

Early life travelling does not increase risk of atopic outcomes until 15 years: results from GINIplus and LISApplus

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Summary

Background Westernized lifestyle has been blamed for allergy epidemics. One of its characteristics is increased distances and frequency of travelling from early life onwards. Early life travelling to places which substantially differ from home environment in terms of climate, vegetation and food could increase the exposure to further unknown allergens and hence promote the development of allergies, but no epidemiological study has investigated this speculation.

Methods Detailed data on travelling during the first 2 years of life as well as a range of atopic outcomes along with potential confounders up to age 15 years were collected prospectively within two large population-based multicentre German birth cohorts – GINI-plus and LISApplus. Farthest travelling destination (within Germany; middle/northern/eastern Europe; southern Europe; outside Europe), total number of trips and their combination were considered as exposures. Six atopic outcomes were used: (1) doctor-diagnosed asthma, (2) doctor-diagnosed allergic rhinitis, (3) nose and eye symptoms, (4) sensitization to food allergens, (5) sensitization to indoor and (6) outdoor inhalant allergens. Longitudinal associations between each exposure and health outcome pair were analysed using generalized estimation equations (GEEs).

Results The results of our longitudinal analyses of 5674 subjects do not support the research hypothesis that travelling abroad to different regions in Europe or beyond Europe and frequency of travelling increase prevalence of doctor-diagnosed asthma and allergic rhinitis, nose and eye symptoms and allergic sensitization up to 15 years of age. Furthermore, there was no indication of age-varying effects.

Conclusions Early life travelling does not seem to increase risk of atopic outcomes. Nevertheless, as we could not account for the type of visited environment or length of stay, these first findings should be interpreted with caution.

Keywords allergic rhinitis, allergic sensitization, asthma, cohort, travelling

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Introduction

The shift to a westernized lifestyle has been blamed for allergy epidemics [1, 2]. The initial lower prevalences of atopic conditions in former East Germany and their

subsequent rapid increase in the early 1990s after the reunification of East and West Germany is one of the brightest illustrations of how westernization of lifestyle leads to allergy epidemics [2]. A range of potential risk factors associated with a westernized lifestyle were

assessed to explain the observed pattern of allergy development in the two parts of Germany [2–4].

Increased distances and frequency of travelling abroad were factors which changed in former East Germany after the reunification. Information on destination of travelling and number of trips by destination was collected in the German birth cohorts, GINIplus and LISAplus, which were established in the mid-1990s. At that time, avoidance of allergens in early childhood was one of the main suggested strategies in preventing atopic diseases [5]. Therefore, it has been speculated that early life travelling to places which substantially differ from home environment in terms of climate, vegetation and food would increase the exposure to further unknown aero- and food allergens and hence promote the development of allergies [3, 6]. However, no epidemiological study has investigated this speculation. In this study, we aimed to answer this historical question and to test whether destination and frequency of travelling during the first 2 years of life were associated with increased prevalence of asthma, allergic rhinitis and allergic sensitization up to 15 years of age.

Methods

Data were obtained from two ongoing multicentre German birth cohort studies – GINIplus and LISAplus [7, 8]. Briefly, healthy full-term neonates with a normal birthweight were recruited at selected maternity hospitals. The GINIplus cohort ($n = 5991$) was recruited in Munich and Wesel between 1995 and 1998, while the LISAplus cohort ($n = 3094$) was recruited in Munich, Leipzig, Wesel and Bad Honnef between 1997 and 1999. GINIplus consists of two study groups: one is an observation group and the second is an intervention group who received a nutritional intervention during the first 4 months of life. In the intervention group, a double-blind controlled trial compared the effect of three hydrolysed formulas vs. cow's milk on allergy development. Newborns with a family history of allergy were invited for the intervention group. Participants with a negative family history or a positive family history but who declined to participate in the intervention trial were included in the observation group. LISAplus is a true population-based cohort.

Both cohort studies have been approved by their local ethics committees (Bavarian General Medical Council, University of Leipzig, Medical Council of North Rhine-Westphalia), and informed consent was obtained from all families.

Doctor diagnoses of childhood asthma and allergic rhinitis (yearly, 3–15 years) as well as nose and eye symptoms (at 4, 6, 10 and 15 years) were obtained using repeatedly administered parent-completed questionnaires. Sensitization to food as well as to indoor

and outdoor aeroallergens (at 6, 10 and 15 years) was defined by measuring specific immunoglobulin E (IgE) in serum. More details on outcome definitions have been described previously by Fuertes *et al.* [9] and are also provided in Appendix S1.

Information on travelling during the first 2 years of life in general as well as travelling by destination (Germany, middle/northern Europe, eastern Europe, southern Europe, outside Europe) was collected at age 2 years in GINIplus, and at 6, 12 and 18 months and at 2 years in LISAplus. Besides the aforementioned dichotomous questions, the number of trips to each travelled destination was also asked. Participants with missing data in any of these travelling variables were excluded.

Firstly, we assessed the hypothesis that early life travelling to places which substantially differ from home environment in terms of climate, vegetation and food increases the risk of developing atopic outcomes. Given that 19% of the study participants travelled to more than one region (Fig. S1), participants were assigned to four categories based on farthest travelling destination: (1) never travellers/only within Germany – used as reference category, (2) farthest to middle/northern/eastern Europe, (3) farthest to southern Europe and (4) outside of Europe. Additionally, to test whether higher frequency of travelling might pose higher risk of developing atopic diseases compared to no/low frequency, categorical variables for total number of trips (0, 1, 2, 3, 4–5 and > 5) and total number of trips weighted by destination (weights: middle/northern/eastern Europe = 1, southern Europe = 2, outside Europe = 3; resulting categories: 0, 1, 2, 3, 4 and > 4) were used as exposure variables. More details on exposure definitions are provided in Appendix S2.

