International Archives of Allergy and Immunology

Clinical Allergy – Review Article

Int Arch Allergy Immunol 2020;181:422–433
DOI: 10.1159/000506807

Received: February 26, 2020
Accepted: February 26, 2020
Published online: May 12, 2020

Cumulative Evidence for Association of Acetaminophen Exposure and Allergic Rhinitis

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Keywords
Acetaminophen · Allergic rhinitis · Meta-analysis · Risk factors

Abstract
Background: Several studies have linked acetaminophen exposure to the risk of allergic rhinitis, with controversial results. ***Methods:*** A systematic search of PubMed, Embase, Cochrane Library, and Web of Science was conducted up to December 1, 2019. We included observational studies that examined the association between acetaminophen exposure and the risk of allergic rhinitis. Two reviewers independently extracted data and assessed study quality. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random-effects meta-analysis. ***Results:*** Eighteen studies with 870,492 participants were included. Analysis showed that acetaminophen exposure was associated with an increased risk of allergic rhinitis (OR: 1.54, 95% CI: 1.41–1.69). Also, early exposure and exposure in the past year to acetaminophen was positively associated with risk of allergic rhinitis (OR: 1.34, 95% CI: 1.21–1.49 and OR: 1.74, 95% CI: 1.48–2.04, respectively). The risk of allergic rhinitis was greater for people who had acetaminophen exposure once per month over the past year (OR: 1.90, 95% CI: 1.60–2.26) compared to once per year (OR: 1.28, 95% CI: 1.11–1.48). ***Conclusion:*** With our meta-analysis, we provide the evidence that exposure to acetaminophen is associated with an increased risk of allergic rhinitis. In addition, acetaminophen exposure in early life and acetaminophen exposure in the past year are positively associated with the risk of allergic rhinitis. Future research is needed to evaluate whether the association is causal.
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Introduction

Allergic rhinitis is estimated to affect 10–30% of the population in the United States and other industrialized countries [1–5]. It is associated with a huge economic burden, causing a total cost of several billion dollars per year [6–8]. Although genetic factors play an important role in susceptibility to allergic rhinitis [9], environmen-

Edited by: H.-U. Simon, Bern.

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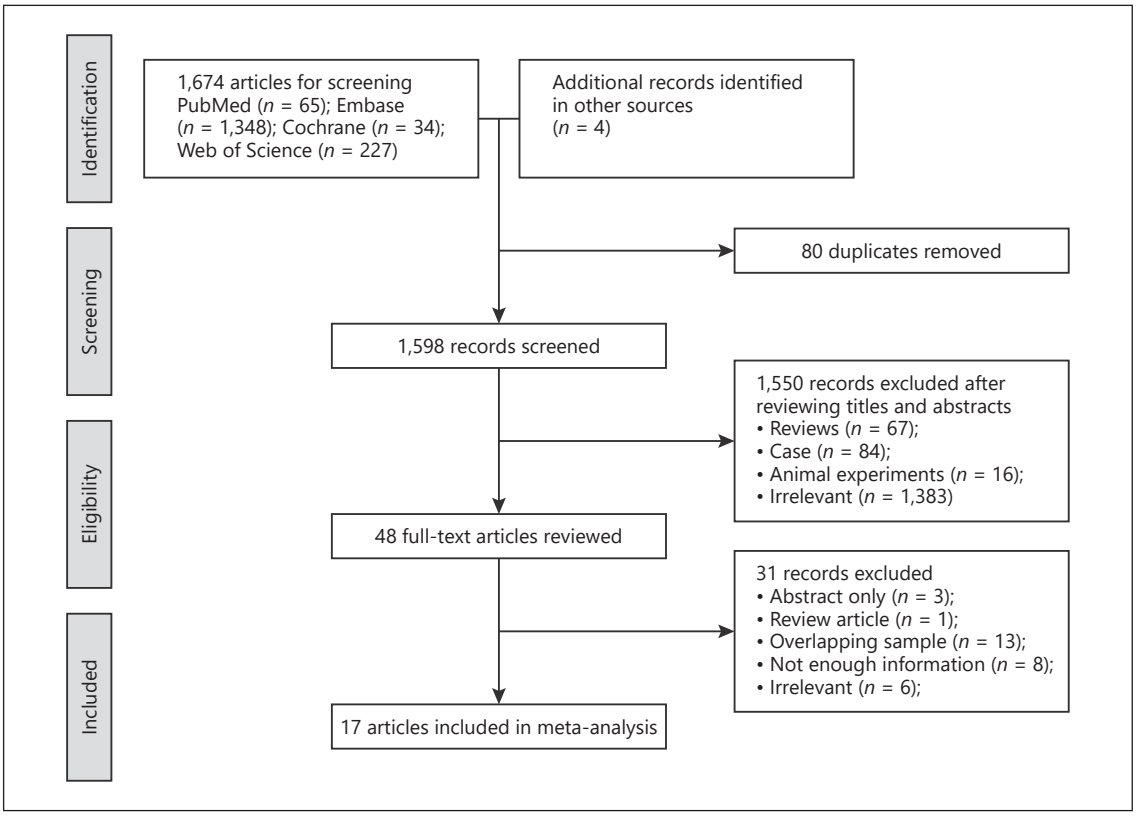

Fig. 1. Flowchart of study inclusion and exclusion process.

tal factors might underlie the increased prevalence [10]. The etiological factors influencing the development of allergic rhinitis remain uncertain.

Acetaminophen, which is generally considered safe, has become the most widely used analgesic antipyretic drug [11]. Recent studies have indicated a possible connection between acetaminophen use and allergic rhinitis. In one study, the increased sales of acetaminophen were associated with the rise in the prevalence of allergic rhinitis in children and adults [12]. In the large, multicenter International Study of Asthma and Allergy in Childhood (ISAAC) phase III, results showed that acetaminophen exposure represents a risk factor for allergic rhinitis in the 6- to 7-year-old and 13- to 14-year-old age groups [13, 14]. Consistent with these findings, several studies found associations between acetaminophen use and risk of allergic rhinitis [15–18]. However, some results are inconsistent [19, 20]. Given the widespread use of acetaminophen and the importance of clarifying the role of its use in the risk of allergic rhinitis, we conducted a meta-analysis with aims to evaluate the association between acetaminophen exposure and risk of allergic rhinitis.

