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SYSTEMATIC REVIEW

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Siblings and risk of allergic rhinitis: A systematic review and meta-analysis

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Abstract

Following the "hygiene hypothesis" and the increase in the prevalence of atopic diseases such as allergic rhinitis, a plethora of studies have investigated the role of sibship composition as a protective factor, but findings are conflicting. The aim of this study was to synthesize the global literature linking birth order and sibship size (number of siblings) to the risk of allergic rhinitis. Fifteen databases were systematically searched, with no restrictions on publication date or language. Observational studies with defined sibship composition (birth order or sibship size) as exposure and allergic rhinitis or allergic rhinoconjunctivitis (self-reported or clinically diagnosed) as outcome were eligible. Study selection, data extraction, and quality assessment were performed independently in pairs. Relevant data were summarized in tables. Comparable numerical data were analyzed using meta-analysis with robust variance estimation (RVE). Seventy-six reports with >2 million subjects were identified. Being second- or later-born child was associated with protection against both current (pooled risk ratio [RR] 0.79, 95% CI 0.73–0.86) and ever (RR 0.77, 95% CI 0.68–0.88) allergic rhinitis. Having siblings, regardless of birth order, was associated with a decreased risk of current allergic rhinitis (RR 0.89, 95% CI 0.83–0.95) and allergic rhinoconjunctivitis (RR 0.92, 95% CI 0.86–0.98). These effects were unchanged across age, time period, and geographical regions. Our findings thus indicate that primarily, a higher birth order, and to a lesser extent the number of siblings, is associated with a lower risk of developing allergic rhinitis.

KEYWORDS
allergic rhinitis, epidemiology, hygiene hypothesis, meta-analysis, systematic review

Abbreviations: 95% CI, 95% confidence interval; I^2, I-squared; IgE, Immunoglobulin E; RR, Risk ratio; RVE, Robust variance estimation; τ^2, Tau-squared.

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1 | INTRODUCTION

Allergic rhinitis is a chronic inflammatory upper airway disease,[1–4] mediated by immunoglobulin E (IgE) response to environmental allergen exposure.[2,3,5] Common symptoms are rhinorrhea, sneezing, and nasal itching and congestion, but ocular symptoms—particularly tearing, redness, and itching of the eyes—also co-occur frequently.[6,7] Although not a fatal disease, allergic rhinitis can pose a significant burden, negatively affecting sleep quality, mental health, work productivity, as well as overall quality of life.[8–10] Following a sharp increase in recent decades, allergic rhinitis is one of the most common noncommunicable diseases globally, both among children and adults.[6,11–13] Given this, a substantial number of studies have investigated potential risk factors for developing allergic rhinitis,[14,15] but the etiology is not yet fully understood, as a large number of interacting factors, such as genetics, epigenetics, lifestyle, and environmental exposures, are at play.[11]

Sibship composition is one of the most studied early-life environmental factors in allergic rhinitis, gaining widespread attention after reports of an inverse association between number of siblings—particularly older siblings—and atopic diseases by Strachan in the late 1980s.[16,17] However, subsequent studies have found conflicting results,[18–23] hampering a clear appreciation of the role of sibship composition in the etiology of allergic rhinitis. Given this important gap, we sought, through a systematic review, to synthesize the global literature on the association of birth order and sibship size (number of siblings) with the risk of allergic rhinitis. Furthermore, by considering the progressive improvement in societal hygiene and changes in lifestyle, we assessed whether these transformations have influenced the hypothesized role of sibship composition in the development of allergic rhinitis. We evaluated this impact by stratifying studies by those published before and after the turn of the millennium, as well as by using the World Bank's classification of countries by income.

Key Message

Results from the 76 studies included in this systematic review and meta-analysis of the global literature indicate that the presence of siblings, particularly older siblings, is associated with a lower risk of ever and current allergic rhinitis. These effects remain stable across age, time period, and geographical regions.

2 | METHODS

We undertook this work following a protocol, which was registered on the International prospective register of systematic reviews (PROSPERO; CRD42020207905) and published[24] prior to undertaking the systematic review. The protocol was composed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[25] The manuscript was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[26] checklist (Table S1) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[27] reporting guidelines (Table S2).

2.1 | Inclusion and exclusion criteria

Studies meeting the following criteria were eligible:

1. Study design: observational studies (cohort studies, case–control studies, and cross-sectional studies)
2. Exposure: defined sibship composition (either birth order or sibship size [number of siblings])
3. Outcome: allergic rhinitis or allergic rhinoconjunctivitis (either self-reported, including symptom-based definitions, or by means of clinical examination or medical records of diagnosis).