Given the longitudinal data structure (i.e. repeated assessment of atopic outcomes), associations between each exposure (as a time-constant variable) and the health outcomes (as time-varying variables) were analysed using generalized estimation equations (GEEs) [10] with logit link and exchangeable correlation structure. Thus, the effect estimates are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Minimally adjusted models were adjusted for time of follow-up (outcome specific), sex, study (GINIplus observation group/GINIplus intervention group/LISAplus) and study area (Munich/Wesel/Leipzig/Bad Honnef). Main models were additionally adjusted for other a priori selected confounders: parental history of atopic diseases, parental education (based on the highest number of years of school education of either parent: < 10 years, $= 10$ years and > 10 years, according to the German educational system), maternal smoking during pregnancy, tobacco smoke exposure at home (birth–4 years) and the presence of older siblings.

Statistical analyses were conducted using the program R, version 3.1.1 (Vienna, Austria) [11]. GEE models were fitted by the *geeglm* function from the *geepack* package [12]. Running the analyses was simplified by using the *manyregs* package [13].

Results

In total, 5674 children (62.5% of the original cohorts) had information on travelling, at least one health outcome at one time point and all confounders (flow chart of study participants is provided in Appendix S1, Fig. S2; study population characteristics are provided in Table 1). Participants included in the current analysis differed from those excluded in a number of characteristics. First of all, they were less likely to participate in the GINIplus observation group and more likely to participate in the LISApplus cohort. Additionally, they were more likely to be from Munich and Bad Honnef than from Leipzig and Wesel. Finally, their parents were more likely to have history of atopic diseases and high level of school education. Period prevalences of all health outcomes were similar across the two cohorts: prevalence of nose and eye symptoms as well as sensitization to aeroallergens increased with age, while asthma, allergic rhinitis and sensitization to food allergens reached maximum levels at 10–11 years (Appendix S1, Table S1). Only 35.8% of the study participants did not travel abroad during the first 2 years of life (among them, 12.0% never travelled even within Germany; Appendix S1, Fig. S1); prevalence and frequency of travelling were similar in the GINIplus and LISApplus cohorts (Appendix S1, Table S2).

Farthest travelling destination did not increase prevalence of childhood asthma, allergic rhinitis or allergic sensitization up to 15 years of age (Fig. 1). In contrast, there was some indication that travelling outside Europe compared to never travelling/travelling within Germany was associated with even lower risk for allergic rhinitis and sensitization to indoor aeroallergens. These results were supported by the two sensitivity analyses. In one analysis, never travellers (used as a reference group) were considered separate from travellers within Germany only. In the other sensitivity analysis, three dichotomous travelling variables for each destination (middle/northern/eastern Europe, southern Europe and outside Europe) were introduced in one model without transforming them into one variable (Appendix S2).

Total number of trips did not reveal any significant results (except for one is most likely due to chance: the association between four to five trips and decreased odds of sensitization to indoor aeroallergens), nor a pattern of exposure–response relationship (Appendix S1, Fig. S3). Similar results were observed for total number of trips weighted by destination of travelling

Table 1. Characteristics of study participants

	n/N	%
General characteristics		
Study		
GINIplus observation	2225/5674	39.2
GINIplus intervention	1416/5674	25.0
LISApplus	2033/5674	35.8
Study area		
Munich	2789/5674	49.2
Leipzig	552/5674	9.7
Bad Honnef	213/5674	3.8
Wesel	2120/5674	37.4
Females	2770/5674	48.8
Parental history of atopy	3144/5674	55.4
Parental school education		
< 10 years	453/5674	8.0
= 10 years	1557/5674	27.4
> 10 years	3664/5674	64.6
Smoking		
During pregnancy	799/5674	14.1
Ever at home (0–4 years)	2176/5674	38.4
Older siblings	2623/5674	46.2
Travelling during the first 2 years		
Farthest travelling destination		
Within Germany	2034/5674	35.8
Middle, northern or eastern Europe	1435/5674	25.3
Southern Europe	1862/5674	32.8
Outside of Europe	343/5674	6.0
Total number of trips		
0	2034/5674	35.8
1	1240/5674	21.9
2	960/5674	16.9
3	533/5674	9.4
4–5	543/5674	9.6
> 5	364/5674	6.4
Total number of trips weighted by destination		
0	2034/5674	35.8
1	655/5674	11.5
2	904/5674	15.9
3	441/5674	7.8
4	529/5674	9.3
> 4	1111/5674	19.6
Early allergic diseases and symptoms (birth–2 years)		
Wheeze	1398/5537	25.2
Nose and eye symptoms	225/5520	4.1
Doctor-diagnosed eczema	920/5518	16.7
Any	2134/5419	39.4
Atopic outcomes at age of 15 years		
Doctor-diagnosed asthma	108/4110	2.6
Doctor-diagnosed allergic rhinitis	389/4061	9.6
Nose and eye symptoms	761/4122	18.5
Sensitization to food allergens	282/2497	11.3
Sensitization to indoor aeroallergens	855/2497	34.2
Sensitization to outdoor aeroallergens	872/2497	34.9

(Appendix S1, Fig. S4). In the latter case, two trips weighted by destination decreased the odds of nose and eye symptoms.