Methods

Search Strategy

We performed this meta-analysis in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [21]. A systematic literature search was conducted in PubMed, Embase, Web of Science, and Cochrane Library databases from inception to December 1, 2019. The following search terms, including Medical Subject Heading terms and free-text terms, were used in search: ("Acetaminophen" OR "Acetominophen" OR "Paracetamol" OR "Hydroxyacetanilide") AND ("Rhinitis, Allergic" OR "Allergic Rhinitis" OR "Allergic Rhinitides" OR "Allergic Rhinosinusitis" OR "Allergic Rhinitis"). The search was limited to English-language studies. In addition, the reference lists and citations of included studies were searched for relevant articles.

Study Selection

Two reviewers (Y. Gao and W. Cao) independently scrutinized the searches. They scanned the titles and abstracts of all articles to exclude irrelevant studies. Full texts of the remaining articles were reviewed to assess which articles met our inclusion criteria. Articles were considered eligible for inclusion in the study when they met the following criteria: (1) cohort, case-control, or cross-sectional studies that examined the association between acetaminophen exposure and allergic rhinitis, (2) odds ratios (ORs), risk estimates, risk ratios, or hazards ratios, and the corresponding 95% confidence in-

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Table 1. Characteristics of the included studies

Author, year	Location	Design	Partici-pants	Age at AR diagnosis, years	Primary outcome	Adjusted confounding factors	NOS	AHRQ
Shaheen et al. [15], 2000	UK	Case-control study	910	16–49	Weekly use ORs = 1.80 (1.11–2.91), daily use ORs = 2.33 (1.09–4.96)	Smoking history, exposure to passive smoke, use of a gas cooker, ethnicity, total individuals living in the household, family history of atopic disease, socioeconomic information, and social class	5	
Cohet et al. [26], 2004	New Zealand	Cross-sectional study	4,123	<4, 6–7	Exposure in the first year ORs = 0.97 (0.68–1.37), exposure in the past year ORs = 1.77 (1.43–2.18)	NA		6
Davey et al. [16], 2005	Ethiopia	Cross-sectional study	7,649	>5	Exposure in the past year ORs = 1.82 (1.50-2.19), ORs = 2.52 (1.99–3.20)	Age, sex, area of residence, presence of any parasite, smoking status, and educational level		7
Beasley et al. [13], 2008	31 countries	Cross-sectional study	205,487	6–7	Exposure in the first year ORs = 1.48 (1.38–1.60), exposure in the past year medium ORs = 1.32 (1.20–1.46), high ORs = 2.81 (2.52–3.14)	Sex, region of the world, language, and gross national income		9
Sultész et al. [27], 2010	Hungary	Cross-sectional study	3,933	6–12	Exposure in the first year ORs = 1.517 (1.293–1.780)	NA		5
Bakkeheim et al. [20], 2010	Norway	Cohort study	1,016	10	Prenatal exposure in the first trimester ORs = 2.42 (1.01–5.79), exposure in the first 6 months ORs = 0.94 (0.51–1.72)	Gender, upper airway infections, and lower airway infections	7	
Lowe et al. [19], 2010	Australia	Cohort study	620	7	Exposure in the first 2 years ORs = 1.17 (0.96–1.43)	Sex, parental history of asthma or eczema, presence of older siblings at the time of birth, and infections	6	
Beasley et al. [14], 2011	50 countries	Cross-sectional study	322,959	13–14	Exposure in the past year medium ORs = 1.34 (1.28–1.40), high ORs = 2.23 (2.13–2.35)	Sex, region of the world, language, and gross national income		9
Muc et al. [17], 2013	Portugal	Cross-sectional study	1,063	6–9	Exposure in the first year ORs = 2.372 (1.682–3.344), exposure in the past year ORs = 5.3 (2.7–10.5)	Age, sex, family history of asthma, rhinitis and prematurity		7
Wang et al. [18], 2013	Taiwan	2 cohort studies	273,530	2–6	1998 study: exposure in the first year ORs = 1.70 (1.63–1.77), ORs = 1.70 (1.64–1.76); 2003 study: exposure in the first year ORs = 1.18 (1.04–1.35), ORs = 1.24 (1.08–1.42)	Gender, enrollee category at birth, geographical area at birth, and healthcare utilization	8	
Amberbir et al. [28], 2014	Ethiopia	Cohort study	1,006	3, 5	ORs = 2.42 (0.72–8.14), ORs = 3.74 (1.27–11.04), ORs = 3.10 (1.00–9.57)	Gender, area of residence, maternal education and respiratory infections in the first year of life	6	
Tamay et al. [29], 2014	Turkey	Cross-sectional study	9,875	6–7	Exposure in the first year ORs = 0.77 (0.60–0.98), exposure in the past year medium ORs = 1.86 (1.55–2.24)	NA		6
Peñaranda et al. [30], 2016	Colombia	Case-control study	5,008	1–17, 18–59	Exposure in the past year ORs = 7.4 (2.9–18.5) (once per week), medium ORs = 5.3 (2.2–12.9), exposure in the past year ORs = 1.9 (1.4–2.4) (once per week), medium ORs = 1.7 (1.3–2.2)	Age, gender, history of atopic eczema in parents or brothers, and health care plan	6	

Table 1 (continued)

Author, year	Location	Design	Partici-pants	Age at AR diagnosis, years	Primary outcome	Adjusted confounding factors	NOS	AHRQ
Fazlollahi et al. [31], 2017	Iran	Cross-sectional study	4,993	6–7	Exposure in the first year ORs =1.40 (1.04–1.89)	NA		5
Sultész et al. [32], 2017	Hungary	Cross-sectional study	3,412	6–12	Exposure in the first year ORs = 1.137 (0.929–1.391)	NA		5
Chinratanapisit et al. [33], 2018	Thailand	Cross-sectional study	6,291	6–7, 13–14	Exposure in the first year ORs = 0.97 (0.76–1.23), exposure in recent year ORs = 1.64 (1.30–2.08)	NA		8
Lipiec et al. [34], 2018	Poland	Cross-sectional study	18,617	6–7, 13–14, 20–44	Exposure in the past year medium ORs = 0.97 (0.82–1.16), high ORs = 1.45 (1.16–1.79), exposure in the past year medium ORs = 1.11 (0.93–1.33), high ORs = 1.58 (1.30–1.92), exposure in the past year medium ORs = 1.03 (0.90–1.33), high ORs = 1.20 (1.05–1.37)	NA		5

AHRQ, Agency for Healthcare Research and Quality; AR, allergic rhinitis; NA, not applicable; NOS, Newcastle-Ottawa scale; OR, odds ratio. Medium exposure in the past year was defined as once or more in the past year. High exposure in the past year was defined as once or more per month in the past year.