There were no restrictions regarding sample size or medical/sociodemographic background of subjects.

2.2 | Data sources and search strategy

We searched AMED, CABI, CINAHL, Embase, Google Scholar, OAIster, Open Access Theses and Dissertations, Open Gray, ProQuest Dissertations & Theses Global, PsycINFO, PubMed, SciELO, Scopus, Web of Science, and WHO Global Index Medicus from inception to the date of search (30th September 2020 and a follow-up search on 20th October 2021). When searching Google Scholar, the first 300 results were screened.[28] Non-English articles were translated using Google Translate.[29] Finally, we hand-searched reference lists in the included articles for additional relevant studies. Details of the search strategy are presented in Table S3.

2.3 | Study selection and data extraction

All records obtained from the databases were exported to EndNote X9 (Clarivate Analytics, 2020), where de-duplication was done following a method suggested by Bramer et al.[30] Two reviewers independently screened the retrieved records and assessed full-texts of reports that potentially met the exclusion criteria. Similarly, data extraction was performed in pairs using an a priori developed and piloted data extraction form. After each step, the decisions were unblinded, and a third reviewer (BIN) arbitrated any differences if needed. From each included report, we extracted: first author; publication year; study design; source of subjects (e.g., from the general population or among pregnant women); number, age, and country of subjects; definition/assessment of exposure and outcome; point estimates; and 95% confidence intervals (CI).

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2.4 | Quality assessment

Pairs of reviewers independently assessed the quality and risk of bias in the individual included reports, using the Effective Public Health Practice Project (EPHPP)[31] tool with modifications based on a systematic review by Smith et al.[32] Six domains (study design, selection bias, confounding, blinding, data collection, and withdrawals/dropouts) were rated as" strong," "moderate," or "weak." The overall rating was based on the number of "weak" domain ratings: "weak" if more than one, "moderate" if one, and "strong" if none of the domains were rated "weak." Ratings were unblinded after completion. Differences were arbitrated by a third reviewer (BIN) if needed.

2.5 | Data synthesis and statistical analysis

Key characteristics of the included studies were summarized in a descriptive table, and overall findings were narratively synthesized. Comparable numerical data—regarding exposure, outcome, and subject characteristics—from ≥2 separate studies[33] were synthesized using random effects meta-analysis with robust variance estimation (RVE).[34] RVE methods provide a means to include dependent estimates—which were common in our data, as most studies tested for multiple cardinalities, for example, sibship sizes, against the same reference group—in a single model.[34] The correlated effects model, small sample correction (for increased accuracy),[35] and the default rho value (defining the within-study effect size correlation) of 0.8 was used in the meta-analyses. The results from the meta-analyses were presented in forest plots. Separate meta-analyses were performed for each type of exposure (birth order and sibship size) in relation to: (a) current allergic rhinitis (in the last year), (b) ever allergic rhinitis, (c) current allergic rhinoconjunctivitis (in the last year), and (d) ever allergic rhinoconjunctivitis. Although allergic rhinitis and allergic rhinoconjunctivitis are closely related and commonly co-occuring,[36] we separated these outcomes, as allergic rhinoconjunctivitis constitutes a more specific condition and an additional organ involvement. For birth order, being first-born was used as the reference group. Similarly, being the only child was used as the reference group for sibship size. In cases of the reference group having a higher cardinality (e.g., sibship size <3 vs. sibship size ≥3), we calculated the reciprocal of the point estimate and the lower and upper bounds of the 95% CI.

We used risk ratio (RR) as the measure of effect, given the intuitive interpretation.[37–39] Data measured as prevalence ratio (PR) were used without conversion, as these are mathematically identical to RR,[37] while odds ratio (OR) and hazard ratio (HR) data were converted to RR estimates in case the outcome was ≥15% (at the end of follow-up) using the following formulae[40]:

$$RR \approx \sqrt{OR}$$

$$RR \approx \frac{1 - 0.5^{\sqrt{HR}}}{1 - 0.5^{\sqrt{\frac{1}{HR}}}}$$

Subgroup analyses were performed in the case of ≥4 comparable studies in ≥2 subgroups,[41] to evaluate the consistency of the associations based on: (a) overall rating; (b) study design; (c) exposure cardinality (e.g., birth order 3); (d) year(s) of data collection, divided into <2000 and ≥2000; (e) classification of country into "high-income," "upper-middle income," "lower-middle income," and "low income" economy, according to the definition by the World Bank at the year the article was published[42]; (f) age of subjects, divided into ≤12 and ≥13 years.[43]

