Research Article

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Meta-analysis of early-life antibiotic use and allergic rhinitis

Abstract: This meta-analysis aimed to investigate the correlation between early-life antibiotic use and allergic rhinitis. PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases were searched for available studies. Eighteen studies covering 1,768,874 children were included. Early-life antibiotics were associated with an increased incidence of allergic rhinitis (effect size (ES) = 5.00, 95% confidence interval [CI]: 4.88–5.13; $I^2 = 95.7\%$, $P_{\text{heterogeneity}} < 0.001$). In Asia, Europe, and the USA, the incidence of allergic rhinitis in the antibiotic group was higher than that in the no medication group (Asia: $ES = 3.68$, 95% CI: 3.38–4.01; Europe: $ES = 3.20$, 95% CI: 3.00–3.42; USA: $ES = 3.68$, 95% CI: 2.74–4.95). Compared with the no medication group, children who received antibiotics in the first 1 week of life ($ES = 5.75$, 95% CI: 2.18–15.18), first 1 year of life ($ES = 3.37$, 95% CI: 3.20–3.55; $I^2 = 64.2\%$, $P_{\text{heterogeneity}} = 0.001$), or first 3 years of life ($ES = 5.21$, 95% CI: 2.42–11.19) had a higher incidence of allergic rhinitis. No individual study influenced the estimates of the meta-analysis. The funnel plot showed moderate symmetry and low publication bias. In conclusion, the use of antibiotics in early life was associated with allergic rhinitis. Still, most included studies analyzed antibiotic exposure as a dichotomous variable, without information on the type and dosage of antibiotics.

Keywords: antibiotics, allergic rhinitis, early life, meta-analysis

1 Introduction

Antibiotics can prevent and cure many infectious diseases, but their irrational use will lead to the emergence of drug-resistant bacteria, aggravation of infection, damage to the whole body, and severe harm to human health [1–3]. Children’s central nervous and cardiovascular systems are immature and sensitive to drugs. Therefore, the unreasonable use of antibiotics will cause more severe damage to children than to adults [4,5]. The use of antibiotics will change the intestinal flora, imbalance the intestinal flora in early life, cause a lack of stimulation of normal beneficial intestinal flora and affect the development of immune function in early life, which might be closely related to the occurrence and development of allergic diseases [6,7].

Allergic diseases, such as asthma, atopic dermatitis, and allergic rhinitis, are common worldwide, imposing a huge economic burden on society with respect to healthcare costs [2]. Therefore, preventing the occurrence and development of allergic diseases in children is essential. Allergic rhinitis is an allergic disease occurring in nasal mucosa with main clinical manifestations as sneezing, itching, and stuffy nose [8,9]. Some patients have itching...
eyes and pharynx [8,9]. Presently, about 600 million individuals worldwide suffer from allergic rhinitis, and the incidence is increasing annually [8–10]. Several studies analyzed the correlation between antibiotics and allergic rhinitis in early life. An early study by Celedon et al. [11] demonstrated a correlation between antibiotics and allergic rhinitis in early life. On the other hand, Fsadni et al. [6] reported a limited association between antibiotics and allergic rhinitis in early life. Therefore, a meta-analysis was performed to evaluate the association between antibiotics and allergic rhinitis in early life.

2 Methods

2.1 Databases and search strategies

PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases were searched for available papers published up to June 2021. Two independent investigators carried out the initial search, deleted the duplicate records, screened the titles and abstracts for relevance, and identified the publications to be excluded or required further assessment. Next, the investigators reviewed the full-text articles for inclusion. In addition, the references of the retrieved articles and previous reviews were manually checked to identify additional eligible studies. The keywords were anti-bacterial agents AND (rhinitis, allergic, OR rhinitis, allergic, seasonal) AND cohort (Table A1). These keywords were used in all possible combinations to retrieve the maximum number of articles. Any discrepancy or disagreement in the study selection process was solved through discussion until a consensus was reached.

This study is a meta-analysis; the data in the article are from published articles, so ethical approval was waived, and informed consent was not applicable.

2.2 Inclusion and exclusion criteria

Studies were included if:
(a) They were considered cohort studies or cross-sectional studies.
(b) They compared antibiotics vs no medications.
(c) They involved patients with allergic rhinitis.

Studies were excluded if:
(a) They were case reports, meta-analyses, or letters to the editors.
(b) No comparisons were made between antibiotics and no medications.
(c) Patients had other diseases.
(d) There were duplicates.

2.3 Data extraction and review

After selection, two authors analyzed the studies, which data were extracted for the following information: article identification (author, year, study location, and study design), sample characteristics (number of patients in each study and age), the diagnosis of AR, timing of antibiotic exposure, and influencing factors. Any disagreement was discussed, and a third reviewer was consulted when necessary.

The methodological quality of the cohort and cross-sectional studies was evaluated using the Newcastle–Ottawa Scale (NOS) [12]. The quality score of the studies was calculated, with a maximum score of nine points for cohort studies and seven points for cross-sectional studies. This study adheres to the Equator guidelines [13].