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Table 2. Results of meta-analysis, publication bias, and trim-and-fill analysis

Category	Studies, *n*	Effect size	Heterogeneity		Publication bias	Trim-and-fill method	
		OR (95% CI)	I^2, %	*p*	Begg's test (*z*, *p*)	potential missing studies, *n*	filled estimates
Acetaminophen exposure for allergic rhinitis	40	1.54 (1.41–1.69)	94	<0.00001	1.85, 0.064	8	1.41 (1.29–1.56)
Prenatal acetaminophen exposure for allergic rhinitis	1	2.42 (1.01–5.80)	–	–	–	–	–
Acetaminophen exposure in early life for allergic rhinitis	15	1.34 (1.21–1.49)	90	<0.00001	0, 1.00	1	1.33 (1.20–1.48)
Acetaminophen exposure in the past year for allergic rhinitis	20	1.74 (1.48–2.04)	96	<0.00001	1.91, 0.056	0	1.74 (1.49–2.03)

OR, odds ratio.

tervals (CIs) were reported, and (3) data to calculate the effect size was provided. Articles were excluded if they were: (1) reviews, letters, case reports, or animal research, or (2) lacking a comparison group. Any discrepancies between the two reviewers were discussed with a third reviewer (Q. Liu) to achieve a consensus.

Data Extraction

Two reviewers (Y. Gao and W. Cao) independently extracted the following information from the eligible studies: first author, year of publication, location, study design, study size, age of allergic rhinitis diagnosis, adjusted confounding factors, and outcome parameters with corresponding 95% CIs. The acetaminophen exposure was classified into 4 categories: prenatal, early life, the past year, and other. Exposure in early life was defined as acetaminophen exposure during the first year of life. Medium exposure was defined as acetaminophen use once or more in the past year. High exposure was defined as acetaminophen use once or more per month in the past year. We included the largest sample from a single study if there were overlapping data between studies. For adjusted results, we included the data from the most adjusted model. Any disagreement was resolved by a third reviewer (J. Li). The authors were contacted if detailed information we required was not provided.

Quality Assessment

Two investigators assessed the risk of bias (Y. Gao and W. Cao). Discrepancies were resolved in discussion with a third investigator (J. Liu). The methodological quality of cohort and case-control studies was evaluated using the Newcastle-Ottawa scale (NOS) [22]. Each study was classified as low (scores of 0–3), medium (scores of 4–6), or high (scores of 7–9) quality. The methodological quality of cross-sectional studies was evaluated using a checklist recommended by the Agency for Healthcare Research and Quality (AHRQ) [23]. Each study was classified as low (scores of 0–3), medium (scores of 4–7), or high (scores of 8–11) quality.

Statistical Analysis

Statistical analysis was performed using Review Manager software (version 5.3) and Stata software (version 12.0). The ORs were used to assess the association between acetaminophen exposure and the risk of allergic rhinitis. The hazard ratios were considered as ORs. A random effect model was used considering the intertrial heterogeneity. Heterogeneity across studies was assessed using the I^2 index and Q statistic, where I^2 >50% indicated substantial heterogeneity and $p < 0.1$ represented statistical significance [24]. Subgroup analyses were stratified by the age of participants, study design, study quality, location, sample size, and acetaminophen exposure. Sensitivity analysis was performed by removing one study at a time while keeping all other variables constant. Publication bias was evaluated by funnel plot analysis as well as Begg's test. A "trim-and-fill" procedure was conducted to assess the possible effect of publication bias [25].

Results

Search Results

A total of 1,678 references were identified in the initial search. After excluding duplicates and screening the abstracts and titles, we reviewed 48 full-text articles. We excluded 31 articles as they did not meet the inclusion criteria. Finally, 17 articles [13–20, 26–34] were included in the final analysis (Fig. 1).

Study Characteristics

A summary of the included studies is presented in Table 1. The 17 articles [13–20, 26–34], including a total of 870,492 participants, were published from 2000 to 2018. Among the 18 studies included in the 17 articles, 5 were cohort studies [18–20, 28], 2 were case-control studies [15, 30], and 11 were cross-sectional studies [13, 14, 16, 17, 26, 27, 29, 31–34]. Six studies were conducted in Europe [15, 17, 20, 27, 32, 34], 5 studies in Asia [18, 29, 31, 33], 2 studies in Africa [16, 28], 2 studies in Oceania [19, 26], 1 study in South America [30], and 2 were multicountry studies [13, 14]. Of the included studies, 6 were assessed as high quality [13, 14, 18, 20, 33] and 12 as moderate quality [15–17, 19, 26–32, 34].

Results of Meta-Analysis

Acetaminophen exposure was associated with an increased risk of allergic rhinitis (OR: 1.54, 95% CI:1.41–1.69) in 18 studies [13–20, 26–34] with 870,492 total participants (Fig. 2) (Table 2). Substantial heterogeneity was found among the studies ($I^2 = 94\%$; $p < 0.00001$). According to the sensitivity analysis, no single study affected the overall results or heterogeneity (Table 3).

For acetaminophen exposure in early life, the meta-analysis of 15 estimates from 11 studies [13, 17, 18, 20, 26–29, 31–33] (510,796 participants) showed significant associations between acetaminophen exposure and allergic rhinitis (OR: 1.34, 95% CI:1.21–1.49) (Fig. 2; Table 2). Substantial heterogeneity was found across the studies ($I^2 = 90\%$; $p < 0.00001$). In the sensitivity analysis, exclusion of any single study did not significantly affect the overall results or heterogeneity (Table 3).

For acetaminophen exposure in the past year, the meta-analysis of 20 estimates from 9 studies [13, 14, 16, 17, 26, 29, 30, 33, 34] (581,072 participants) showed significant associations between acetaminophen exposure and allergic rhinitis (OR: 1.74, 95% CI: 1.48–2.04) (Fig. 2; Table 2). Substantial heterogeneity was found across the studies ($I^2 = 96\%$; $p < 0.00001$). In the sensitivity analyses, no single study altered the overall results or heterogeneity (Table 3).

Subgroup Analysis

The results of the subgroup analysis are presented in Table 4.