Furthermore, we performed a sensitivity analysis to evaluate the robustness of our findings by re-running the meta-analyses after excluding: (a) studies where the outcome was not confirmed clinically (either by medical records or clinical assessment); (b) studies of "low" overall rating. We also performed sensitivity analysis based on the rho value used in the meta-analyses, re-running the meta-analysis with rho ranging from 0 to 1 with 0.2 increments. The *I*-squared (I^2) statistic was calculated to quantify the amount of heterogeneity between studies,[44] and Tau-squared (τ^2) was calculated to quantify the inter-study variance.[45] Findings from meta-analyses with Satterwhite degrees of freedom (*df*) <4 were considered unreliable.[35]

We assessed publication bias in exposure-outcome pairs with ≥10 studies[46] (a) visually, for signs of asymmetry in funnel plots; (b) with Egger's regression test[47] and Begg and Mazumdar rank correlation test,[48] considering $p < .05$ as statistically significant. Furthermore, we estimated the number of studies needed to normalize asymmetric funnel plots with the trim-and-fill method.[49]

The R scripts and data used in our work can be found at Open Science Framework (https://osf.io/4ks29/). Details regarding utilized R packages can be found in Appendix S1.

3 | RESULTS

Out of 17,466 records identified from the database searches, 8819 remained after de-duplication. These were screened by title and/or abstract, leaving 462 full-text reports that were assessed for eligibility. After full-text assessment, in total, 76 reports based on 66 studies were included in this work (Figure 1).

3.1 | Study characteristics

Forty-nine reports were cross-sectional studies, 26 cohort studies, and one case–control study. Thirty studies were given an overall rating of "strong," 34 "moderate," and 12 "weak" (Figure S1). Studies with a "strong" rating were mostly published in recent years (Figure S2). In total, the data represented >2 million individuals across 70 countries (Figure S3). See Table S4 for characteristics and details about the included reports.

3.2 | Current allergic rhinitis

Current allergic rhinitis was assessed with meta-analysis in 24 studies for birth order and 11 studies for sibship size (Figure 2;

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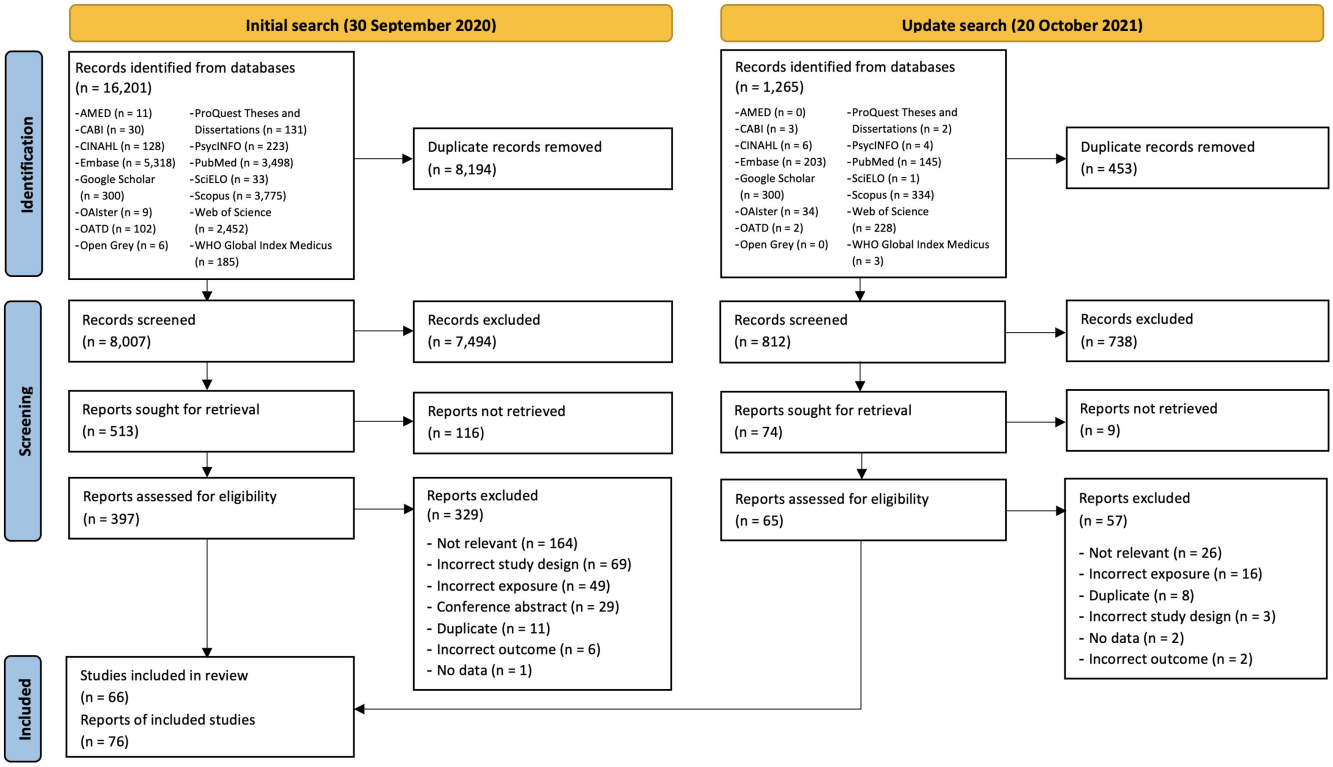

