni correction, a p-value of 0.003 had been considered significant and the only significant association had been the association between AD the past year and emotional problems at 6.5 years. However, our main findings regarding the association between asthma and AD symptoms the past year with emotional problems are consistent and risk estimates are higher for more severe disease. Thus, we do not believe that type 1 errors explain our findings.

In a German birth cohort study including 770 children from the general population, information on AD before age 4 years was obtained by questionnaires to parents and physicians. AD was strongly associated with parental reports of doctor-diagnosed ADHD or ADHD medication up to age 8 years (adjusted relative risk, 5.17; 95% CI, 2.18 -12.3).(28) Another German birth cohort study including 2,916 individuals evaluated with parental SDQ at age 10 years found that children with parental reports of AD during infancy had an increased risk of emotional symptoms (adjusted OR, 1.62; 95% CI, 1.25 - 2.09) and AD limited to infancy was associated with conduct problems (adjusted OR, 1.75; 95% CI, 1.18 - 2.60).(29) These studies found that AD early in life increases the risk for ADHD. The findings are in line with the theory of a neuro-immunologic pathway and the important question whether targeted preventive measures for infants with AD could reduce behavioural problems has been raised.(23) In contrast to previous studies that defined AD based on

questionnaires,(28-31) we used clinical examinations by a physician at several follow-up visits during the first year of life to evaluate AD in infancy. The only significant association with behaviour was a reduced odds of hyperactivity/inattention at 6.5 years. This finding is difficult to explain clinically and might be due to chance, since multiple hypotheses were tested. Thus, our results do not confirm previous findings of higher risk of behavioural problems among children with AD in infancy.

Most studies regarding atopic diseases and child behaviour have investigated the association with ADHD, rather than other forms of altered child behaviour, and positive associations have been found both for asthma and AD.(44) In line with previous research we found a significant association between AD symptoms and 'probable' hyperactivity/inattention disorder. In general, risk estimates were higher in the sensitivity analysis evaluating ORs for 'probable' hyperactivity/inattention disorder as compared to ORs for 'possible/probable' hyperactivity/inattention disorder. However, no other significant associations for hyperactivity/inattention disorder were detected. In contrast, risk estimates for 'probable' emotional disorder in the sensitivity analysis were similar to risk estimates for 'possible/probable' emotional disorder. A recent meta-analysis (n=188,495) showed that AD among adults and adolescents is associated with increased risk for depression (pooled RR, 2.02; 95% CI, 1.76-2.31).(45) Our study indicates that emotional problems among individuals with AD and asthma start already in childhood. We found positive associations of concurrently assessed AD and asthma symptoms during the past year with emotional problems at 6.5 years, with the highest odds of emotional problems observed in children with persistent AD symptoms in the previous year, probably representing more severe disease. Schmitt et al, also found an increased risk of emotional problems at 10 years (adjusted OR, 1.74; 95% CI, 1.29 - 2.35) among children with AD at 3-10 years.(29) In contrast, a cross-sectional Danish study (n= 9,215) did not find evidence of an association between current AD

and emotional problems among children (adjusted OR, 1.29; 95% CI, 0.98 - 1.71).(46) In the same study, however, current asthma was associated with emotional problems (adjusted OR, 1.83; 95% CI, 1.44 - 2.33), which is similar to our findings.

In summary, we found no evidence of a positive association between physician-diagnosed AD in infancy with behavioural problems later in childhood. Thus, in relation to previously suggested potential pathways for the associations between allergic diseases and behavioural problems our findings do not support the theory of a neuro-immunologic pathway or shared genetic vulnerability. Nor did we find evidence that sleep disturbance among children with AD added to the risk for behavioural problems. In conclusion, recent AD seems to be associated with increased odds for 'probable' hyperactivity/inattention disorder and both asthma and AD symptoms, especially when persistent and severe, were associated with an increased odds of concomitant emotional problems already at 6.5 years of age. Based on our findings we think that physicians taking care of children with AD and asthma, especially when severe, should consider screening for emotional problems.