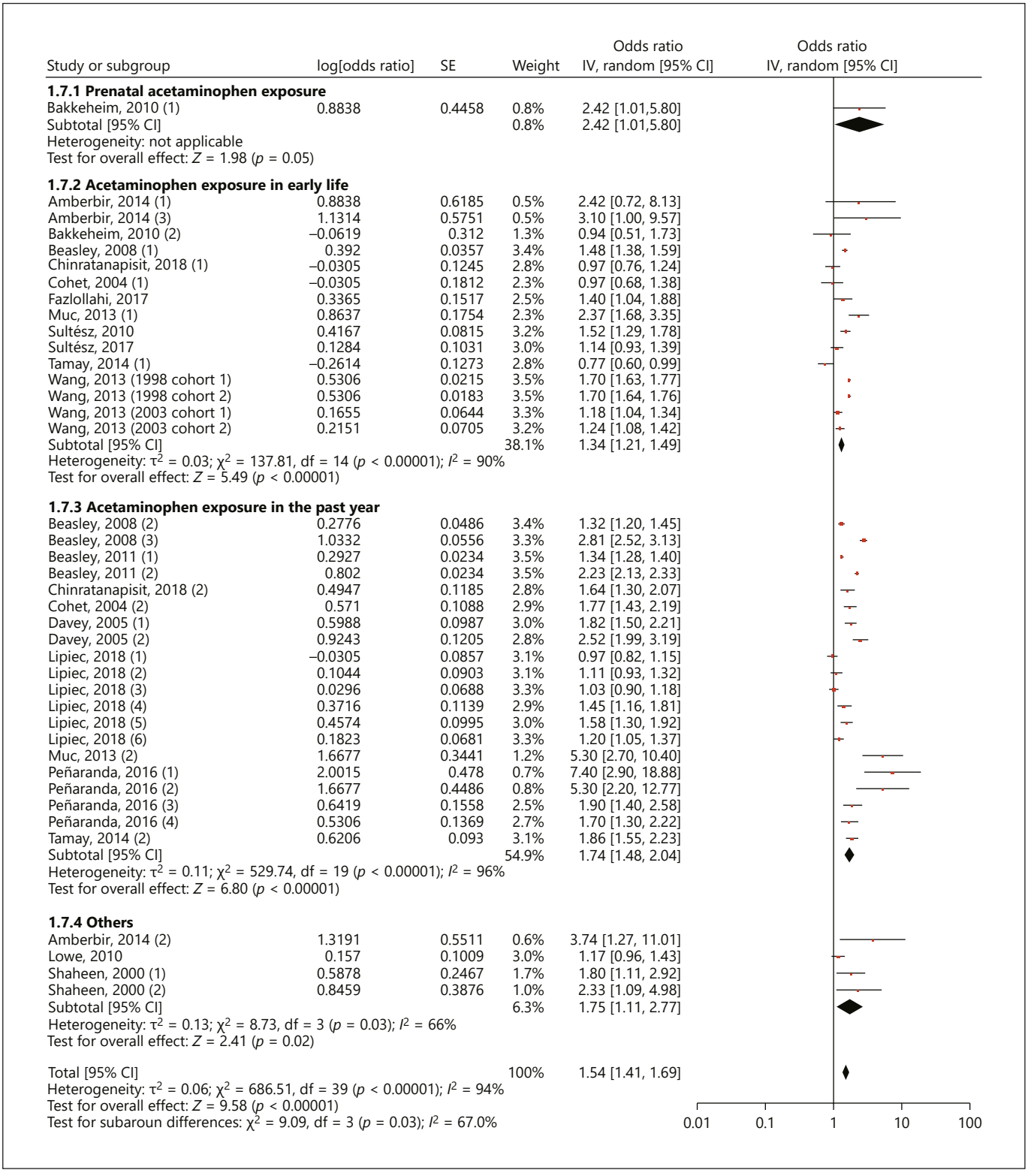

Fig. 2. Forest plot of the association between acetaminophen exposure and allergic rhinitis. CI, confidence interval.