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Figure S4A,B). The pooled effect size indicated that birth order ≥2 versus 1 was associated with 21% lower risk (RR 0.79, 95% CI 0.73–0.86) and sibship size ≥2 versus 1 with 11% lower risk (RR 0.89, 95% CI 0.83–0.95) of current allergic rhinitis. However, the effect was nonsignificant in most subgroup analyses for sibship size, while birth order was associated with a lower risk for both subjects older and younger than 12 years (RR 0.79, 95% CI 0.72–0.87 and RR 0.78, 95% CI 0.66–0.91, respectively), both before and after the turn of the millennium, as well as for all but one cardinality, with possibly a dose-dependent effect (Figure 5). Heterogeneity was high for birth order ($I^2 = 86.1\%$, $\tau^2 = 0.02$) and moderate for sibship size ($I^2 = 73.7\%$, $\tau^2 = 0.01$).

3.3 | Ever allergic rhinitis

Ever allergic rhinitis was assessed with meta-analysis in 13 studies for birth order and 7 studies for sibship size (Figure 3; Figure S5A,B). The pooled effect size indicated that birth order ≥2 versus 1 was associated with 23% lower risk of the outcome (RR 0.77, 95% CI 0.68–0.88). A possibly dose-dependent effect could be discerned in terms of cardinality, with all birth orders indicating protection. However, the association was nonsignificant for subjects aged ≥13 years. The pooled effect size was nonsignificant for sibship size ≥2 versus 1 (RR 0.90, 95% CI 0.78–1.03). Only one subgroup analysis (by cardinality) could be performed for sibship size, in which the associated risk of ever allergic rhinitis was 10% lower for sibship size 3 versus 1 and 4% lower for sibship size 2 versus 1 (Figure 3B). Heterogeneity was high for both birth order ($I^2 = 81.3\%$, $\tau^2 = 0.03$) and sibship size ($I^2 = 92.0\%$, $\tau^2 = 0.02$).

3.4 | Current allergic rhinoconjunctivitis

Current allergic rhinoconjunctivitis was assessed with meta-analysis in 8 studies for birth order and 5 studies for sibship size (Figure 4; Figure S6A,B). The pooled effect size indicated that birth order ≥2 versus 1 was associated with 8% reduced risk of current allergic rhinoconjunctivitis (RR 0.92, 95% CI 0.88–0.98), while sibship size ≥2 versus 1 was borderline significantly associated with a 2% reduced risk of current allergic rhinoconjunctivitis (0.98, 95% CI 0.91–1.05). None of the subgroup analyses demonstrated any significant association. Heterogeneity was moderate for birth order ($I^2 = 67.4\%$, $\tau^2 = 0.01$) and low for sibship size ($I^2 = 17.9\%$, $\tau^2 = 0$).

3.5 | Ever allergic rhinoconjunctivitis

Ever allergic rhinoconjunctivitis was assessed with meta-analysis in 2 studies (Figure 5) for birth order and 1 report[50] for sibship size. The overall pooled effect size indicated that birth order ≥2 versus 1 was associated with 21% lower risk of the outcome (RR 0.79, 95% CI 0.7–0.9). Similarly, the report investigating sibship size as exposure found a protective effect from the presence of siblings.[50]