Acknowledgments

We thank the children and parents participating in the PROBIT cohort and all staff involved in the study through the years. We are also grateful to Dr Benjamin Baig, Child and Adolescent Psychiatrist, Institute of Psychiatry, King's College London, for his advice on the design of the study and the analysis of the SDQ data.

Funding sources

This study was supported by grant MOP-53155 from the Canadian Institutes of Health Research and grant R01 HD050758 from the US National Institutes of Health. EO was supported by grants K24 HD069408 and P30 DK092924 from the US National Institutes of

Health. RM work in the Integrative Epidemiology Unit supported by the UK Medical Research Council and the University of Bristol (grant code MC_UU_12013/1-9). The Bristol Nutrition Biomedical Research Centre is funded by the National Institute for Health Research (NIHR) and is a partnership between the University Hospitals Bristol National Health Services Foundation Trust and the University of Bristol. CF is funded through a NIHR Career Development Fellowship (CDF-2014-07-037) and also supported by the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NIH, the EU, the Canadian Institutes of Health Research, the UK National Health Service, the UK NIHR, MRC or the UK Department of Health. The funders had no role in the conduct or reporting of the study.

Author contributions: CF and NB had full access to all study data and take responsibility for the integrity of the data and the data analysis. Concept and design: CF, NB, RM, MK, and EO. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: NB, RM, and CF. Critical revision of the manuscript for important intellectual content: RM, MK, RP, JT, SY, KV, NBo, MD, JH, EO. Statistical analysis: NB, CF.

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Table I Baseline characteristics for the original PROBIT cohort and for included children

	PROBIT n=17,046		**Study population n= 11,668**	
Characteristic	**n**	**%**	**n**	**%**
Measured at child's birth				
Maternal age, y				
<20	2,394	14.1	1,471	12.6
20-34	13,931	81.7	9,705	83.2
≥35	720	4.2	492	4.2
Maternal education				
Completed university	2,316	13.6	1,637	14.0
Advanced secondary or partial university	8,570	50.3	6,032	51.7
Common secondary	5,497	32.2	3,632	31.1
Incomplete secondary or unknown	663	3.9	367	3.2
Paternal education				
Completed university	2,292	13.4	1,561	13.4
Advanced secondary or partial university	7,689	45.1	5,488	47.0
Common secondary	6,080	35.7	4,326	37.1
Incomplete secondary or unknown	985	5.8	293	2.5
Maternal occupation				
Non-manual	7,239	42.5	5,257	45.1
Manual	5,634	33.0	3,931	33.7
Unemployed	4,173	24.5	2,480	21.2
Paternal occupation				
Non-manual	4,855	28.5	3,431	29.4
Manual	8,964	52.6	6,551	56.2
Unemployed	2,466	14.5	1,548	13.6
Unknown	761	4.5	138	1.2
Parental allergy				
No	15,949	96.7	11,315	97.0
Yes	548	3.3	353	3.0
Intervention				
No	8,181	48.0	5,759	49.4
Yes	8,865	52.0	5,909	50.6
Child sex				
Female	8,217	48.2	5,561	47.7

Male	8,829	51.8	6,107	52.3
	Mean	**SD**	**Mean**	**SD**
Birthweight, mean (SD), kg	3.44	0.42	3.47	0.41
Measured in child's first year	**n**	**%**	**n**	**%**
Exclusive breastfeeding ≥3 months				
No	12,256	73.2	8,516	73.0
Yes	4,483	26.8	3,152	27.0
Measured at 6.5 years PROBIT phase II				
Parental alcohol consumption				
Heavy drinking	1,199	9.7	1,102	9.4
Moderate drinking	1,487	12.0	1,387	11.9
Light drinking	9,724	78.4	9,179	78.7
Family situation				
Stable two-parent since birth	11,289	82.6	10,642	91.2
New two-parent	675	4.9	347	3.0
Single parent	1,703	12.5	679	5.8