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DOI: 10.1159/000506807

Table 3. Sensitivity analysis of acetaminophen exposure and allergic rhinitis

Study excluded	Acetaminophen exposure in early life for allergic rhinitis			Acetaminophen exposure in the past year for allergic rhinitis			Overall		
	effect size	heterogeneity		effect size	heterogeneity		effect size	heterogeneity	
	OR (95% CI)	I^2, %	p	OR (95% CI)	I^2, %	p	OR (95% CI)	I^2, %	p
Amberbir et al. [28], 2014 (1)	1.33 (1.20–1.48)	91	<0.00001	–	–	–	1.54 (1.41–1.68)	94	<0.00001
Amberbir et al. [28], 2014 (3)	1.33 (1.20–1.48)	90	<0.00001	–	–	–	1.54 (1.41–1.68)	94	<0.00001
Bakkeheim et al. [20], 2010 (2)	1.35 (1.22–1.50)	90	<0.00001	–	–	–	1.55 (1.42–1.70)	94	<0.00001
Beasley et al. [13], 2008 (1)	1.32 (1.17–1.49)	90	<0.00001	–	–	–	1.55 (1.41–1.70)	94	<0.00001
Chinratanapisit et al. [33], 2018 (1)	1.37 (1.24–1.52)	89	<0.00001	–	–	–	1.56 (1.43–1.71)	94	<0.00001
Cohet et al. [26], 2004 (1)	1.36 (1.23–1.51)	90	<0.00001	–	–	–	1.56 (1.43–1.70)	94	<0.00001
Fazlollahi et al. [31], 2017	1.34 (1.20–1.49)	91	<0.00001	–	–	–	1.55 (1.41–1.69)	94	<0.00001
Muc et al. [17], 2013 (1)	1.30 (1.17–1.45)	90	<0.00001	–	–	–	1.53 (1.40–1.67)	94	<0.00001
Sultész et al. [27], 2010	1.32 (1.18–1.48)	91	<0.00001	–	–	–	1.54 (1.41–1.69)	94	<0.00001
Sultész et al. [32], 2017	1.36 (1.22–1.51)	90	<0.00001	–	–	–	1.56 (1.42–1.70)	94	<0.00001
Tamay et al. [29], 2014 (1)	1.40 (1.27–1.54)	88	<0.00001	–	–	–	1.57 (1.44–1.72)	94	<0.00001
Wang et al. [18], 2013 (1998 cohort 1)	1.30 (1.14–1.48)	90	<0.00001	–	–	–	1.55 (1.40–1.71)	94	<0.00001
Wang et al. [18], 2013 (1998 cohort 2)	1.30 (1.14–1.48)	89	<0.00001	–	–	–	1.55 (1.40–1.71)	94	<0.00001
Wang et al. [18], 2013 (2003 cohort 1)	1.36 (1.23–1.51)	89	<0.00001	–	–	–	1.56 (1.42–1.70)	94	<0.00001
Wang et al. [18], 2013 (2003 cohort 2)	1.35 (1.21–1.50)	90	<0.00001	–	–	–	1.55 (1.42–1.70)	94	<0.00001
Beasley et al. [13], 2008 (2)	–	–	–	1.32 (1.20–1.45)	96	<0.00001	1.55 (1.42–1.70)	94	<0.00001
Beasley et al. [13], 2008 (3)	–	–	–	1.68 (1.43–1.96)	96	<0.00001	1.50 (1.38–1.64)	94	<0.00001
Beasley et al. [14], 2011 (1)	–	–	–	1.78 (1.49–2.12)	96	<0.00001	1.55 (1.42–1.70)	94	<0.00001
Beasley et al. [14], 2011 (2)	–	–	–	1.69 (1.46–1.97)	94	<0.00001	1.51 (1.39–1.64)	92	<0.00001
Chinratanapisit et al. [33], 2018 (2)	–	–	–	1.74 (1.48–2.06)	94	<0.00001	1.54 (1.41–1.69)	92	<0.00001
Cohet et al. [26], 2004 (2)	–	–	–	1.74 (1.47–2.05)	97	<0.00001	1.54 (1.40–1.68)	94	<0.00001
Davey et al. [16], 2005 (1)	–	–	–	1.73 (1.47–2.05)	97	<0.00001	1.54 (1.40–1.68)	94	<0.00001
Davey et al. [16], 2005 (2)	–	–	–	1.70 (1.44–2.00)	97	<0.00001	1.52 (1.39–1.66)	94	<0.00001
Lipiec et al. [34], 2018 (1)	–	–	–	1.79 (1.53–2.10)	96	<0.00001	1.56 (1.43–1.71)	94	<0.00001
Lipiec et al. [34], 2018 (2)	–	–	–	1.78 (1.51–2.10)	96	<0.00001	1.56 (1.42–1.70)	94	<0.00001
Lipiec et al. [34], 2018 (3)	–	–	–	1.79 (1.52–2.10)	96	<0.00001	1.56 (1.43–1.71)	94	<0.00001
Lipiec et al. [34], 2018 (4)	–	–	–	1.76 (1.49–2.07)	97	<0.00001	1.55 (1.41–1.69)	94	<0.00001
Lipiec et al. [34], 2018 (5)	–	–	–	1.75 (1.48–2.06)	97	<0.00001	1.54 (1.41–1.69)	94	<0.00001
Lipiec et al. [34], 2018 (6)	–	–	–	1.78 (1.51–2.09)	96	<0.00001	1.56 (1.42–1.70)	94	<0.00001
Muc et al. [17], 2013 (2)	–	–	–	1.68 (1.43–1.97)	97	<0.00001	1.52 (1.39–1.66)	94	<0.00001
Peñaranda et al. [30], 2016 (1)	–	–	–	1.69 (1.44–1.98)	97	<0.00001	1.52 (1.40–1.67)	94	<0.00001
Peñaranda et al. [30], 2016 (2)	–	–	–	1.69 (1.44–1.99)	97	<0.00001	1.53 (1.40–1.67)	94	<0.00001
Peñaranda et al. [30], 2016 (3)	–	–	–	1.73 (1.47–2.04)	97	<0.00001	1.53 (1.40–1.68)	94	<0.00001
Peñaranda et al. [30], 2016 (4)	–	–	–	1.74 (1.48–2.05)	97	<0.00001	1.54 (1.41–1.68)	94	<0.00001
Tamay et al. [29], 2014 (2)	–	–	–	1.73 (1.47–2.04)	97	<0.00001	1.53 (1.40–1.68)	94	<0.00001
Bakkeheim et al. [20], 2010 (1)	–	–	–	–	–	–	1.54 (1.41–1.68)	94	<0.00001
Amberbir et al. [28], 2014 (2)	–	–	–	–	–	–	1.53 (1.40–1.68)	94	<0.00001
Lowe et al. [19], 2010	–	–	–	–	–	–	1.56 (1.42–1.70)	94	<0.00001
Shaheen et al. [15], 2000 (1)	–	–	–	–	–	–	1.54 (1.41–1.68)	94	<0.00001
Shaheen et al. [15], 2000 (2)	–	–	–	–	–	–	1.54 (1.41–1.68)	94	<0.00001

OR, odds ratio.

Table 4. The results of subgroup analysis

Variables	Acetaminophen exposure in early life for allergic rhinitis					Acetaminophen exposure in the past year for allergic rhinitis				
	studies, *n*	effect size	heterogeneity		*p* for the subgroup	studies, *n*	effect size	heterogeneity		*p* for the subgroup
		OR (95% CI)	I^2, %	*p*			OR (95% CI)	I^2, %	*p*	
Total	11	1.34 (1.21–1.49)	90	<0.00001		9	1.74 (1.48–2.04)	96	<0.00001	
Age of study participants										
<18 years	–	–	–	–	–	7	1.79 (1.51–2.13)	97	<0.00001	0.19
>18 years	–	–	–	–		2	1.42 (1.06–1.92)	87	<0.0001	
Study design										
Cohort	3	1.46 (1.29–1.65)	89	<0.00001	0.19	0	NA	NA	NA	0.06
Case-control	0	NA	NA	NA		1	2.73 (1.65–4.53)	78	0.003	
Cross-sectional	8	1.25 (1.04–1.52)	86	<0.00001		8	1.63 (1.37–1.93)	97	<0.00001	
Study quality										
Moderate	7	1.35 (1.03–1.76)	83	<0.00001	0.86	6	1.71 (1.42–2.05)	90	<0.00001	0.80
High	4	1.39 (1.24–1.55)	92	<0.00001		3	1.79 (1.32–2.42)	99	<0.00001	
Location										
Single country	10	1.32 (1.17–1.49)	90	<0.00001	0.1	7	1.70 (1.43–2.01)	89	<0.00001	0.71
Multiple countries	1	1.48 (1.38–1.59)	NA	NA		2	1.82 (1.29–2.57)	99	<0.00001	
Sample size										
<10,000	9	1.26 (1.00–1.58)	80	<0.00001	0.22	6	2.10 (1.77–2.50)	70	0.0004	0.006
≥10,000	2	1.47 (1.32–1.63)	93	<0.00001		3	1.43 (1.14–1.78)	98	<0.00001	
Acetaminophen exposure at different frequency										
Once per year	–	–	–	–	–	5	1.28 (1.11–1.48)	88	<0.00001	0.001
Once per month	–	–	–	–		7	1.90 (1.60–2.26)	93	<0.00001	
Other	–	–	–	–		2	3.48 (0.93–13.08)	86	0.007	
Adjustment factors										
Adjusted	6	1.45 (1.30–1.62)	89	<0.00001	0.08	6	2.14 (1.73–2.65)	97	<0.00001	0.0006
Unadjusted	5	1.14 (0.88–1.47)	83	<0.00001		3	1.32 (1.12–1.57)	87	<0.00001	
Adjusted for gender										
Yes	4	1.53 (1.38–1.70)	89	<0.00001	0.005	5	2.21 (1.76–2.77)	97	<0.00001	0.0006
No	7	1.09 (0.89–1.35)	77	0.0002		4	1.35 (1.15–1.59)	86	<0.00001	
Adjusted for respiratory tract infection										
Yes	3	1.46 (1.29–1.65)	89	<0.00001	0.19	0	NA	NA	NA	NA
No	8	1.25 (1.04–1.52)	86	<0.00001		9	1.74 (1.48–2.04)	96	<0.00001	