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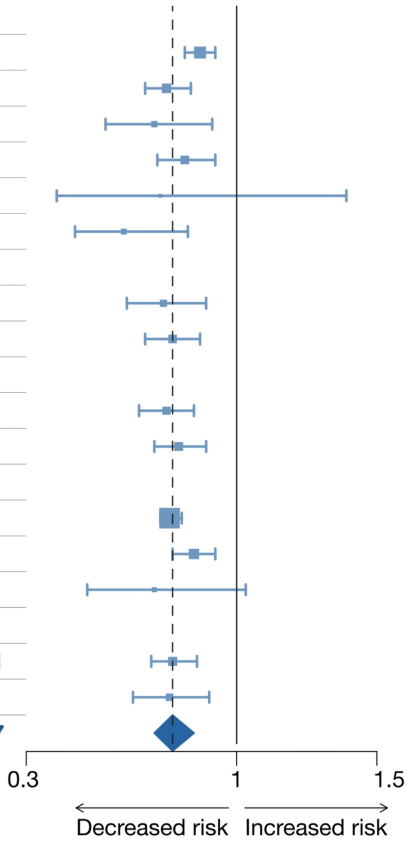
(A) Birth order and current allergic rhinitis

Subgroup	No. of studies	N	RR (95% CI)	I^2	τ^2	df
Birth order						
2	14	191,854	0.88 (0.83-0.93)	69.85	0	8.13
3	9	134,511	0.77 (0.7-0.85)	80.04	0.01	5.91
4	6	114,361	0.73 (0.57-0.92)	89.34	0.03	4.79
≥2	9	43,518	0.83 (0.74-0.93)	88.98	0.01	6.3
≥3	6	13,141	0.75 (0.41-1.36)	88.49	0.18	4.87
≥5	5	92,594	0.63 (0.47-0.84)	87.4	0.04	3.8
Data collected (years)						
< 2000	7	156,192	0.76 (0.64-0.9)	89.79	0.03	5.56
≥ 2000	11	54,159	0.79 (0.7-0.88)	74.8	0.01	7.19
Study design						
Cohort	10	178,360	0.77 (0.68-0.86)	91.15	0.03	7.99
Cross-sectional	14	57,866	0.81 (0.73-0.9)	74.21	0.01	9.18
Quality rating						
Strong	7	34,375	0.78 (0.75-0.82)	10.78	0	1.58
Moderate	10	168,829	0.86 (0.79-0.93)	78.91	0.01	6.55
Weak	7	33,022	0.73 (0.51-1.03)	88.28	0.08	5.52
Age (years)						
≤12	17	64,829	0.79 (0.72-0.87)	73.88	0.01	11.71
≥13	7	161,051	0.78 (0.66-0.91)	93.6	0.03	5.82
Overall	**24**	**292,067**	**0.79 (0.73-0.86)**	**86.09**	**0.02**	**18.27**



(B) Sibship size and current allergic rhinitis

Subgroup	No. of studies	N	RR (95% CI)	I^2	τ^2	df
Sibship size						
2	6	47,610	1 (0.88-1.13)	0	0	1.83
3	5	26,977	0.92 (0.85-1)	15.16	0	2.19
≥2	4	45,842	0.88 (0.81-0.96)	56.07	0	2.75
Quality rating						
Strong	4	45,312	0.9 (0.77-1.04)	67.89	0	2.55
Moderate	7	48,769	0.87 (0.76-0.99)	78.91	0.01	4.77
Age (years)						
≤12	5	28,343	0.81 (0.64-1.03)	81.73	0.01	3.09
≥13	6	47,818	0.93 (0.85-1.02)	60.51	0.01	4.11
Overall	**11**	**133,926**	**0.89 (0.83-0.95)**	**73.7**	**0.01**	**7.87**

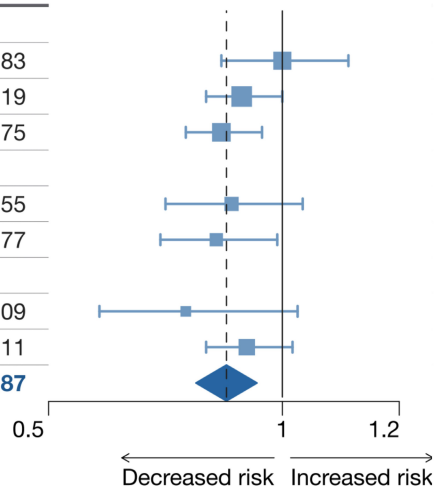


FIGURE 2 Forest plot for birth order ≥2 versus 1 (A) and sibship size ≥2 versus 1 (B) in relation to current (in last year) allergic rhinitis. df, Satterwhite degrees of freedom; I^2, *I*-squared; *N*, number of subjects (if not available, the number of subjects for the most similar exposure-outcome pair or for the whole study is stated); RR (95% CI), risk ratio (95% confidence interval); τ^2, Tau-squared.

