

Risk factors for atopic diseases and recurrent respiratory tract infections in children

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Abstract

Background The simultaneous increased prevalence of atopic diseases and decreased prevalence of infectious diseases might point to a link between the two entities. Past work mainly focused on either atopic diseases or recurrent infections. We aim to investigate whether risk factors for atopic diseases (i.e. asthma, allergic rhinitis, atopic dermatitis and/or food allergy) differ from risk factors for recurrent respiratory tract infections (RRTIs) in children.

Methods Cross-sectional data were used from 5516 children aged 1-18 years who participated in an Electronic Portal for children between 2011 and 2019. Univariable/multivariable logistic regression analyses were performed to determine risk factors for any atopic disease and RRTIs.

Results Children aged ≥ 5 years were more likely to have any atopic disease (adjusted Odds Ratio, OR, 1.49-2.80) and less likely to have RRTIs (OR 0.77-0.82) compared to children aged < 5 years. Female sex (OR 0.72; 95% CI 0.64-0.82), low birth weight (OR 0.74; 95% CI 0.56-0.98) and dog ownership (OR 0.79; 95% CI 0.66-0.95) reduced the odds of any atopic disease, but not of RRTIs. Day care attendance (OR 1.31; 95% CI 1.09-1.58) was associated with RRTIs, but not with atopic diseases. A family history of asthma, allergic rhinitis, atopic dermatitis and RRTIs was significantly associated with the same entity in children, with OR varying from 1.58 (95% CI 1.36-1.84) in allergic rhinitis to 2.19 (95% CI 1.85-2.60) in asthma.

Conclusions Risk factors for atopic diseases are distinct from risk factors for RRTIs, suggesting that the changing prevalence of both entities is not related to shared risk factors.

Background

Atopic diseases are common diseases in childhood. The prevalence of asthma, allergic rhinitis, atopic dermatitis and food allergy has been estimated at approximately 20%, 15%, 8% and 6%, respectively.(1,2) The prevalence of atopic diseases has been steadily rising in the past decades.(3) Simultaneously, the prevalence of infectious diseases has decreased.(4) These two trends in prevalence have been linked, leading to the hypothesis that a decline in infections or a lack of exposure to microbes could have an etiological role in the increased prevalence of atopic diseases. The known geographical variation in the prevalence of atopic diseases is in line with this hypothesis: a high prevalence in industrialized, urban environments concurrent with low microbial exposure, and a low prevalence in the developing or rural world concurrent with high microbial exposure.(5) It is known that early, repeated exposure to infectious agents stimulates the immune system to develop regulatory T-cells, and hereby the development of atopic diseases may be prevented.(6)

Environmental factors associated with a reduced risk of atopic diseases are often described as being associated with an increased risk of infections, such as day care attendance, growing up in a rural environment, having older siblings and having pets.(7–10) A large number of epidemiological studies have described that other environmental factors, such as maternal smoking during pregnancy, postnatal

exposure to cigarette smoke, air pollution and a family history of atopic diseases, are associated with an increased prevalence of atopic diseases.(11)

Although the opposing trends in the prevalence of atopic diseases and infections have been linked, studies investigating demographic, environmental and family history risk factors for both atopic diseases and recurrent infections in conjunction are lacking. Large studies investigating a broad range of risk factors for atopic diseases and recurrent infections that enable adjustment for each other may lead to a better understanding of the development of these disease entities in children. A large set of data on this topic is available in the so-called Electronic Portal developed by the UMC Utrecht. This is a standardized data collection tool used in multiple centres across the Netherlands that includes data of several validated questionnaires on atopic diseases and recurrent respiratory tract infections in childhood.(12) The primary aim of this study was to investigate how risk factors associated with any atopic disease (i.e. asthma, allergic rhinitis, atopic dermatitis and/or food allergy) are different from risk factors associated with recurrent respiratory tract infections (RRTIs) in children. Our secondary aim was to investigate how these risk factors are associated with individual atopic disease entities.

Methods

Domain and data collection

We performed a questionnaire-based study among children aged 1 to 18 years old who participated in the Electronic Portal between June 2011 and September 2019. The Electronic Portal is a web-based application established by a nationwide collaborative network of Dutch caregivers. The details of the Electronic Portal have been previously published.(12) Children were included in the Electronic Portal as part of a first outpatient visit for respiratory or allergic symptoms in a participating secondary care (n=9) or tertiary care (n=1) centre or as part of the WHISTLER birth cohort study.(13) Of the 9,558 children who were invited to participate in the Electronic Portal, 5,516 (58%) children started the questionnaire and were evaluated in this study. Informed consent was obtained from all parents (and/or children as applicable) before enrolment. The study was reviewed and approved by the medical ethics committee of the University Medical Centre Utrecht (No. 10/348).