NA, not available; OR, odds ratio.

Acetaminophen Exposure in Early Life

Three cohort studies [18, 20, 28] resulted in a pooled OR of 1.46 (1.29–1.65), whereas 8 cross-sectional studies [13, 17, 26, 27, 29, 31–33] had a pooled OR of 1.25 (1.04–1.52) ($\chi^2 = 1.74$; $p = 0.19$; $I^2 = 42.4\%$). Four high-quality studies [13, 18, 20, 33] had a pooled OR of 1.39 (1.24–1.55), whereas 7 moderate-quality studies [17, 26–29, 31, 32] had a pooled OR of 1.35 (1.03–1.76) ($\chi^2 = 0.03$; $p = 0.86$; $I^2 = 0$). The test for subgroup differences by adjustment for respiratory tract infection showed no significant differences ($\chi^2 = 1.74$; $p = 0.19$; $I^2 = 42.4\%$). The 3 studies (7 estimates) [18, 20, 28] adjusted for respiratory tract infection had a pooled OR of 1.46 (1.29–1.65), whereas 8 studies [13, 17, 26, 27, 29, 31–33] unadjusted for respiratory tract infection had a pooled OR of 1.25 (1.04–1.52). The test for subgroup differences with adjustment for confounding factors showed no significant differences ($\chi^2 = 2.97$; $p = 0.08$; $I^2 = 66.3\%$). Six studies (10 estimates) [13, 17, 18, 20, 28, 33] adjusted for confounding factors had a pooled OR of 1.45 (1.30–1.62), whereas 5 studies [26, 27, 29, 31, 32] unadjusted for confounding factors resulted in a pooled OR of 1.14 (0.88–1.47). The test for subgroup differences by adjustment for gender indicated a significant difference ($\chi^2 = 7.99$; $p = 0.005$; $I^2 = 87.5\%$). Four studies (8 estimates) [13, 17, 18, 28] adjusted for gender resulted in a pooled OR of 1.53 (1.38–1.70), whereas 7 studies [20, 26, 27, 29, 31–33] unadjusted for gender resulted in a pooled OR of 1.09 (0.89–1.35).

Acetaminophen Exposure in the Past Year

The test for subgroup differences by exposure frequency indicated a significant difference between once per month and once per year ($\chi^2 = 13.53$; $p = 0.001$; $I^2 = 85.2\%$). People who were exposed to acetaminophen once per month in the past year [13, 14, 16, 26, 29, 30, 34] (OR: 1.90, 95% CI: 1.60–2.26) had a greater risk for allergic rhinitis compared with those who were exposed once per year [13, 14, 17, 33, 34] (OR: 1.28, 95% CI: 1.11–1.48).

One case-control study [30] resulted in a pooled OR of 2.73 (1.65–4.53), whereas 8 cross-sectional studies [13, 14, 16, 17, 26, 29, 33, 34] had a pooled OR of 1.63 (1.37–1.93) ($\chi^2 = 3.61$; $p = 0.06$; $I^2 = 72.3\%$). Three high-quality studies [13, 14, 33] had a pooled OR of 1.79 (1.32–2.42), whereas 6 moderate-quality studies [16, 17, 26, 29, 30, 34] resulted in a pooled OR of 1.71 (1.42–2.05) ($\chi^2 = 0.07$; $p = 0.80$; $I^2 = 0$). The test for subgroup differences with adjustment for confounding factors showed significant differences ($\chi^2 = 11.92$; $p = 0.0006$; $I^2 = 91.6\%$). Six studies (12 estimates) [13, 14, 16, 17, 30, 33] adjusted for confounding factors had a pooled OR of 2.14 (1.73–2.65), whereas 3 studies (8 estimates) [26, 29, 34] unadjusted for confounding factors had a pooled OR of 1.32 (1.12–1.57). The test for subgroup differences by adjustment for gender showed significant differences ($\chi^2 = 11.86$; $p = 0.0006$; $I^2 = 91.6\%$). Five studies (11 estimates) [13, 14, 16, 17, 30] adjusted for gender had a pooled OR of 2.21 (1.76–2.77), whereas 4 studies (9 estimates) [26, 29, 33, 34] unadjusted for gender had a pooled OR of 1.35 (1.15–1.59). The test for subgroup differences between participants below 18 years old [13, 14, 16, 17, 26, 29, 33] (OR: 1.79, 95% CI: 1.49–2.16) and participants above 18 years old [30, 34] (OR: 1.53, 95% CI: 1.23–1.91) showed no significant differences ($\chi^2 = 1.74$; $p = 0.19$; $I^2 = 42.5\%$).

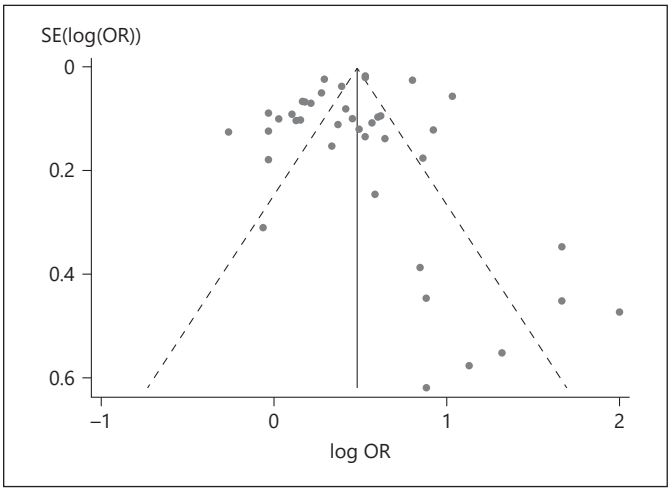

Fig. 3. Funnel plot of the association between acetaminophen exposure and allergic rhinitis. OR, odds ratio; SE, standard error.