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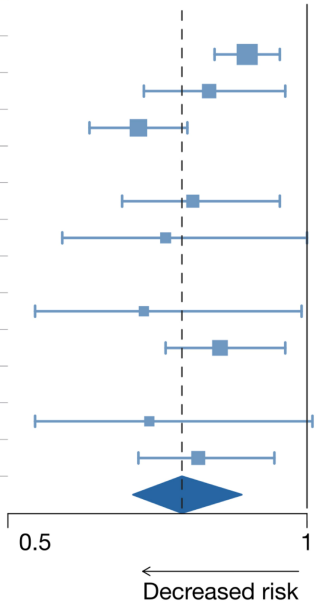
(A) Birth order and ever allergic rhinitis

Subgroup	No. of studies	N	RR (95% CI)	I^2	τ^2	df
Birth order						
2	10	88,668	0.89 (0.83-0.95)	54.46	0	7.08
3	7	53,916	0.82 (0.7-0.96)	72.3	0.01	5.39
≥4	5	39,602	0.69 (0.6-0.78)	47.65	0.01	2.95
Study design						
Cohort	8	49,708	0.79 (0.66-0.95)	74.87	0.03	6.61
Cross-sectional	5	44,818	0.74 (0.55-1)	88.65	0.05	3.69
Quality rating						
Strong	5	11,183	0.7 (0.5-0.99)	76.89	0.05	3.84
Moderate	7	77,062	0.84 (0.74-0.96)	82.1	0.02	5.45
Age (years)						
≤12	5	29,007	0.71 (0.5-1.01)	77.41	0.05	3.81
≥13	8	65,519	0.8 (0.69-0.94)	84.34	0.03	6.54
Overall	**13**	**135,046**	**0.77 (0.68-0.88)**	**81.25**	**0.03**	**11.15**



(B) Sibship size and ever allergic rhinitis

Subgroup	No. of studies	N	RR (95% CI)	I^2	τ^2	df
Sibship size						
2	5	579,291	0.96 (0.88-1.05)	43.34	0	2.39
3	5	571,760	0.9 (0.81-0.99)	31.67	0	2.09
Overall	**7**	**699,896**	**0.9 (0.78-1.03)**	**92.01**	**0.02**	**5.64**

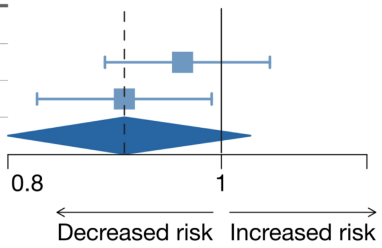


FIGURE 3 Forest plot for birth order ≥2 versus 1 (A) and sibship size ≥2 versus 1 (B) in relation to ever allergic rhinitis. df, Satterwhite degrees of freedom; I^2, *I*-squared; *N*, number of subjects (if not available, the number of subjects for the most similar exposure-outcome pair or for the whole study is stated); RR (95% CI), risk ratio (95% confidence interval). τ^2, Tau-squared.

3.6 | Publication bias and sensitivity analysis

While the *p*-value for Egger's regression test indicated asymmetry for birth order on current allergic rhinitis, sibship size on current allergic rhinitis, and birth order on ever allergic rhinitis, Begg and Mazumdar rank correlation test was nonsignificant for all (Table S6). Modest right-side asymmetry could be discerned for birth order on current allergic rhinitis and sibship size on current allergic rhinitis in funnel plots (Figure S7A,B). Although publication bias cannot be totally excluded, it is unlikely to have affected the results notably, given the overall distribution of results at the center, including many high-precision studies (Figure S8). Sensitivity analysis indicated that the results were robust concerning study quality, with estimates and 95% CIs of pooled effect sizes practically unaffected by the exclusion of "weak"-rated reports. When performing meta-analysis only on studies with clinically assessed outcomes, however, the 95% CIs were substantially wider than those around the overall pooled effect sizes (Table S7). The value of rho did not notably affect the pooled effect size estimates or 95% CIs (Table S8).