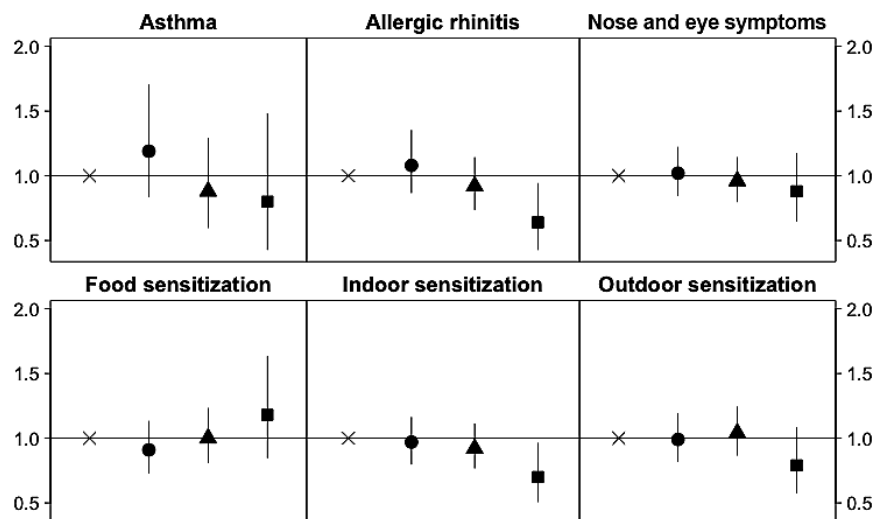


Fig. 1. Results of GEE models (odds ratios and corresponding 95% confidence intervals) for associations of atopic outcomes with farthest travelling destination. All models are adjusted for time of follow-up (outcome-specific), sex, study, study area, parental atopy, parental education, maternal smoking during pregnancy, smoking at home (0–4 years) and the presence of older siblings. The reference category is 'never travelling/travelling only within Germany'. Circles stand for farthest travelling to middle/northern/eastern Europe, triangles for farthest travelling to southern Europe and squares for farthest travelling outside Europe.

Regression results were very similar when compared to the minimally adjusted model (Appendix S2) and also after exclusion of participants with partially missing outcome data (Appendix S2). Stratification by cohort (GINIplus vs. LISAplus) did not reveal any substantial differences between the two cohorts (Appendix S2). Importantly, all above-mentioned associations did not reach statistical significance in most of the mentioned sensitivity analyses (minimally adjusted models, restriction to participants with complete outcome data and stratification by cohort).

No age-varying effects of farthest travelling destination, total number of trips and total number of trips weighted by destination (tested by introducing an interaction term with outcome-specific time of follow-up to the models) were identified.

Discussion

To our knowledge, this is the first study to investigate prospectively the role of early life travelling for future development of atopic outcomes. The results of our longitudinal analysis, conducted in two large population-based German birth cohorts, do not support the hypothesis that travelling abroad during the first 2 years of life increases the risk for asthma, allergic rhinitis or atopic sensitization up to 15 years of age.

It has to be acknowledged that travelling in relation to atopic outcomes is a very complex issue to evaluate. Firstly, only unspecific information on travelling was available. In particular, it was not possible to verify whether the type of visited environment (urban, seaside, mountains, countryside, etc.) and length of stay could

be influential factors. The observed lack of association between travelling and atopic outcomes in our study might well be explained by presumably insufficient exposure (i.e. short time spent away) to a different environment which is unlikely to have an effect on the immune system and thus, to increase risk of atopic outcomes later in life. An observation made in the classical studies on migrants – that allergic diseases typically manifest only several years after migration [14–16] – rather supports such an assumption.

Secondly, the possibility that parents of particular characteristics avoided travelling with a child should be taken into account. We attempted to address this issue in two ways. As parental history of atopic diseases could have been a factor that restrained parents from travelling with a child, it was accounted for in the models. Moreover, we excluded participants with any allergic diseases and symptoms – wheeze, nose and eye symptoms and doctor-diagnosed eczema – as well as participants without such information ($n = 2389$, i.e. 42.1% of the study population) during the time frame where travelling occurred (first 2 years of life), and reran the models. This resulted in similar effect estimates (Appendix S2).

The strengths of this study include the longitudinal analysis of prospectively collected data on travelling and on several atopic outcomes up to 15 years, as well as the availability of detailed information on several well-established risk factors, which could confound associations with asthma, allergies and sensitization. However, as with many longitudinal cohort studies, selection is present by design and due to loss to follow-up which limits generalizability of the findings. Only

German-speaking families where a child was born with a normal birthweight and at full term were invited to participate initially. Moreover, participants in our study population differed from the original cohorts in several characteristics, including that they were more likely to have a middle or high socio-economic status as indicated by the highest achieved school education of their parents. Finally, there were some differences between the two cohorts, including time of recruitment and the fact that data on travelling were collected once in GINI-plus and four times in LISApplus. Nevertheless, similar prevalences of all three exposure variables and six outcome variables across the two cohorts, as well as the similar regression analysis results, speak for the reliability of our findings.

In conclusion, early life travelling abroad does not seem to increase risk of atopic outcomes. Although our analysis is based on data collected almost 20 years ago within one country and deals with rather unspecific information on travelling, our results are somewhat in line with the current scepticism regarding the efficiency of allergen avoidance in prevention of atopic outcomes. Indeed, a recent meta-analysis by Huiyan *et al.* [17] based on 14 randomized controlled trials has resulted in mixed findings: while for asthma/whoeeze, allergen avoidance had a protective effect, no such evidence could be found for rhinitis, eczema or cough. Nevertheless, as we could not account for the type of visited environment and length of stay, these first findings should still be interpreted with caution. Studies with more detailed information on travelling are needed to confirm or refute our findings.