Measurements

Outcome definitions

Information on the presence of atopic diseases and RRTIs was extracted from the answers to the questionnaires in the Electronic Portal (Additional table 1). The definition of asthma, allergic rhinitis and atopic dermatitis was adopted from the ISAAC questionnaires.(14) Food allergy was defined as suggestive allergic symptoms within 2 hours after ingestion of the suspected food. Recurrent respiratory tract infections (RRTIs) was defined as having a minimum number of upper or lower respiratory infection per year.(15) The minimum number depended on the child's age (Additional table 1).

Demographic, environmental and family history factors

All risk factors were selected based on prior research and clinical expertise of the authors.(7–11) Information on the presence of the selected risk factors was extracted from answers to the questionnaires in the Electronic Portal. Included demographic factors were age, sex, gestational age, birth weight, maternal and paternal ethnicity and education level. Included environmental factors were exclusive breastfeeding, pacifier use, having siblings, number of older siblings, day care attendance in the first year of life, living environment (i.e. rural or urban), having a dog, having a cat, maternal smoking during pregnancy, indoor smoking, adoption, vaccination status (i.e. complete age-appropriate vaccinations according to the Dutch vaccination schedule), flooring in the house and flooring in the child's bedroom (i.e. solid or carpet). Included factors on family history were having a family history (i.e. one or both parents and/or sibling(s) with the disease) of asthma, allergic rhinitis, atopic dermatitis, food allergy or recurrent respiratory tract infections.

Statistical analysis

Descriptive statistics including numbers (percentages) and medians (interquartile range) were used to describe the study population. Data on all risk factors and outcomes were complete in 61% of the children and 92% of the values. Missing values were imputed by using multiple imputations (20 iterations) using SPSS. First, the crude association between risk factors and the disease outcome (i.e. any of the atopic diseases or RRTIs) was assessed using univariable logistic regression analyses. Second, the adjusted association between the risk factors and outcome was assessed using multivariable logistic regression analyses. The multivariable regression analyses included all risk factors (no prior selection based on p-values) and the analyses were controlled for inclusion setting (i.e. secondary care, tertiary care or birth cohort) and the child's comorbidity. Thus, RRTIs was incorporated in the analysis of any atopic disease and vice versa. The same analyses were performed per individual atopic disease entity. Results of the univariable and multivariable regression analyses were expressed as respectively crude odds ratios and adjusted odds ratios (OR) with 95% confidence intervals (95% CI). A p-value of < 0.05 was considered statistically significant. Data were analysed using SPSS version 25.0 for Windows (SPSS, INC, Chicago, IL, USA).

Results

Patients

The median age of the 5,516 included children was 6 years (interquartile range 3 to 10) and 43% were girls (Table 1). Children were included after referral to a secondary care centre (56%), a tertiary care centre (30%) or as part of the WHISTLER birth cohort (14%). Sixty-two percent of children had one or more atopic disease(s), 28% had recurrent respiratory tract infections (RRTIs) and 29% had no atopic diseases or RRTIs (Figure 2).

Risk factors for atopic diseases and recurrent respiratory tract infections

Table 2 and Figure 1 report the results from the multivariable regression analyses, exploring the association between demographic, environmental and family history risk factors and the presence of any atopic disease or RRTIs. Table 3 reports the results from the multivariable regression analyses per individual atopic disease entity. The results of the univariable analyses are presented in Additional table 2 and 3.

Demographic factors

Several demographic factors were associated with any atopic disease, while only age was associated with RRTIs (Table 2). Children aged 5 years and older had a higher chance of any atopic disease (adjusted Odds Ratio, OR, 1.49 to 2.80), but a lower chance of RRTIS (adjusted OR, 0.77 to 0.82), compared to children aged < 5 years. Female sex (OR, 0.72; 95% CI, 0.64-0.82) and low birth weight (OR, 0.74; 95% CI, 0.56-0.98) were associated with a reduced odds of any atopic disease.

In the analyses per individual atopic disease entity, children aged 5 years and older had a higher chance of asthma (OR, 3.03 to 4.98) and allergic rhinitis (adjusted OR, 2.24 to 6.70) compared to children aged < 5 years (Table 3). Children aged 5 years and older had a lower chance of atopic dermatitis (adjusted OR, 0.45 to 0.77) compared to children aged < 4 years. Female sex was associated with a reduced odds of asthma (adjusted OR, 0.83; 95% CI, 0.71-0.98) and allergic rhinitis (adjusted OR, 0.71; 95% CI, 0.63-0.82). Low birth weight was associated with a reduced odds of allergic rhinitis (adjusted OR, 0.71; 95% CI, 0.52-0.97) only.

Environmental factors

Children who had a pet dog (adjusted OR, 0.79; 95% CI, 0.66-0.95) had a lower chance of any atopic disease. Day care attendance increased the odds of RRTIs (adjusted OR, 1.31; 95% CI, 1.09-1.58), but was not associated with any atopic disease.