4 | DISCUSSION

4.1 | Summary of key findings

This comprehensive synthesis of the global literature identified a significantly decreased risk of allergic rhinitis (both current and ever) in the presence of older siblings. While the number of siblings demonstrated a similar effect, the association was weaker for ever allergic rhinitis. For both birth order and number of siblings, the association was also weaker for allergic rhinoconjunctivitis, although birth order

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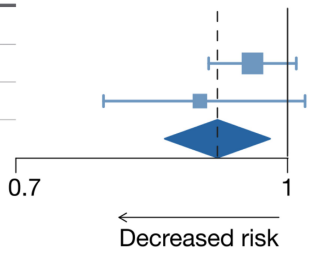
(A) Birth order and current allergic rhinoconjunctivitis

Subgroup	No. of studies	N	RR (95% CI)	I^2	τ^2	df
Birth order						
2	7	52,475	0.96 (0.91-1.01)	37.59	0	5.02
≥3	5	43,783	0.9 (0.79-1.02)	77.86	0.01	3.71
Overall	**8**	**63,059**	**0.92 (0.86-0.98)**	**67.42**	**0.01**	**5.76**



(B) Sibship size and current allergic rhinoconjunctivitis

Subgroup	No. of studies	N	RR (95% CI)	I^2	τ^2	df
Sibship size						
2	5	564,511	1 (0.94-1.07)	0	0	1.24
3	4	561,899	0.97 (0.84-1.11)	0	0	1.1
Overall	**5**	**585,268**	**0.98 (0.91-1.05)**	**17.93**	**0**	**1.76**

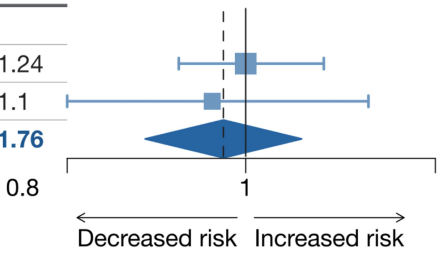


FIGURE 4 Forest plot for birth order ≥2 versus 1 (A) and sibship size ≥2 versus 1 (B) in relation to current (in last year) allergic rhinoconjunctivitis. df, Satterwhite degrees of freedom; I^2, *I*-squared; *N*—number of subjects (if not available, the number of subjects for the most similar exposure-outcome pair or for the whole study is stated); RR (95% CI), risk ratio (95% confidence interval); τ^2, Tau-squared.

Study	N	Outcome	Age/subgroup	Birth order	RR (95% CI)
Pekkanen 1999	5,246	Self-reported (ever)	13-14	≥3	0.74 (0.64-0.85)
Schmitz 2012	16,447	Physician-diagnosed (ever)	0-17	≥2	0.8 (0.71-0.89)
Pekkanen 1999	7,050	Self-reported (ever)	13-14	2	0.83 (0.75-0.93)
Overall	**25,837**				**0.79 (0.7-0.9)**

I^2: 0; τ^2: 0; df: 1

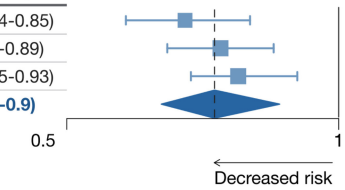


FIGURE 5 Forest plot for birth order ≥2 versus 1 in relation to ever allergic rhinoconjunctivitis. df, Satterwhite degrees of freedom; I^2, *I*-squared; *N*,number of subjects (if not available, the number of subjects for the most similar exposure-outcome pair or for the whole study is stated); RR (95% CI), risk ratio (95% confidence interval); τ^2—Tau-squared.

remained a protective factor. There were not enough studies to assess whether the associations varied between countries of different World Bank economic classification, but the effect appeared to be comparable between studies from before and after the turn of the millennium.

4.2 | Strengths and limitations

The exhaustive search of 15 databases, without restrictions on the definition or assessment method of the outcome, allowed for a comprehensive synthesis of the global literature, as well as assessment of the association by various socio-economic, symptomatic, and diagnostic aspects. Furthermore, the vast amount of data enabled us to perform precise meta-analyses. Although several of the effect estimates were correlated, the use of RVE, a robust approach for undertaking a meta-analysis of correlated effect estimates, enabled us to overcome any issue of multi-collinearity between the effect estimates. However, a number of limitations must also be noted. The breadth of studies was associated with substantial heterogeneity, reducing the number of studies eligible for meta-analysis and the generalizability of findings. This includes insufficient data to assess the association with allergic rhinitis/rhinoconjunctivitis in the presence of allergen-specific IgE (sIgE) or positive skin prick test (SPT). As most studies were undertaken in high-income countries, we were unable to do subgroup analysis by this metric. Similarly, the impact of sex,[51] urbanization,[52] and other factors that have been reported to affect the risk and prevalence of the investigated outcomes could not be stratified in the present study. Although only handful studies were written in languages other than English, the method undertaken in the present study of translation through Google Translate is associated with the risk of mistranslation and misinterpretation.[29] The observational design of the included studies, particularly studies with a cross-sectional design, is limited for causal inference.