Table II. AD, asthma (exposures) and behaviours (outcomes) for girls and boys in the study population (n=11,668)

	Girls		Boys		Total	
	N	**%**	**N**	**%**	**N**	**%**
Age 0-1 year skin examinations						
Infantile AD	230	4.1	347	5.7	577	5.0
Severe infantile AD*	47	0.9	68	1.2	115	1.0
Age 6.5 years ISAAC questions						
AD symptoms past year	74	1.3	82	1.3	156	1.3
Persistent AD symptoms past year	21	0.4	24	0.4	45	0.4
Sleep-disturbed AD symptoms past year	16	0.3	27	0.5	43	0.4
Asthma symptoms past year	140	2.5	211	3.5	351	3.0
Severe asthma symptoms past year	25	0.5	49	0.8	74	0.7
Child behaviour at age 6.5 years according to SDQ						
Hyperactivity/inattention						
Unlikely	4,675	84.1	4,439	72.7	9,114	78.1
Possible	752	13.5	1,333	21.8	2,085	17.9
Probable	134	2.4	335	5.5	469	4.02
Emotional problems						
Unlikely	4,668	84.3	5,116	83.8	9,804	84.0
Possible/ Probable	470	8.5	611	10.0	1,081	9.3
Probable	403	7.2	380	6.2	783	6.7
Conduct problems						
Unlikely	4,622	83.1	4,220	69.1	8,842	75.8
Possible	622	11.2	1,103	18.1	1,725	14.8
Probable	317	5.7	784	12.8	1,101	9.4
Peer problems**						
Low (scale 0-3)	4,711	84.7	5,040	82.5	9,751	83.6
High (scale 4-10)	850	15.3	1,067	17.5	1,917	16.4
Prosocial behaviour**						
High (scale 7-10)	5,015	90.2	4,874	79.8	9,889	84.7
Low (scale 0-6)	546	9.8	1,233	20.2	1,779	15.3

* Subgroup within the group having infantile AD, including infants with persistent (AD present at two or more follow-up visits the first year of life) and widespread AD (AD affecting two or more body sites).

******Teacher and parent SDQ scores were added and divided by two and for individuals with only one assessment that score was used.

Table III. OR estimates calculated by logistic regression for child behaviour at 6.5 years (SDQ probable/possible versus unlikely) in relation to atopic dermatitis (AD) in infancy based on repeated skin examinations during the first year of life (n=11,668)

Outcome°	**Cluster-adjusted analysis**			**Cluster & sex-adjusted analyses**			**Fully-adjusted analysis□**		
Exposure									
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Hyperactivity/inattention									
Atopic dermatitis in infancy	0.98	0.82 - 1.16	0.78	0.92	0.78 - 1.10	0.36	0.91	0.77 - 1.08	0.29
Severe AD in infancy*	0.71	0.48 - 1.03	0.07	0.67	0.46 - 0.97	0.03	0.65	0.44 - 0.98	0.04
Emotional problems									
Atopic dermatitis in infancy	1.14	0.94 - 1.37	0.18	1.13	0.94 - 1.37	0.19	1.04	0.86 - 1.25	0.68
Severe AD in infancy*	1.05	0.64 - 1.71	0.85	1.05	0.64 - 1.71	0.86	0.92	0.56 - 1.53	0.76
Conduct problems									
Atopic dermatitis in infancy	1.18	1.01 - 1.37	0.04	1.11	0.95 - 1.30	0.17	1.12	0.95 - 1.31	0.18
Severe AD in infancy*	0.92	0.61 - 1.40	0.70	0.87	0.58 - 1.30	0.50	0.89	0.59 - 1.33	0.57
Peer problems									
Atopic dermatitis in infancy	0.89	0.73 - 1.08	0.23	0.87	0.72 - 1.07	0.18	0.87	0.70 - 1.08	0.22
Severe AD in infancy*	1.13	0.73 - 1.74	0.58	1.12	0.72 - 1.73	0.61	1.17	0.73 - 1.86	0.52
Prosocial behaviour									
Atopic dermatitis in infancy	1.08	0.88 - 1.35	0.45	1.02	0.82- 1.27	0.87	1.01	0.82 - 1.26	0.90
Severe AD in infancy*	0.90	0.55 - 1.47	0.68	0.85	0.51 - 1.42	0.53	0.83	0.51 - 1.38	0.48