Publication Bias

Results of the publication bias and trim-and-fill analysis are shown in Table 2. Visual inspection of the funnel plot showed a potential publication bias (Fig. 3; online suppl. eFig. 1, and 2; for all online supplementary material, see www.karger.com/doi/10.1159/000506807), although the result of the Begg's test showed no statistical significance (Table 3). We conducted the "trim-and-fill" analysis to estimate the number of missing studies that may have led to funnel plot asymmetry. As a result, one study on total acetaminophen exposure and 8 studies on acetaminophen exposure in early life, all with negative results, were found to be missing (Table 2). However, analysis with missing-value estimates did not produce different results (total acetaminophen exposure: OR 1.41 [95% CI: 1.29–1.56]; acetaminophen exposure in early life: OR 1.33 [95% CI: 1.20–1.48]).

Discussion

In this meta-analysis based on 18 observational studies [13–20, 26–34] with 870,492 participants, we systematically evaluated the association between acetaminophen exposure and the risk of allergic rhinitis. The results reveal that acetaminophen exposure is associated with an increased risk of allergic rhinitis. In addition, acetaminophen exposure in early life is positively associated with the risk of allergic rhinitis, and individuals exposed to acetaminophen in the past year tend to have a higher risk of allergic rhinitis. Importantly, our results also show that there may be an exposure-dependent association between acetaminophen exposure in the past year and the risk of allergic rhinitis.

The current findings are biologically plausible. First, acetaminophen has been shown to reduce the levels of glutathione, an antioxidant present in the lung and respiratory mucosae [35, 36]. The depletion of glutathione may increase the T-helper cell type 2 (TH2)-mediated immunological response found in allergic disorders [37]. Second, acetaminophen may influence cyclooxygenase-2 activity and promote prostaglandin E2 synthesis and in turn, the TH2 response [38]. In addition, it has been demonstrated that chronic exposure to acetaminophen increases the mast cell infiltration of nasal mucosa in rat models [39].

Some potential confounding factors also need to be considered. For example, findings might be affected by respiratory infections, recall bias, and gender. Epidemiological studies have found an association between respiratory tract infection and risk of allergic rhinitis [40, 41]. Acetaminophen exposure for such episodes could cause confounding. Lowe et al. [19] reported that the association between acetaminophen use in the first 2 years of life and risk of allergic rhinitis vanished after adjustment for respiratory tract infections. However, a cohort study [18] of 263,620 children found acetaminophen use in early life was associated with an increased risk of allergic rhinitis in a group without respiratory infections. In our subgroup analysis, results showed a significant association between acetaminophen exposure in early life and the risk of allergic rhinitis after adjustment for respiratory tract infection. Therefore, early acetaminophen exposure might be a risk factor for allergic rhinitis.

Self-reports of acetaminophen use may be affected by recall bias. These limitations are addressed by prospective cohort study designs, which reduces recall bias. In our subgroup analysis, the findings from the prospective cohort studies subgroup indicated a significant association between acetaminophen exposure in early life and the risk of allergic rhinitis. Gender may also affect the risk of allergic rhinitis [42, 43]. In our subgroup analysis, the association between acetaminophen exposure and allergic rhinitis was even stronger when adjusted for gender.

Several factors suggest that there is a positive association between acetaminophen exposure and allergic rhinitis. First, our study showed an exposure-dependent association between acetaminophen exposure in the past year and the risk of allergic rhinitis. Second, acetaminophen exposure in early life and acetaminophen exposure later in childhood were associated with an increased risk of allergic rhinitis. Third, according to subgroup analysis, there was a consistent association between acetaminophen exposure and allergic rhinitis in groups of participants below 18 years old and above 18 years old. Finally, per capita acetaminophen sales have been positively associated with the prevalence of allergic rhinitis in children and adults [12].

Our study has several strengths. First, this meta-analysis evaluated the association between acetaminophen exposure and allergic rhinitis using the recommended guidelines to ensure rigor. Second, our analysis included 870,492 participants from 18 studies. The study was multinational with a wide range of geographical representation. Third, by using the frequency of acetaminophen exposure as a categorical variable, we found an exposure-dependent association with the risk of allergic rhinitis. Fourth, the pooled risk remained consistent in the sensitivity analysis, suggesting that the results were stable.

The limitations of our study also need to be considered. First, some diagnosis of allergic rhinitis was based on parental questionnaires without objective clinical examinations. Second, self-report of acetaminophen use may be subject to recall bias. Third, the substantial heterogeneity indicates that methodological diversity existed among the included studies. Finally, the residual confounding factors without being fully adjusted may confuse the results. However, the associations were still significant when controlled for confounding factors in subgroup analysis.

In this meta-analysis, we evaluated the relationship between acetaminophen exposure and allergic rhinitis. There was only one study that focused on the relationship between maternal acetaminophen exposure and allergic rhinitis in offspring, which limited our ability to analyze this subgroup. More high-quality research is needed in this area. In addition, there were no studies that assessed the association between acetaminophen exposure and

objective atopy measurements, such as allergen-specific immunoglobulin E levels or skin prick testing. Finally, causality cannot be established based on the present results. Further studies, in which confounders are fully adjusted and objective biological assessment, are needed to explore the exact relationship between acetaminophen exposure and allergic rhinitis to establish whether the association is causal.

Conclusions

This study provides evidence that exposure to acetaminophen is associated with an increased risk of allergic rhinitis. In addition, acetaminophen exposure in early life and acetaminophen exposure in the past year are positively associated with the risk of allergic rhinitis. Future research is needed to evaluate whether the association is causal.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This work was supported by the Science and Technology Project of the Health Planning Committee of Sichuan (17PJ066), the Grants from the Project of Sichuan Medical Association (2018SHD4-4), the Grants from the Youth Innovation Project of Sichuan Medical Research (Q16029), the Grants from Science and Technology Bureau of Deyang City (2015SZ063).

Author Contributions

Drs Song and Zeng conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Drs Gao, Cao, and Qianfang Liu designed the data collection form, collected data, and carried out the initial analyses. Drs Li and Jian Liu coordinated and supervised data collection. All authors reviewed the final manuscript as submitted and agree to be accountable for all aspects of the work.