In the analyses per individual atopic disease entity, children who had a pet dog had a lower chance of atopic dermatitis (adjusted OR, 0.83; 95% CI, 0.69-0.99) and food allergy (adjusted OR, 0.52; 95% CI, 0.38-0.73). Furthermore, children who had a pet cat had a lower chance of allergic rhinitis (adjusted OR, 0.71; 95% CI, 0.59-0.87). In addition, children with 1 or 2 siblings had a lower chance of allergic rhinitis (adjusted OR, 0.84; 95% CI, 0.70-1.00 and adjusted OR, 0.72; 95% CI 0.55-0.95, respectively). Children who were exclusively breastfed for 6 months or longer had a higher chance of food allergy (adjusted OR, 1.35; 95% CI, 1.06-1.73). An unexpected finding was that we observed an inverse association between maternal smoking during pregnancy and atopic dermatitis (adjusted OR 0.57; 95% CI 0.40-0.82).

Family history

The associations between family history and disease outcomes were disease-specific. Children who reported a family history of one of the atopic diseases were more likely to have any atopic disease, but were not likely to have more RRTIs. Children who reported a family history of recurrent infections were

more likely to have RRTIs (adjusted OR, 1.89; 95% CI, 1.65-2.17), but were not likely to have more atopic disease.

In the analyses per individual atopic disease entity, the disease-specific association between a family history and disease outcome was further confirmed for asthma, allergic rhinitis and atopic dermatitis (adjusted OR 2.19, 1.58, 1.73, respectively).

Discussion

Here, we present an overview of demographic, environmental and family history risk factors for atopic diseases compared to risk factors for recurrent respiratory tract infections (RRTIs) in a large cohort of Dutch children. Our data show that risk factors for atopic diseases and RRTIs differ. As an example, girls, children with low birthweight and children with a pet dog were more likely to have atopic diseases, but were not more likely to have RRTIs. Furthermore, a corresponding family history was a disease-specific risk factor for both atopic diseases and for RRTIs.

Children aged 5 years and older had a higher chance of asthma and allergic rhinitis compared to children younger than 5 years, while older children had a lower chance of atopic dermatitis. These findings are consistent with the so called "atopic march".(16) The atopic march is thought to start with atopic dermatitis, followed by food allergy, asthma and allergic rhinitis. Furthermore, female sex was associated with a reduced odds of atopic diseases as has been previously acknowledged.(17) Epidemiological studies have reported a predominance of atopic diseases in males before puberty and in females after puberty, possibly explained by hormonal influences or sex-specific genetic, environmental or social factors.(18) We did not observe an association between sex and RRTIs, although previous studies suggest that males are more susceptible to most types of respiratory tract infections.(19) The possible protective effect of low birthweight on atopic disease has been previously reported(20), and may be explained by differences in immune system development, gastrointestinal tract permeability and exposure to antigens between children with low and normal birthweight.

We found an increased risk of food allergy in children who were exclusively breastfed for more than 6 months. These children may have introduced allergenic foods later in life. Our data consolidate existing evidence that early introduction of allergenic foods prevents the development of food allergies.(21) Day care attendance increased the risk of RRTIs as has been acknowledged in previous research.(9) The finding that dog ownership was associated with a reduced risk of atopic diseases confirms evidence that having a pet dog protects against atopic diseases and sensitization.(7) The possible protective effect of pet ownership might be explained by an immunomodulatory effect of exposure to allergens, endotoxins or bacteria(7) or by affecting DNA methylation.(22) However, the protective effect of pet ownership may be partly attributed to selective avoidance of pets in households with allergic family members (reverse causality).(23)

The association between family history and the child's outcome was disease-specific, i.e. children with asthma, allergic rhinitis, atopic dermatitis or RRTIs were significantly more likely to have a parent and/or

sibling reporting the same condition. Especially the association between family history and RRTIs is intriguing and requires further investigation, as it has not been described before. A family history of RRTIs is often overlooked although it is particularly important to identify children at increased risk of RRTIs and children with genetic disorders or immune deficiencies.(24) Given the rarity of single-gene immunodeficiency diseases(25), it is suggestive that this association can be more readily explained by a polygenic inheritance pattern. Host genetic factors have been implicated in respiratory infections of varying aetiology, but no consistent associations are observed.(26) Most likely, gene-environment interactions play a role in the pathogenesis of both atopic diseases and RRTIs. Regardless of the aetiology of the observed association between family history and disease phenotype, our results do emphasize the importance of assessing the family history when confronted with a child with suspected atopic disease or RRTIs.

There are a number of limitations to our study. First, this was a questionnaire-based survey. Thus, we measured the self-reported prevalence of atopic diseases and RRTIs without objectively assessing clinical parameters such as lung capacity by spirometry or specific IgE results. However, we did use validated and widely used instruments including the ISAAC questionnaires.(14) A second limitation to our study is the cross-sectional study design. As we measured the prevalence rather than the incidence of diseases, it remains unknown whether the identified factors are a risk factor involved in the aetiology of the diseases. This study is strengthened by standardized data collection in a large group of children from both a birth cohort and hospital setting.

Conclusion

To conclude, our findings indicate that the demographic, environmental and family history risk factors for atopic diseases are distinct from the risk factors for RRTIs. Thus, the changing prevalence of both disease entities might not be related to shared risk factors.