□Adjusted for cluster, sex, trial arm, birth weight, maternal age, breastfeeding, maternal and paternal education, maternal and paternal occupation, parental allergy, parental alcohol consumption, family situation, asthma and AD symptoms past year at 6.5 years.

° SDQ disorder prediction was used comparing 'probable/possible' versus 'unlikely' for the outcomes hyperactivity/inattention, emotional problems and conduct problems. For the outcomes peer problems and prosocial behaviour a cut of including 15 percent of children assessed with most problems were compared to the others for each scale respectively.

* Infants with persistent (AD present at two or more follow-up visits) and widespread AD (AD affecting two or more body sites)

Reference group for all AD exposures were children with no infantile AD.

Table IV. OR estimates calculated by logistic regression for child behaviour at 6.5 years in relation to AD and asthma in the past year (n=11,668)

Outcome	**Cluster-adjusted analysis**	**Cluster & sex-adjusted analysis**	**Fully-adjusted analysis□**

Exposure									
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Hyperactivity/inattention									
AD symptoms in the past year	1.19	0.77 - 1.86	0.44	1.19	0.74 - 1.93	0.47	1.21	0.76 - 1.92	0.43
Persistent AD symptoms in the past year	0.89	0.32 - 2.51	0.83	0.89	0.31 - 2.53	0.82	0.95	0.34 - 2.65	0.92
Sleep-disturbed AD symptoms past year	1.38	0.66 - 2.90	0.39	1.30	0.59 - 2.84	0.51	1.27	0.57 - 2.80	0.56
Asthma symptoms past year	1.00	0.81 - 1.23	0.98	0.95	0.77 - 1.18	0.65	0.97	0.79 - 1.18	0.74
Severe asthma symptoms past year	1.23	0.77 - 1.97	0.38	1.13	0.70 - 1.82	0.63	1.12	0.69 - 1.81	0.65
Emotional problems									
AD symptoms in the past year	2.23	1.60 - 3.11	<0.001	2.23	1.59 - 3.12	<0.001	2.24	1.62- 3.12	<0.001
Persistent AD symptoms in the past year	2.67	1.36 - 5.20	0.004	2.67	1.37 - 5.20	0.004	2.69	1.38 - 5.22	0.004
Sleep-disturbed AD symptoms past year	1.83	0.88 - 3.83	0.11	1.82	0.87 - 3.83	0.11	1.69	0.81 - 3.55	0.16
Asthma symptoms past year	1.50	1.11 - 2.03	0.009	1.49	1.10 - 2.02	0.01	1.45	1.07 - 1.96	0.02
Severe asthma symptoms past year	2.11	1.26 - 3.55	0.005	2.10	1.25 - 3.55	0.005	1.93	1.13 - 3.32	0.02
Conduct problems									
AD symptoms in the past year	0.97	0.63 - 1.50	0.90	0.97	0.63 - 1.50	0.89	0.99	0.66 - 1.50	0.98
Persistent AD symptoms in the past year	1.27	0.72 - 2.25	0.41	1.27	0.70 - 2.30	0.43	1.34	0.78 - 2.31	0.29
Sleep-disturbed AD symptoms past year	0.61	0.29 - 1.27	0.19	0.56	0.26 - 1.18	0.13	0.57	0.27 - 1.21	0.14
Asthma symptoms past year	0.88	0.69 - 1.11	0.28	0.82	0.64 - 1.06	0.13	0.86	0.65 - 1.14	0.29
Severe asthma symptoms past year	0.73	0.44 - 1.20	0.21	0.65	0.38 - 1.09	0.10	0.67	0.38 - 1.17	0.16