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examinations of the GINIplus study were covered from the respective budgets of the five study centres (Helmholtz Zentrum Munich (former GSF), Marien-Hospital Wesel, LMU Munich, TU Munich and from 6 years onward also from IUF – Leibniz Research Institute for Environmental Medicine) and a grant from the Federal Ministry for Environment (IUF, FKZ 20462296). The LISApplus study was mainly supported by grants from the Federal Ministry for Education, Science, Research and Technology and in addition from Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research – UFZ, Leipzig, Marien-Hospital Wesel, Pediatric Practice, Bad Honnef for the first 2 years. The 4-year, 6-year and 10-year follow-up examinations of the LISApplus study were covered from the respective budgets of the involved partners (Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research – UFZ, Leipzig, Marien-Hospital Wesel, Pediatric Practice, Bad Honnef, IUF – Leibniz Research Institute for Environmental Medicine) and in addition by a grant from the Federal Ministry for Environment (IUF, FKZ 20462296). The recent 15-year follow-up examinations of the GINI plus and LISApplus studies were supported by the Commission of the European Communities, the 7th Framework Program (MeDALL project) and the Mead Johnson and Nestlé companies (GINIplus only). The aforementioned funding sources had no involvement in the design of the study, collection, analysis and interpretation of data, writing of the report and decision to submit the article for publication.

Author contributions

IM designed the analyses, interpreted the data, drafted the initial manuscript, revised the manuscript and approved the final manuscript as submitted. CB programmed the analysis and contributed to the design of the analysis. MS and JH also contributed to the design of the analysis. SK, IL, AvB, DB, C-PB, BH, MS and JH contributed to the data collection, interpreted the data, reviewed and revised the manuscript and approved the final manuscript as submitted. All authors agree to be accountable for this work.

Conflict of interests

The authors declare no conflict of interest.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. Outcome definitions.

Appendix S2. Exposure definitions.

Figure S1. Distribution of study participants ($n = 5674$) by travelling destination during the first 2 years of life.

Figure S2. Flow chart of study participants.

Figure S3. Results of GEE models (odds ratios and corresponding 95% confidence intervals) for associations of atopic outcomes with total number of trips.

Figure S4. Results of GEE models (odds ratios and corresponding 95% confidence intervals) for associations of atopic outcomes with total number of trips weighted by destination (weights: 1 for middle/northern/eastern Europe, 2 for southern Europe, 3 for outside of Europe).

Table S1. Period prevalences of atopic outcomes, n/N (%).

Table S2. Prevalence of travelling exposures, n (%).

Appendix S3. Results from the sensitivity analyses.

Appendix S1. Outcome definitions

Outcome data were collected using parent-completed questionnaires administered when the child was 3, 4, 6, 10 and 15 years old for GINIplus and that at 4, 6, 10 and 15 years old for LISAplus participants.

A doctor diagnosis of **asthma** was defined as a positive response to “In the last 12 months, has your child been diagnosed with asthma?” Yearly diagnoses for asthma were available for ages 3 to 15 years.

A doctor diagnosis of **allergic rhinitis** was defined as a positive response to “In the last 12 months, has your child been diagnosed with hay fever or allergic rhinitis?” For GINIplus, this information was collected in one question at the 3, 4 and 6 year follow-ups (diagnosis of hay fever or allergic rhinitis, as aforementioned). For the data collected at the 10 and 15 year follow-ups of GINIplus and for all LISAplus follow-ups, this information was collected in two separate questions which were subsequently combined. Yearly diagnoses for allergic rhinitis were available for ages 3 to 15 years.

Eye and nose symptoms were assessed at ages 4, 6, 10 and 15 years and were defined based on two concomitant positive responses to “In the past 12 months, has your child had a clogged or itchy nose when he/she did not have a cold?” and “In the past 12 months, has your child had a clogged or itchy nose accompanied by watery eyes?”, which is consistent with the rhinoconjunctivitis definition used in the International Study of Asthma and Allergies in Childhood¹ (Äit-Khaled et al., 2009).

Specific immunoglobulin E (IgE) against common allergens was assessed at ages 6, 10 and 15 years using the standardized CAP-RAST FEIA method (ThermoFischer, Freiburg, Germany). **Allergic sensitization to food allergens** (milk, peanut, eggs, soya, cod, wheat flour) as well as **allergic sensitization to indoor aeroallergens** (Dermatoph. Pteroyssinus (house dust mites), cats, dogs, and cladosporium (mold)) and **outdoor aeroallergens** (birch, rye, mugwort and timothy grass) was defined as IgE above 0.35 kU/L against any of the tested groups of allergens.

¹ Äit-Khaled N, Pearce N, Anderson H, Ellwood P, Montefort S, Shah J, ISAAC Phase Three Study Group. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy* 2009;**64**:123-148.

Appendix S2. Exposure definitions

In GINIplus, data on travelling were collected at 2 years while in LISApplus these data were collected repeatedly at four time points – 6 months, 1 year, 1.5 years and 2 years. Parents were asked whether they travelled with a child during the first 2 years/last 6 months, and then by 5 separate questions whether they travelled within Germany, to middle or northern Europe, to eastern Europe, to southern Europe, and outside of Europe (Americas, Africa, Asia, Australia and South Pacific region). All the aforementioned 6 questions were dichotomous (yes/no). Additionally, parents were asked how many trips took place for every destination, which resulted in 5 additional questions. Thus, in GINIplus, exposure variables were created based on a total of 11 questions (1+5+5) while in LISApplus – based on 44 questions (11x4).