Abbreviations

CI confidence interval

ISAAC International Study of Asthma and Allergies in Childhood

IQR interquartile range

n number

OR Odds Ratio

RRTIs recurrent respiratory tract infections

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the medical ethics committee of the University Medical Centre Utrecht (No. 10/348).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing interests

The authors declare no conflict of interests related to the manuscript content.

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Authors' contributions

HK, ML, JM and LV substantially contributed to design, concept, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published and agreed to be accountable for all aspects of the work. FE, ME, EV and KE substantially contributed to design, acquisition of data, interpretation of data, revising critically for important intellectual content, final approval of the version to be published and agreed to be accountable for all aspects of the work. SP and TL substantially contributed to design, interpretation of data, revising critically for important intellectual content, final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Tables

Table 1. Baseline characteristics of the cohort (n=5516)

		n (%)
Demographics		
Age in years, median (IQR)		6.00 (3-10)
Female sex		2369 (43)
Inclusion centre	Secondary care	3063 (56)
	Tertiary care	1676 (30)
	Birth cohort	777 (14)
Gestational age	< 37 weeks	610 (11)
	37-43 weeks	4803 (87)
	≥ 43 weeks	103 (2)
Low birth weight		430 (8)
Dutch maternal ethnicity		5119 (93)
Dutch paternal ethnicity		5002 (91)
Maternal education level	Low	538 (10)
	Middle	1884 (34)
	High	3094 (56)
Paternal education level	Low	614 (11)
	Middle	1943 (35)
	High	2959 (54)
Environment		
Exclusive breastfeeding	Never	3582 (65)
	< 6 months	948 (17)
	≥ 6 months	986 (18)
Pacifier use		3600 (65)
Having siblings		4457 (81)
Day care attendance		4685 (85)
Urban living environment		2348 (43)
Having a pet dog		967 (18)
Having a pet cat		968 (18)
Maternal smoking during pregnancy		228 (4)
Indoor smoking		293 (5)
Adopted		69 (1)
Vaccinated		4944 (90)
Flooring house	Solid	5408 (98)
	Carpet	108 (2)
Flooring bedroom child	Solid	4585 (83)
	Carpet	931 (17)
Family history		
Asthma		2238 (41)
Allergic rhinitis		3616 (66)
Atopic dermatitis		3320 (60)
Food allergy		1925 (35)
RRTIs		3107 (56)
Disease outcome child		
Asthma		960 (17)
Allergic rhinitis		1913 (35)
Atopic dermatitis		2081 (38)
Food allergy		552 (10)
Recurrent respiratory tract infections (RRTIs)		1556 (28)
Combined disease outcome child		
Any atopic disease		3405 (62)

Both any atopic disease and RRTIs	1024 (19)
No atopic disease or RRTIs	1579 (29)

Percentages do not always add up to 100 due to rounding. Abbreviations: IQR, interquartile range; n, number; RRTI, recurrent respiratory tract infections.