Peer problems									
AD symptoms in the past year	0.92	0.60 - 1.43	0.72	0.92	0.60 - 1.43	0.72	1.02	0.63 - 1.64	0.95
Persistent AD symptoms in the past year	1.64	0.85 - 3.17	0.14	1.64	0.85 - 3.17	0.14	1.97	0.99 - 3.91	0.05
Sleep-disturbed AD symptoms past year	0.38	0.13 - 1.15	0.09	0.37	0.12 - 1.13	0.08	0.42	0.14 - 1.22	0.11
Asthma symptoms past year	1.01	0.82 - 1.23	0.95	1.00	0.81 - 1.22	0.96	1.06	0.87 - 1.30	0.55
Severe asthma symptoms past year	1.29	0.78 - 2.16	0.32	1.27	0.75 - 2.14	0.37	1.45	0.85 - 2.47	0.17
Prosocial behaviour									
AD symptoms in the past year	0.91	0.57 - 1.45	0.69	0.91	0.58 - 1.43	0.68	0.94	0.57 - 1.54	0.80
Persistent AD symptoms in the past year	1.02	0.45 - 2.30	0.96	1.01	0.44 - 2.32	0.97	1.05	0.45 - 2.47	0.91
Sleep-disturbed AD symptoms past year	0.73	0.19 – 1.74	0.64	0.67	0.18 - 2.49	0.55	0.73	0.20 - 2.74	0.64
Asthma symptoms past year	0.99	0.72 - 1.36	0.94	0.93	0.66 - 1.29	0.66	0.97	0.69 - 1.38	0.88
Severe asthma symptoms past year	0.77	0.38 - 1.56	0.47	0.69	0.34 - 1.38	0.29	0.76	0.37 - 1.57	0.46

□Adjusted for cluster, sex, trial arm, birth weight, maternal age, breastfeeding, maternal and paternal education, maternal and paternal occupation, parental allergy, parental alcohol consumption, family situation and AD in previous follow-ups. For AD outcomes adjustment was made for concomitant asthma symptoms and *vice versa*. Reference group for all AD exposures are children with no AD symptoms in past year and for asthma symptoms the reference group is children with no asthma symptoms in the past year.

* SDQ disorder prediction was used comparing probable/possible versus unlikely for the outcomes hyperactivity/inattention, emotional problems and conduct problems. For the outcomes peer problems and prosocial behaviour a cut of including around 15 percent of children assessed with most problems were compared to the others for each scale respectively.

Supplementary Table 1. Sensitivity analysis

OR estimates calculated by logistic regression for child behaviour (SDQ probable versus unlikely) at 6.5 years in relation to atopic dermatitis (AD) in infancy based on repeated skin examinations during the first year of life

Outcome SDQ probable versus unlikely	**Cluster-adjusted analysis**			**Cluster & sex-adjusted analyses**			**Fully-adjusted analysis**□		
Exposure									
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Hyperactivity/inattention									
Atopic dermatitis in infancy	0.85	0.62-1.18	0.33	0.79	0.58-1.08	0.13	0.72	0.53-0.99	0.04
Severe AD in infancy*	0.40	0.10-1.61	0.20	0.37	0.10-1.46	0.16	0.31	0.08-1.20	0.09
Emotional problems									
Atopic dermatitis in infancy	1.09	0.79-1.49	0.61	1.10	0.80-1.51	0.56	1.02	0.73-1.42	0.91
Severe AD in infancy*	0.92	0.47-1.78	0.80	0.93	0.48-1.80	0.82	0.82	0.42-1.63	0.58
Conduct problems									
Atopic dermatitis in infancy	0.95	0.70-1.29	0.76	0.89	0.65-1.22	0.47	0.87	0.63-1.20	0.40
Severe AD in infancy*	0.72	0.39-1.33	0.29	0.67	0.36-1.24	0.20	0.68	0.36-1.27	0.22

□Adjusted for cluster, sex, trial arm, birth weight, maternal age, breastfeeding, maternal and paternal education, maternal and paternal occupation, parental allergy, parental alcohol consumption, family situation, asthma and AD symptoms past year at 6.5 years.