Participants with missing data in any of the original travelling variables were excluded.

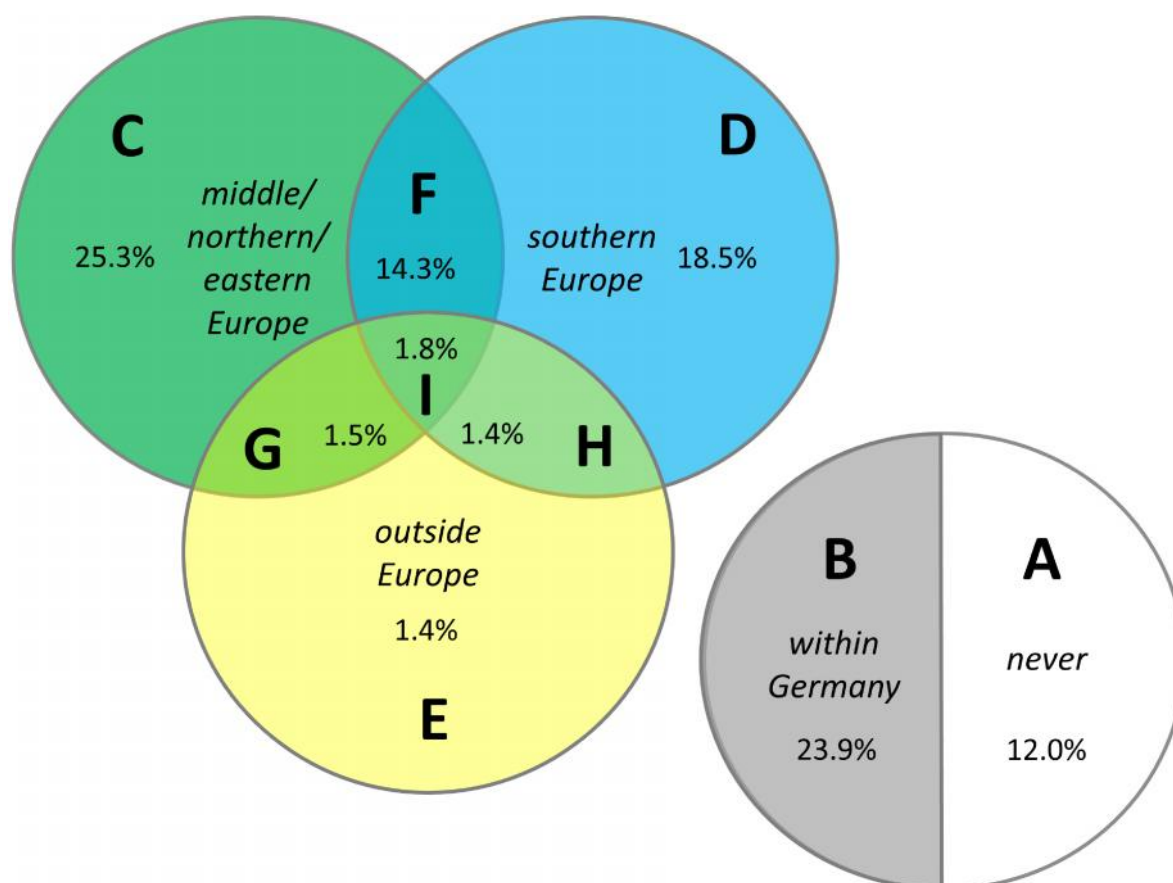


Figure S1. Distribution of study participants (n=5674) by travelling destination during the first two years of life.

First, we assessed the hypothesis that early life travelling to places which substantially differ from home environment in terms of climate, vegetation and food, increases the risk of developing atopic outcomes. Given that 19% of the study participants travelled to more than one destination (Fig.

S1), participants were assigned to 4 categories based on **farthest travelling destination**: (1) non-travellers or travellers only within Germany (Fig. S1: A+B); (2) middle/northern/eastern Europe (Fig. S1: C); (3) southern Europe (Fig. S1: D+F); (4) outside of Europe (Fig. S1: E+G+I+H). As sensitivity analyses, we (a) used three separate dichotomous travelling variables for each destination (middle/northern/eastern Europe, southern Europe and outside Europe) in one model without transforming them into one variable and (b) modified farthest travelling destination variable by creating separate categories for non-travellers and travellers only within Germany.

Second, we assumed that frequency of travelling and prevalence of allergic outcomes are positively related and that the pattern of exposure-outcome relationship is either linear or close to it. Therefore, we created a **total number of trips** variable with 6 categories ignoring the direction of travelling: non-travellers or travellers only within Germany (zero trips); 1; 2; 3; 4-5; >5 trips.

Third, we decided to take into account both number of trips and the direction of travelling and therefore created the variable **total number of trips weighted by destination of travelling** (weights: middle/northern/eastern Europe =1, southern Europe =2; outside of Europe =3): 0; 1; 2; 3; 4; >4.