Table 2. Independent risk factors for respectively any atopic disease and RRTIs

	Any atopic disease		RRTIs	
	adjusted OR (95% CI)	<i>P</i> value*	adjusted OR (95% CI)	<i>P</i> value*
Demographics				
Age (in years)				
5 to 8 (vs. 1 to 4)	1.49 (1.27-1.75)	<0.001	0.82 (0.69-0.97)	0.02
9 to 12 (vs. 1 to 4)	2.03 (1.71-2.43)	<0.001	0.77 (0.64-0.94)	<0.01
13 to 17 (vs. 1 to 4)	2.80 (2.23-3.51)	<0.001	0.81 (0.65-1.02)	0.07
Female sex	0.72 (0.64-0.82)	<0.001	1.01 (0.88-1.14)	0.93
Gestational age (weeks)				
37-43 weeks (vs. < 37)	0.98 (0.78-1.23)	0.85	0.88 (0.70-1.11)	0.29
≥ 43 weeks (vs. < 37)	0.96 (0.57-1.62)	0.87	0.92 (0.54-1.57)	0.77
Low birth weight (vs. normal)	0.74 (0.56-0.98)	0.04	1.00 (0.77-1.30)	0.98
Non-Dutch mother (vs. Dutch)	0.93 (0.68-1.26)	0.63	0.78 (0.56-1.08)	0.14
Non-Dutch father (vs. Dutch)	1.43 (1.07-1.89)	0.02	1.02 (0.77-1.34)	0.91
Education level mother				
Middle (vs. low)	1.34 (1.05-1.71)	0.02	1.10 (0.86-1.42)	0.44
High (vs. low)	1.26 (0.97-1.64)	0.08	1.06 (0.82-1.38)	0.66
Education level father				
Middle (vs. low)	1.02 (0.80-1.31)	0.85	0.86 (0.68-1.07)	0.18
High (vs. low)	1.05 (0.82-1.34)	0.71	0.81 (0.64-1.03)	0.09
Environment				
Exclusive breastfeeding				
< 6 months (vs. never)	1.01 (0.85-1.20)	0.89	0.84 (0.70-1.01)	0.06
≥ 6 months (vs. never)	1.07 (0.90-1.28)	0.43	1.03 (0.86-1.23)	0.75
Pacifier use	1.04 (0.91-1.19)	0.54	1.14 (1.00-1.31)	0.06
Having siblings	0.91 (0.73-1.14)	0.42	0.99 (0.78-1.25)	0.91
Number of siblings				
1 (vs. 0)	0.94 (0.80-1.10)	0.44	1.05 (0.89-1.24)	0.58
2 (vs. 0)	0.82 (0.65-1.04)	0.10	0.99 (0.77-1.28)	0.96
≥ 3 (vs. 0)	0.76 (0.43-1.36)	0.35	0.83 (0.53-1.31)	0.42
Day care attendance	1.11 (0.93-1.32)	0.27	1.31 (1.09-1.58)	<0.01
Urban living environment (vs. rural)	0.96 (0.84-1.10)	0.59	0.94 (0.82-1.08)	0.39
Having a pet dog	0.79 (0.66-0.95)	0.01	1.18 (1.00-1.40)	0.05
Having a pet cat	0.87 (0.74-1.02)	0.08	1.14 (0.96-1.36)	0.14
Maternal smoking during pregnancy	1.00 (0.71-1.43)	0.98	1.01 (0.73-1.42)	0.93
Indoor smoking	1.27 (0.92-1.76)	0.15	0.98 (0.71-1.36)	0.90
Adopted	1.73 (0.94-3.20)	0.08	0.69 (0.29-1.19)	0.14
Vaccinated	0.92 (0.75-1.14)	0.44	1.32 (1.07-1.63)	0.01
Carpet floor house (vs. solid)	1.91 (1.13-3.22)	0.02	1.11 (0.67-1.85)	0.68
Carpet floor bedroom child (vs. solid)	0.82 (0.69-0.98)	0.03	0.86 (0.71-1.04)	0.11
Family history				
Asthma	1.24 (1.08-1.42)	<0.01	1.02 (0.88-1.17)	0.83
Allergic rhinitis	1.31 (1.13-1.50)	<0.001	0.91 (0.79-1.06)	0.22
Atopic dermatitis	1.67 (1.45-1.91)	<0.001	0.99 (0.85-1.14)	0.84
Food allergy	1.30 (1.12-1.51)	<0.01	0.98 (0.85-1.14)	0.79
Recurrent respiratory infections	0.90 (0.79-1.03)	0.13	1.89 (1.65-2.17)	<0.001

Analyses were mutually adjusted within the model, for centre (secondary care, tertiary care

or

birth cohort) and for the child's comorbidities.

* Significant P values are in bold.

Abbreviations: adjusted OR, adjusted odds ratio; CI, confidence interval; RRTIs, recurrent respiratory tract infections.

Table 3. Independent risk factors for individual atopic disease entities

	Asthma		Allergic rhinitis		Atopic dermatitis		Food allergy	
	adjusted OR (95% CI)	<i>P</i> value*	adjusted OR (95% CI)	<i>P</i> value*	adjusted OR (95% CI)	<i>P</i> value*	adjusted OR (95% CI)	<i>P</i> value*
Demographics								
Age (in years)								
5 to 8 (vs. 1 to 4)	3.03 (2.40- 3.83)	<0.001	2.24 (1.86- 2.71)	<0.001	0.77 (0.66- 0.90)	<0.01	1.12 (0.87- 1.45)	0.37
9 to 12 (vs. 1 to 4)	3.45 (2.71- 4.39)	<0.001	4.04 (3.29- 4.96)	<0.001	0.58 (0.48- 0.69)	<0.001	1.16 (0.88- 1.53)	0.30
13 to 17 (vs. 1 to 4)	4.98 (3.81- 6.49)	<0.001	6.70 (5.28- 8.49)	<0.001	0.45 (0.36- 0.56)	<0.001	1.07 (0.77- 1.50)	0.69
Female sex	0.83 (0.71- 0.98)	0.02	0.71 (0.63- 0.82)	<0.001	0.97 (0.86- 1.09)	0.57	0.89 (0.73- 1.08)	0.22
Gestational age								
37-43 weeks (vs. < 37)	0.82 (0.63- 1.08)	0.16	0.88 (0.69- 1.13)	0.31	1.03 (0.83- 1.29)	0.78	1.33 (0.93- 1.91)	0.12
≥ 43 weeks (vs. < 37)	1.23 (0.69- 2.20)	0.48	0.83 (0.49- 1.41)	0.49	0.82 (0.49- 1.37)	0.45	0.99 (0.43- 2.29)	0.97
Low birth weight (vs. normal)	1.03 (0.75- 1.41)	0.86	0.71 (0.52- 0.97)	0.03	0.80 (0.61- 1.04)	0.10	1.11 (0.74- 1.68)	0.62
Non-Dutch mother (vs. Dutch)	0.58 (0.38- 0.89)	0.01	0.96 (0.68- 1.34)	0.79	1.11 (0.81- 1.51)	0.53	0.81 (0.51- 1.27)	0.35
Non-Dutch father (vs. Dutch)	1.06 (0.75- 1.49)	0.75	1.36 (1.02- 1.81)	0.04	1.21 (0.93- 1.58)	0.16	1.31 (0.90- 1.91)	0.16
Maternal education level								
Middle (vs. low)	1.13 (0.82- 1.55)	0.44	1.18 (0.91- 1.54)	0.22	1.12 (0.88- 1.44)	0.35	1.00 (0.68- 1.47)	0.99
High (vs. low)	1.05 (0.75- 1.47)	0.77	1.07 (0.81- 1.41)	0.64	1.09 (0.84- 1.40)	0.53	0.97 (0.64- 1.47)	0.89
Paternal education level								
Middle (vs. low)	0.78 (0.59- 1.03)	0.08	1.20 (0.93- 1.55)	0.16	0.99 (0.79- 1.24)	0.95	1.30 (0.90- 1.89)	0.16
High (vs. low)	0.79 (0.59- 1.05)	0.11	1.08 (0.84- 1.40)	0.55	1.01 (0.80- 1.28)	0.91	1.38 (0.93- 2.04)	0.11
Environment								
Exclusive								