* Infants with persistent (AD present at two or more follow-up visits) and widespread AD (AD affecting two or more body sites)

Reference group for all AD exposures were children with no infantile AD.

Supplementary Table 2. Sensitivity analysis

OR estimates calculated by logistic regression for child behaviour (SDQ probable versus unlikely) at 6.5 years in relation to AD and asthma symptoms in the past year

Outcome SDQ probable versus unlikely	**Cluster-adjusted analysis**			**Cluster & sex-adjusted analyses**			**Fully-adjusted analysis**□		
Exposure									
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Hyperactivity/inattention									
AD symptoms in the past year	2.02	1.10-3.71	0.02	2.01	1.06-3.81	0.03	2.05	1.09-3.84	0.02
Persistent AD symptoms in the past year	2.19	0.66-7.20	0.20	2.11	0.65-6.81	0.21	2.39	0.72-7.98	0.16
Sleep-disturbed AD symptoms past year	2.54	0.74-8.77	0.14	2.29	0.65-8.13	0.20	1.93	0.50-7.41	0.34

Asthma symptoms past year	1.44	1.04-1.99	0.03	1.34	0.94-1.90	0.10	1.30	0.93-1.80	0.12
Severe asthma symptoms past year	2.50	1.30-4.82	0.006	2.19	1.09-4.39	0.03	1.93	0.91-4.09	0.09
Emotional problems									
AD symptoms in the past year	2.07	1.35-3.17	0.001	2.07	1.36-3.17	0.001	2.09	1.36-3.20	0.001
Persistent AD symptoms in the past year	2.53	1.18-5.43	0.02	2.54	1.19-5.41	0.02	2.61	1.19-5.70	0.02
Sleep-disturbed AD symptoms past year	1.58	0.56-4.50	0.39	1.60	0.56-4.60	0.38	1.51	0.54-4.23	0.43
Asthma symptoms past year	1.34	0.91-1.96	0.13	1.35	0.92-1.98	0.12	1.31	0.89-1.93	0.18
Severe asthma symptoms past year	1.91	1.00-3.65	0.05	1.96	1.02-3.77	0.04	1.83	0.93-3.60	0.08
Conduct problems									
AD symptoms in the past year	0.94	0.58-1.55	0.82	0.96	0.59-1.56	0.86	0.97	0.59-1.60	0.92
Persistent AD symptoms in the past year	1.50	0.66-3.44	0.33	1.57	0.66-3.71	0.31	1.84	0.81-4.16	0.14
Sleep-disturbed AD symptoms past year	0.22	0.03-1.66	0.14	0.21	0.03-1.57	0.13	0.21	0.03-1.58	0.13
Asthma symptoms past year	1.00	0.73-1.36	0.98	0.92	0.66-1.29	0.64	0.98	0.70-1.39	0.93
Severe asthma symptoms past year	0.54	0.20-1.41	0.21	0.47	0.17-1.29	0.14	0.50	0.17-1.43	0.20

*****Adjusted for cluster, sex, trial arm, birth weight, maternal age, breastfeeding, maternal and paternal education, maternal and paternal occupation, parental allergy, parental alcohol consumption, family situation and AD in previous follow-ups. For AD outcomes adjustment was made for concomitant asthma symptoms and *vice versa*. Reference group for all AD exposures are children with no AD symptoms in past year and for asthma symptoms the reference group is children with no asthma symptoms in the past year.

Figure 1. Flow of the current study