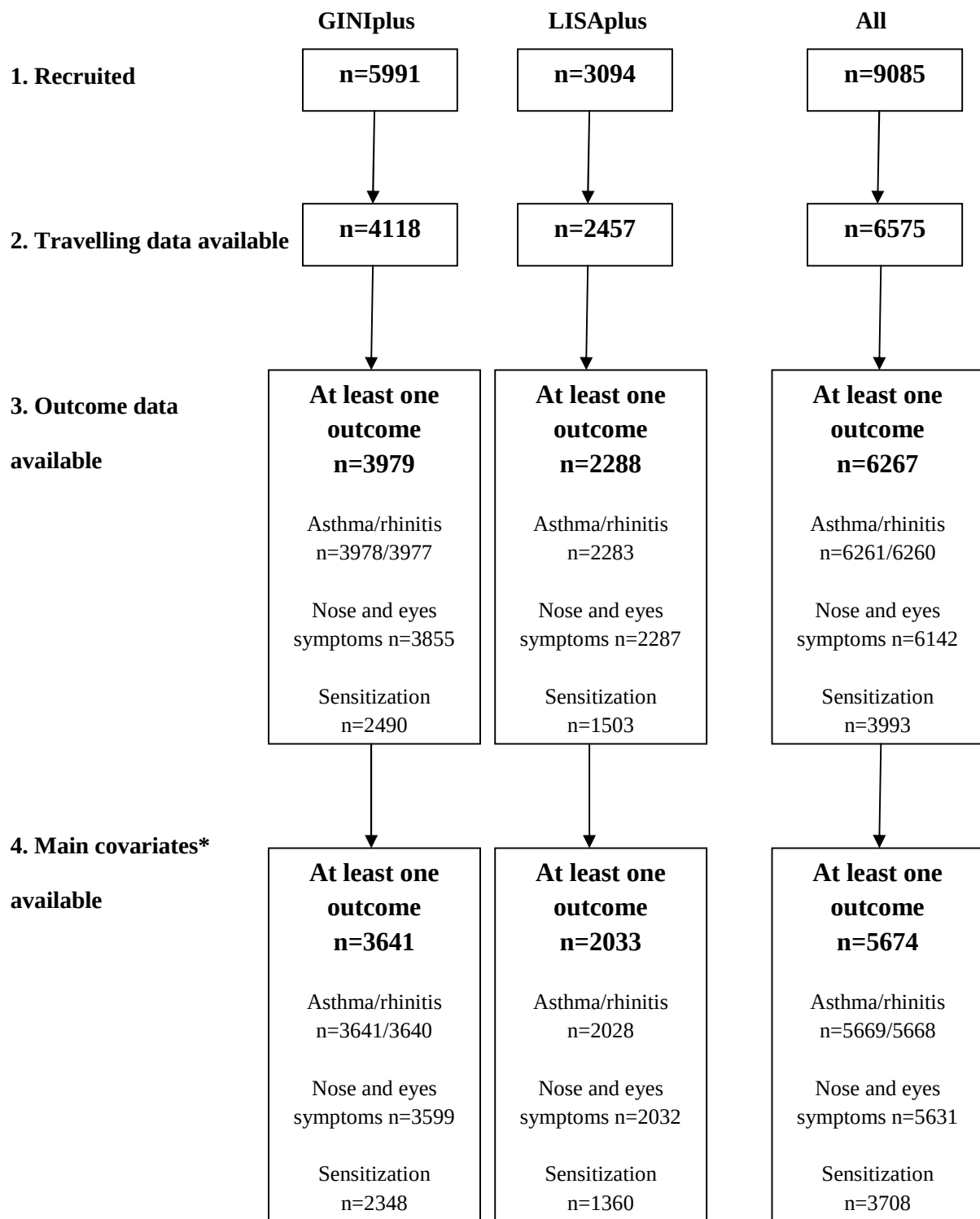


Figure S2. Flow chart of study participants.

* Main covariates: sex, study, study area, parental history of atopic diseases, parental education maternal smoking during pregnancy, tobacco smoke exposure at home (birth-4 years) and presence of older siblings.

Table S1. Period prevalences of atopic outcomes, n/N (%)

Outcome variable	Age	GINIplus	LISAplus	All
Doctor diagnosed asthma	3	37/3617 (1.0)	18/1991 (0.9)	55/5608 (1.0)
	4	48/3530 (1.4)	20/1961 (1.0)	68/5491 (1.2)
	5	68/3306 (2.1)	45/1824 (2.5)	113/5130 (2.2)
	6	70/3208 (2.2)	41/1821 (2.3)	111/5029 (2.2)
	7	75/2756 (2.7)	42/1414 (3.0)	117/4170 (2.8)
	8	70/2756 (2.5)	34/1414 (2.4)	104/4170 (2.5)
	9	90/2756 (3.3)	44/1414 (3.1)	134/4170 (3.2)
	10	101/2756 (3.7)	41/1414 (2.9)	142/4170 (3.4)
	11	118/2691 (4.4)	42/1419 (3.0)	160/4110 (3.9)
	12	85/2691 (3.2)	38/1419 (2.7)	123/4110 (3.0)
	13	87/2691 (3.2)	43/1419 (3.0)	130/4110 (3.2)
	14	84/2691 (3.1)	38/1419 (2.7)	122/4110 (3.0)
	15	73/2691 (2.7)	35/1419 (2.5)	108/4110 (2.6)
Doctor diagnosed allergic rhinitis	3	62/3617 (1.7)	27/1994 (1.4)	89/5611 (1.6)
	4	102/3527 (2.9)	46/1966 (2.3)	148/5493 (2.7)
	5	148/3302 (4.5)	75/1823 (4.1)	223/5125 (4.4)
	6	173/3202 (5.4)	104/1817 (5.7)	277/5019 (5.5)
	7	190/2733 (7.0)	78/1363 (5.7)	268/4096 (6.5)
	8	204/2731 (7.5)	85/1366 (6.2)	289/4097 (7.1)
	9	252/2734 (9.2)	109/1368 (8.0)	361/4102 (8.8)
	10	262/2737 (9.6)	136/1367 (9.9)	398/4104 (9.7)
	11	296/2646 (11.2)	137/1417 (9.7)	433/4063 (10.7)
	12	222/2644 (8.4)	105/1412 (7.4)	327/4056 (8.1)
	13	271/2648 (10.2)	123/1414 (8.7)	394/4062 (9.7)
	14	259/2644 (9.8)	124/1414 (8.8)	383/4058 (9.4)
	15	271/2648 (10.2)	118/1413 (8.4)	389/4061 (9.6)
Nose and eyes symptoms	4	138/3538 (3.9)	74/2021 (3.7)	212/5559 (3.8)
	6	214/3313 (6.5)	114/1832 (6.2)	328/5145 (6.4)
	10	356/2782 (12.8)	187/1425 (13.1)	543/4207 (12.9)
	15	516/2697 (19.1)	245/1425 (17.2)	761/4122 (18.5)
Sensitization to food allergens	6	212/1694 (12.5)	121/1024 (11.8)	333/2718 (12.3)
	10	289/1543 (18.7)	182/929 (19.6)	471/2472 (19.1)
	15	194/1633 (11.9)	88/864 (10.2)	282/2497 (11.3)