breastfeeding									
< 6 months (vs. never)	0.99 (0.79- 1.23)	0.90	1.04 (0.87- 1.25)	0.66	1.04 (0.88- 1.23)	0.65	0.91 (0.69- 1.19)	0.48	
≥ 6 months (vs. never)	1.02 (0.82- 1.27)	0.84	1.07 (0.89- 1.29)	0.48	0.94 (0.79- 1.11)	0.43	1.35 (1.06- 1.73)	0.02	
Pacifier use	1.28 (1.08- 1.51)	<0.01	1.03 (0.89- 1.19)	0.72	0.98 (0.86- 1.11)	0.69	1.08 (0.88- 1.32)	0.49	
Having siblings	1.05 (0.78- 1.40)	0.76	1.03 (0.81- 1.30)	0.84	0.80 (0.66- 0.96)	0.02	1.25 (0.89- 1.75)	0.20	
Number of siblings									
1 (vs. 0)	1.16 (0.95- 1.40)	0.15	0.84 (0.70- 1.00)	<0.05	1.05 (0.90- 1.24)	0.51	0.88 (0.69- 1.12)	0.29	
2 (vs. 0)	1.14 (0.86- 1.51)	0.37	0.72 (0.55- 0.95)	0.02	1.05 (0.84- 1.32)	0.65	0.84 (0.59- 1.18)	0.31	
≥ 3 (vs. 0)	0.99 (0.53- 1.85)	0.97	0.81 (0.45- 1.44)	0.46	1.01 (0.67- 1.51)	0.98	0.74 (0.37- 1.48)	0.39	
Day care attendance	1.05 (0.83- 1.32)	0.69	1.14 (0.92- 1.41)	0.22	0.96 (0.80- 1.15)	0.66	1.19 (0.88- 1.59)	0.26	
Urban living (vs. rural)	1.11 (0.94- 1.32)	0.22	0.94 (0.82- 1.09)	0.43	1.01 (0.88- 1.14)	0.93	0.96 (0.78- 1.17)	0.67	
Having a pet dog	1.06 (0.85- 1.31)	0.61	0.84 (0.69- 1.03)	0.09	0.83 (0.69- 0.99)	0.04	0.52 (0.38- 0.73)	<0.001	
Having a pet cat	0.91 (0.72- 1.16)	0.45	0.71 (0.59- 0.87)	<0.01	0.94 (0.80- 1.12)	0.49	0.92 (0.69- 1.22)	0.57	
Maternal smoking pregnancy	1.31 (0.82- 2.08)	0.26	1.16 (0.81- 1.67)	0.42	0.57 (0.40- 0.82)	<0.01	1.04 (0.59- 1.84)	0.90	
Indoor smoking	1.04 (0.74- 1.45)	0.84	1.05 (0.76- 1.44)	0.78	1.13 (0.83- 1.55)	0.45	1.75 (1.13- 2.70)	0.01	
Adopted	1.53 (0.78- 2.99)	0.22	1.02 (0.55- 1.89)	0.95	1.62 (0.93- 2.82)	0.09	0.38 (0.11- 1.29)	0.12	
	Asthma		Allergic rhinitis		Atopic dermatitis		Food allergy		
	adjusted OR (95% CI)	<i>P</i> value*	adjusted OR (95% CI)	<i>P</i> value*	adjusted OR (95% CI)	<i>P</i> value*	adjusted OR (95% CI)	<i>P</i> value*	