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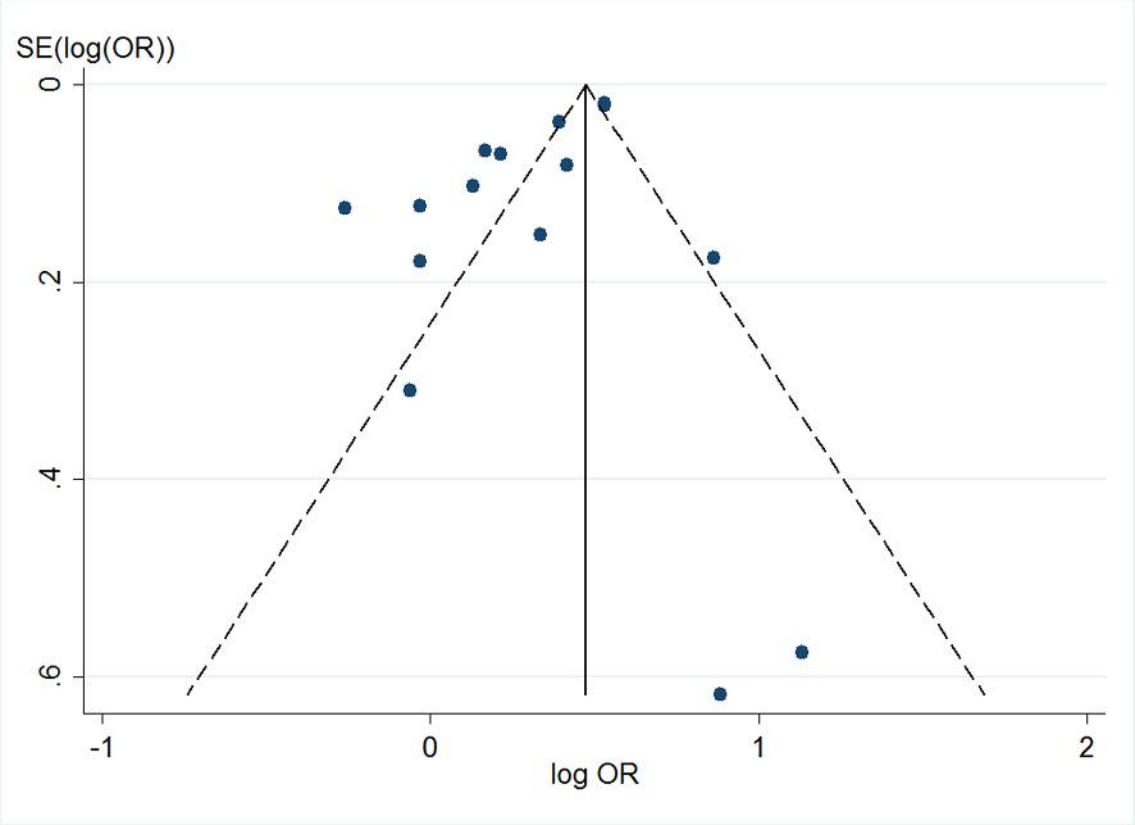
eFigure 1. Funnel plot-acetaminophen exposure in early life and the risk of allergic rhinitis. OR, odds ratio; SE, standard error.

eFigure 2. Funnel plot-acetaminophen exposure in the last year and the risk of allergic rhinitis. OR, odds ratio; SE, standard error.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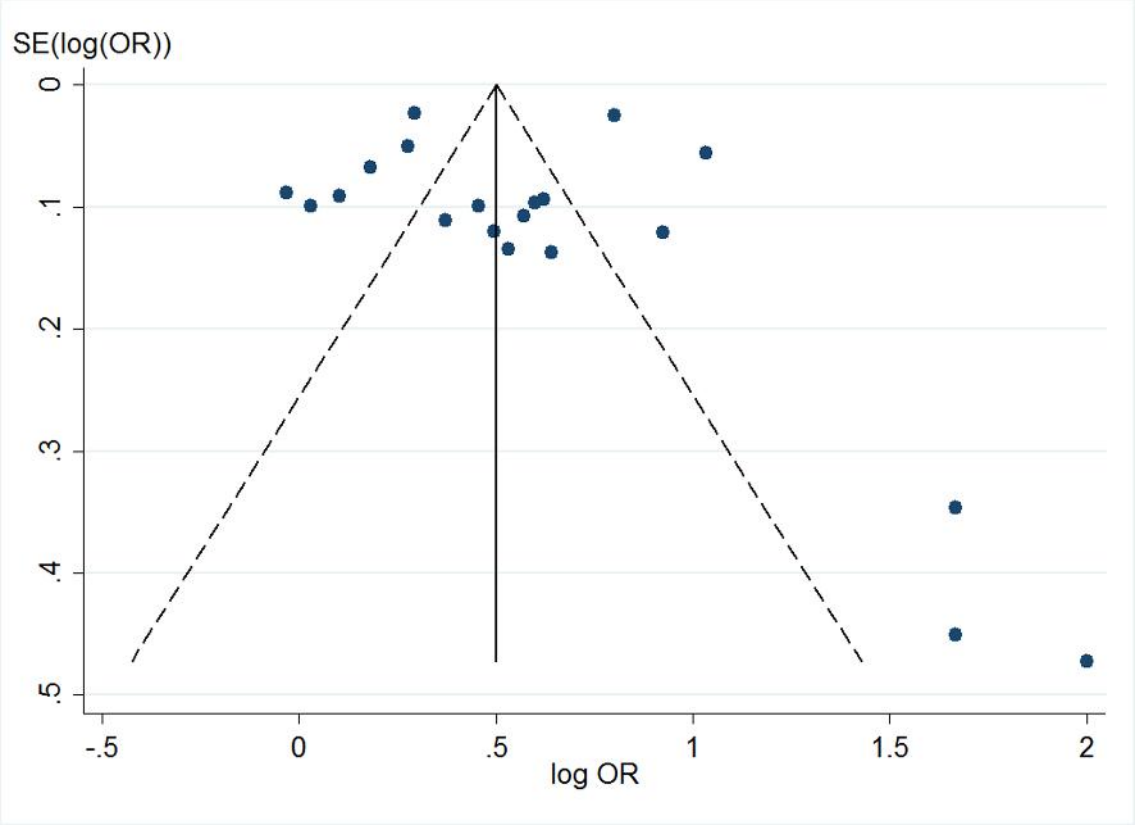
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