Sensitization to indoor	6	334/1693 (19.7)	158/1023 (15.4)	492/2716 (18.1)
aeroallergens	10	425/1541 (27.6)	242/928 (26.1)	667/2469 (27.0)
	15	577/1633 (35.3)	278/864 (32.2)	855/2497 (34.2)
Sensitization to outdoor	6	364/1693 (21.5)	186/1023 (18.2)	550/2716 (20.3)
aeroallergens	10	459/1542 (29.8)	265/929 (28.5)	724/2471 (29.3)
	15	593/1633 (36.3)	279/864 (32.3)	872/2497 (34.9)

Table S2. Prevalence of travelling exposures, n (%)

Exposure variable	GINIplus (n=3641)	LISAplus (n=2033)	All (n=5674)
Farthest travelling destination			
within Germany	1380 (37.9)	654 (32.2)	2034 (35.8)
middle, northern or eastern Europe	937 (25.7)	498 (24.5)	1435 (25.3)
southern Europe	1104 (30.3)	758 (37.3)	1862 (32.8)
outside Europe	220 (6.0)	123 (6.1)	343 (6.0)
Total number of trips			
0	1380 (37.9)	654 (32.2)	2034 (35.8)
1	804 (22.1)	436 (21.4)	1240 (21.9)
2	647 (17.8)	313 (15.4)	960 (16.9)
3	318 (8.7)	215 (10.6)	533 (9.4)
4-5	294 (8.1)	249 (12.2)	543 (9.6)
>5	198 (5.4)	166 (8.2)	364 (6.4)
Total number of trips weighted by destination			
0	1380 (37.9)	654 (32.2)	2034 (35.8)
1	412 (11.3)	243 (12.0)	655 (11.5)
2	623 (17.1)	281 (13.8)	904 (15.9)
3	270 (7.4)	171 (8.4)	441 (7.8)
4	342 (9.4)	187 (9.2)	529 (9.3)
>4	614 (16.9)	497 (24.4)	1111 (19.6)