**Environment
(continued)**

Vaccinated	0.72 (0.57-0.92)	<0.01	0.82 (0.64-1.04)	0.10	1.10 (0.90-1.34)	0.35	1.36 (0.98-1.89)	0.07
Carpet floor house (vs. solid)	1.47 (0.85-2.56)	0.17	1.29 (0.77-2.15)	0.34	1.27 (0.80-2.01)	0.32	0.96 (0.48-1.95)	0.92
Carpet floor bedroom child	0.82 (0.63-1.06)	0.12	0.88 (0.72-1.07)	0.19	0.85 (0.71-1.00)	0.06	1.11 (0.84-1.45)	0.46
Family history								
Asthma	2.19 (1.85-2.60)	<0.001	1.07 (0.93-1.24)	0.33	1.00 (0.88-1.15)	0.95	0.93 (0.76-1.15)	0.50
Allergic rhinitis	0.94 (0.78-1.14)	0.55	1.58 (1.36-1.84)	<0.001	1.14 (0.99-1.30)	0.07	1.20 (0.95-1.53)	0.13
Atopic dermatitis	1.20 (1.01-1.44)	0.04	1.01 (0.87-1.17)	0.95	1.73 (1.51-1.97)	<0.001	1.19 (0.94-1.50)	0.14
Food allergy	0.99 (0.82-1.21)	0.94	1.12 (0.93-1.34)	0.23	1.25 (1.09-1.43)	<0.01	1.22 (0.93-1.61)	0.16
Recurrent respiratory infections	0.92 (0.78-1.09)	0.36	1.16 (1.00-1.34)	0.05	0.88 (0.77-1.00)	0.04	0.84 (0.69-1.03)	0.09

Analyses were mutually adjusted within the model, for centre (secondary care, tertiary care or birth cohort) and for the child's comorbidities.

* Significant P values are in bold.

Abbreviations: adjusted OR, adjusted odds ratio; CI, confidence interval.