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Inadequate collection and adjustment of all potential confounding factors, especially in older studies,[53,54] and given that a substantial number of the studies used self-reported disease as outcome, the clinical validity and precision of outcome assessment may have been suboptimal.[55]

4.3 | Comparison of findings to previous studies

To the best of our knowledge, our work is the first systematic review of the association between birth order and sibship size and risk of allergic rhinitis.

4.4 | Interpretation of findings

Both birth order and sibship size were inversely associated with the risk of allergic rhinitis. However, having older siblings specifically constituted a stronger protection, particularly for lifetime prevalence of disease, and in allergic rhinitis with ocular involvement. There was some indication that the protection increases with the number of (older) siblings, but the higher cardinalities had inadequate number of studies to make a clear assessment. In the light of the "hygiene hypothesis," the association with birth order may be explained by older siblings having more outdoor activities from which they can transmit infections to younger siblings at home.[17,56] Children attending daycare are exposed to similar cross-infection and have also been reported to have a lower risk of allergic rhinitis,[57–59] further indicating that microbial environment during early childhood influences immune development and subsequent risk of allergic diseases. It is also possible, however, that other types of exposures, behaviors, or even immunological in utero interactions associated with specific birth order positions may contribute or be the driving factor(s),[60,61] and to this date, none of the investigated underlying mechanistic factors have emerged as a robust explanation for the effect of sibship composition.[62]

The weaker association of birth order and sibship size with allergic rhinoconjunctivitis may be because of increased recall bias and misinterpretation, given the more specified symptom definition. Another possible explanation is that ocular symptoms, while commonly co-occurring with nasal symptoms, are not affected as much in those sensitized to certain allergens such as house dust mite, for which substantial regional differences in exposure have been reported.[63–65] Regarding the wide 95% CIs in the sensitivity analysis using only clinically confirmed outcomes rendering these associations nonsignificant, the explanation could be that the number of studies with such assessment methods was too low. Although the majority of included studies indicated a protective association with (older) siblings, some studies reported no significant association or increased risk. Statistical power may explain part of the discrepancy. Of 12 studies with <1000 subjects, more than half reported no association or increased risk. Similarly, cases of allergic rhinitis may have been less accurately defined and/or identified in the studies that did not show a decreased risk, as indicated in the meta-analysis on birth order and current allergic rhinitis, for which the 95% CI widened in a linear fashion in studies rated from "strong" to "weak," with the pooled estimate from the "weak" studies indicating a nonsignificant association. Interestingly, sibship composition does not appear to have the same effect on the development of asthma,[66,67] suggesting differing underlying pathophysiological mechanisms.[68]

4.5 | Clinical and research implications

While the findings from this systematic review support the "hygiene hypothesis"—namely that early infectious burden, such as cross-infection between siblings, contribute to changes in the immune system that reduce the risk of allergic diseases[69]—in the context of allergic rhinitis, previous reviews report that results are more mixed for asthma.[17] Thus, our work highlights the heterogeneity and complexity in pathophysiology of these diseases,[70] and can potentially be used as a stepping-stone in elucidating their underlying pathophysiological mechanisms.

5 | CONCLUSION

Our findings indicate that having siblings is associated with a decreased risk of current allergic rhinitis. The association is particularly strong for the presence of older siblings, in both current and lifetime prevalence of allergic rhinitis, as well as allergic rhinoconjunctivitis. The effect of older siblings remained similar between pre- and postpubertal age and has not notably changed since the turn of the millennium. Furthermore, the protection appears to be stronger with a higher number of older siblings.

AUTHOR CONTRIBUTIONS

Daniil Lisik: Conceptualization; investigation; writing – original draft; visualization; validation; methodology; software; formal analysis; project administration; data curation. **Saliha Selin Özuygur Ermis:** Investigation; validation; formal analysis; data curation; project administration. **Athina Ioannidou:** Investigation; data curation. **Gregorio Paolo Milani:** Investigation; data curation. **Sungkutu Nyassi:** Investigation; data curation. **Giulia Carla Immacolata Spolidoro:** Investigation; data curation. **Hannu Kankaanranta:** Supervision; validation. **Emma Goksör:** Supervision; validation. **Göran Wennergren:** Supervision; validation; methodology. **Bright Ibeabughichi Nwaru:** Supervision; conceptualization; validation; investigation; methodology; project administration; data curation.

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CONFLICT OF INTEREST STATEMENT

Hannu Kankaanranta reports personal fees for lectures and consulting from AstraZeneca, Boehringer-Ingelheim, Chiesi Pharma, GSK, MSD, Novartis, Orion Pharma, and Sanofi Genzyme outside the current work. Other authors declare no conflict of interest in relation to this work.

PEER REVIEW

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