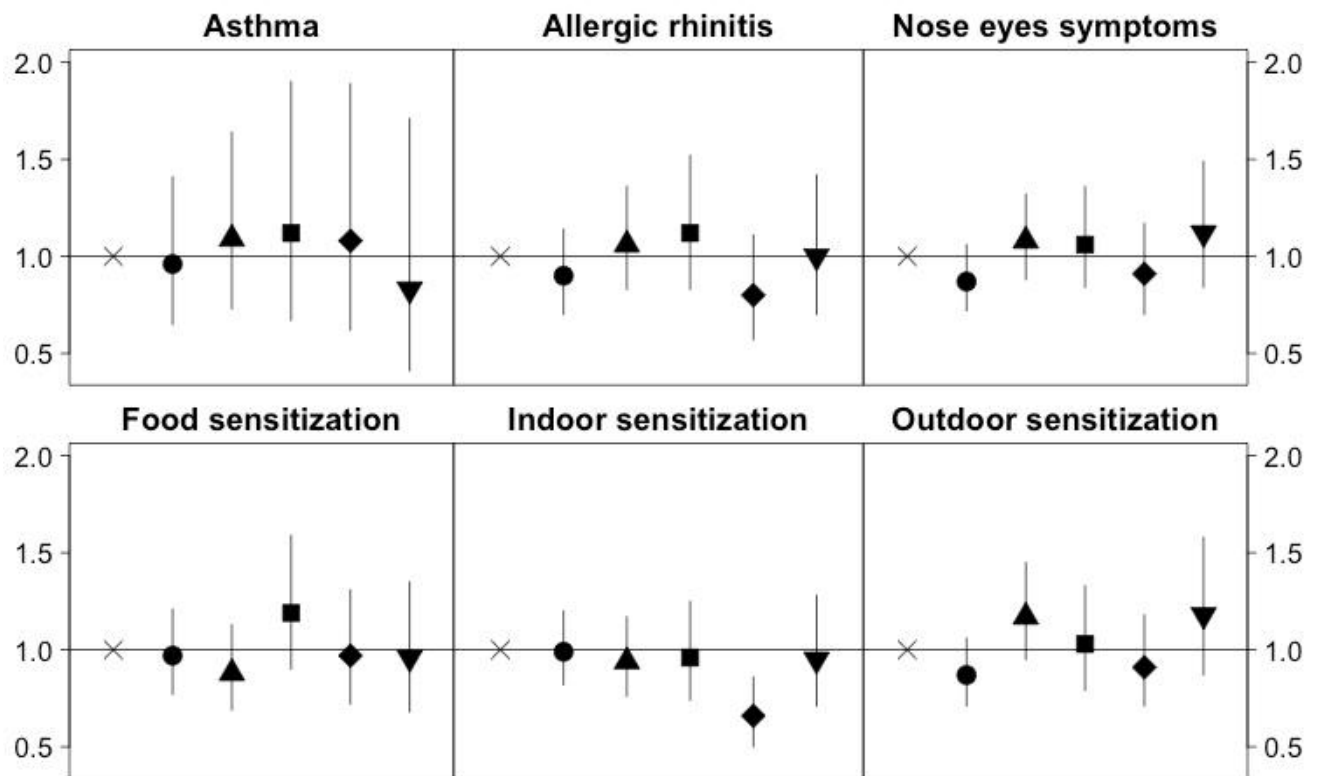


Figure S3. Results of GEE models (odds ratios and corresponding 95% confidence intervals) for associations of atopic outcomes with total number of trips. All models are adjusted for time of follow-up (outcome-specific), sex, study, study area, parental atopy, parental education, maternal smoking during pregnancy, smoking at home (0-4 years) and presence of older siblings. The reference category is "never travelling/travelling only within Germany" (zero trips). Circles stand for 1 trip, triangles for 2 trips, squares for 3 trips, diamonds for 4-5 trips and inversed triangles for more than 5 trips.

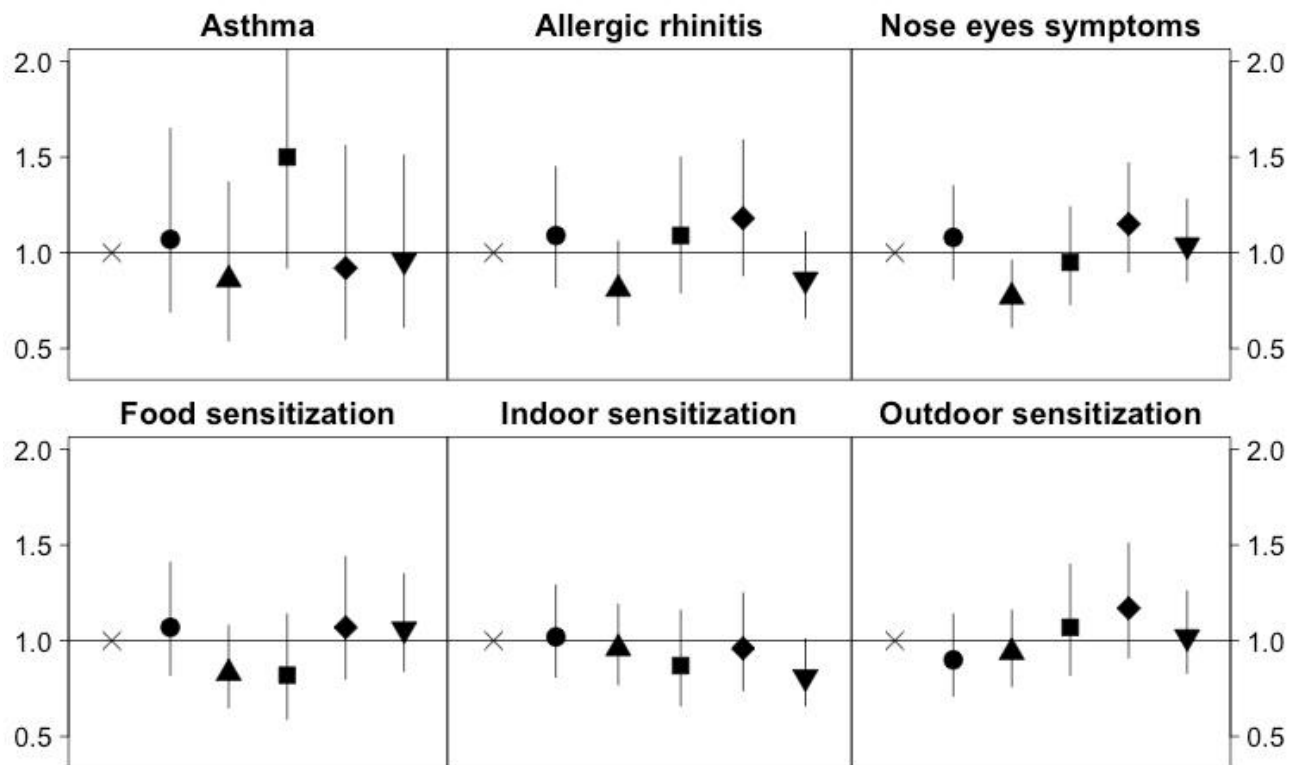


Figure S4. Results of GEE models (odds ratios and corresponding 95% confidence intervals) for associations of atopic outcomes with total number of trips weighted by destination (weights: 1 for middle/northern/eastern Europe, 2 for southern Europe, 3 for outside of Europe). All models are adjusted for time of follow-up (outcome-specific), sex, study, study area, parental atopy, parental education, maternal smoking during pregnancy, smoking at home (0-4 years) and presence of older siblings. The reference category is “never travelling/travelling only within Germany” (zero trips). Circles stand for 1 trip weighted by destination, triangles for 2 trips weighted by destination, squares for 3 trips weighted by destination, diamonds for trips 4 weighted by destination and inversed triangles for more than 4 trips weighted by destination.