Figures

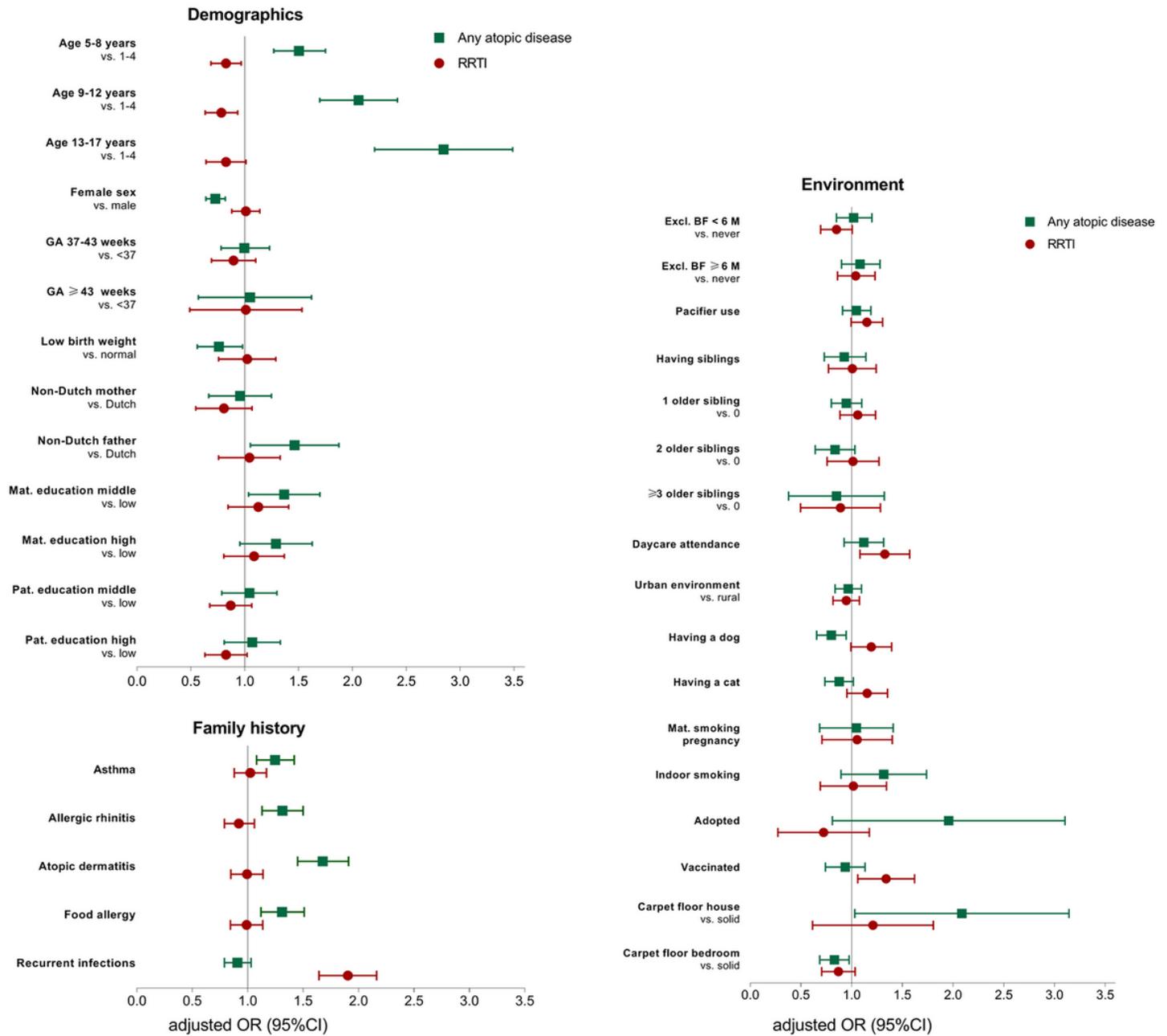


Figure 1

Association between risk factors and any atopic disease and recurrent respiratory tract infections
 Abbreviations: GA, gestational age; mat, maternal; pat, paternal; RRTI, recurrent respiratory tract infections.

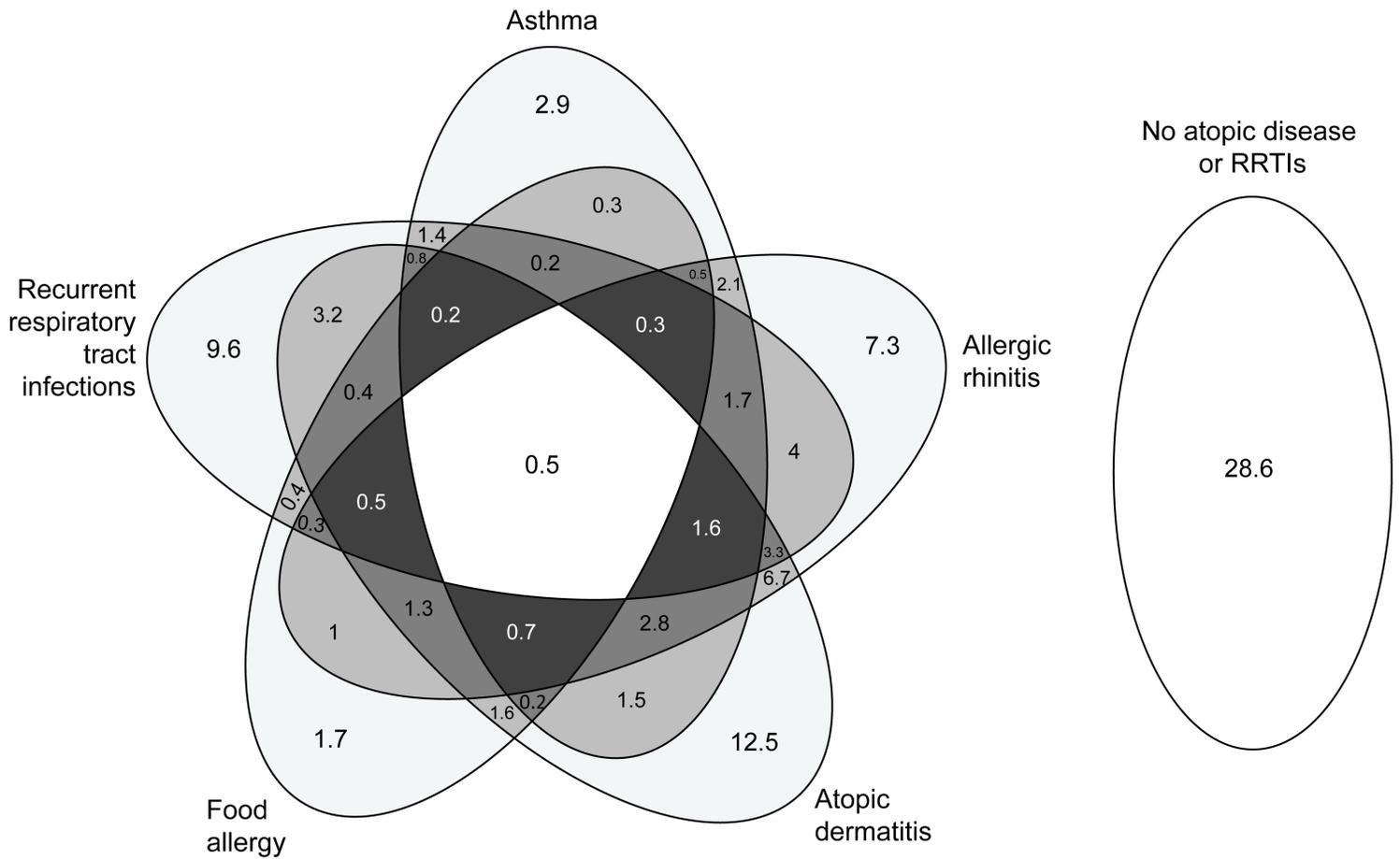


Figure 2

Venn diagram displaying the proportion of atopic diseases and respiratory tract infections in all included children. Numbers are percentages.

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