2.4 Statistical analysis

STATA SE 14.0 (StataCorp, College Station, TX, USA) was used to calculate the odds ratios (ORs) with 95% confidence intervals (CIs). The significance and the extent of statistical heterogeneity were calculated using the Q-test and I² index, respectively. The random-effects model was applied if the P-value for the test of heterogeneity was <0.10. ORs were calculated for each analysis with the corresponding 95% CIs. Funnel plots were used to detect the possibility of publication bias by evaluating the asymmetry [14]. In addition, a sensitivity analysis was performed to identify individual study effects on pooled results and test the reliability of the results [14].

3 Results

3.1 Search results

The electronic search retrieved 401 articles; 353 reports were removed before screening (Figure 1). Forty-eight reports were screened, retrieved, and assessed for eligibility. Thirty were excluded because of the outcome (n = 27) and no data available (n = 3). Finally, 18 studies fulfilled the inclusion criteria.
3.2 Main features of the studies

Table 1 summarizes the type of study reported and the total number of patients associated with each group. There were nine cohort studies \([1,15–22]\) and nine cross-sectional studies \([23–31]\) for a total of 1,768,874 children.

3.3 Quality assessment

The quality assessment of the included studies is presented in Figure 2. Among the cohort studies, three scored seven points, one scored eight points, and five scored nine points. Among the cross-sectional studies, three scored six points, and six scored seven points (Table 2).

3.4 Results of the meta-analysis

3.4.1 Meta-analysis of the incidence of allergic rhinitis

Fifteen studies entered the meta-analysis of the incidence of allergic rhinitis. Early-life antibiotics were associated with an increased incidence of allergic rhinitis in children (effect size (ES) = 5.00, 95% CI: 4.88–5.13; \(I^2 = 95.7\%\), \(P_{heterogeneity} < 0.001\) (Figure 2). The incidence of allergic rhinitis in the antibiotic group was higher than that of the no medication group.
| Author, year | Design          | Country | Source of subjects | The diagnosis of AR | Sample size | Age (years) | Male (%) | Timing antibiotic exposure | Influencing factor                                                                                                                                 |
|-------------|----------------|---------|--------------------|---------------------|-------------|-------------|----------|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------ |
| Ortqvist et al., 2014 [1] | Prospective cohort | Sweden | Population | Questionnaire | 4,033 | 8 | 61.10 | In the first week of life | Maternal age, paternal education, rural residence first year, living on a farm with animals at preschool age, daily outdoor time, family history of allergic disease, exposure to cat and dog first year, frequent consumption of fish and fermented food, allergic disease first year, maternal medication during pregnancy, neonatal antibiotics, large for gestational age, pacifier, and sex |
| Aversa et al., 2021 [15] | Retrospective cohort | USA | Population | ICD-9/10 | 14,572 | / | 51.78 | In the first 2 years of life | Male sex, birth weight, ethnicity, and cesarean section, age, education, smoking, and antibiotic use during pregnancy |
| Celedón et al., 2002 [16] | Prospective cohort | USA | Population | Questionnaire | 498 | / | 53.80 | In the first 1 year of life | Sex, household income, and history of hay fever (ever) in either parent |
| Harris et al., 2007 [17] | Prospective cohort | UK | Population | Standard questions (ISAAC) | 641 | 8 | 53.35 | In the first 5 years of life | Maternal atopy, paternal atopy, birth order, and current exposure to cigarette smoke |
| Ho and Wu, 2021 [23] | Cross-sectional | China | Population | Questionnaire (modified ISAAC) | 23,630 | 6–8 | 51.80 | In the first 1 year of life | Sex, bronchiolitis before the age of two, older siblings, diagnosed asthma, diagnosed eczema |
| Kim et al., 2018 [24] | Cross-sectional | Korea | Population | ICD-10 | 1,541,869 | <10, 81.28% | 51.30 | / | Basic, age and sex, inpatient and outpatient days, income, and place of residence |
| Mai et al., 2010 [18] | Prospective cohort | Sweden | Population | BAMSE questionnaire | 4,089 | 4–8 | / | In the first 1 year of life | Sex, young maternal age, older sibling, maternal smoking, parental allergy, and exclusive breast-feeding |
| Metzler et al., 2019 [19] | Prospective cohort | European | Population | Questionnaire | 1,019 | 6 | 51.03 | In the first 1 year of life | Farmer, center, parental atopic status, gender, smoking during pregnancy, number of siblings, pets (dogs and cats) during pregnancy, cesarean section, maternal education |
| Mitre et al., 2018 [20] | Retrospective cohort | USA | Population | ICD-9-CM | 131,708 | / | 53.90 | In the first 0.5 years of life | Prematurity, cesarean delivery, sex, the other drug classes, and any significant first-order interaction terms |
| Ni et al., 2019 [21] | Retrospective cohort | USA | Population | ICD-9/10 | 2,398 | 5.7 | 51.00 | In the first 1 year of life, lifetime | Race/ethnicity, age, sex, delivery method, prematurity, birth weight, NICU admission status, and socioeconomic status |

(Continued)
| Author, year | Design          | Country      | Source of subjects | The diagnosis of AR | Sample size       | Age (years)         | Male (%) | Timing antibiotic exposure | Influencing factor                                                                                                                                                                                                 |
|-------------|-----------------|--------------|--------------------|---------------------|-------------------|-------------------|----------|-----------------------------|--------------------------------------------------------------------------------------------------------|
| Penaranda et al. [25] | Cross-sectional | Colombia     | Population         | Self-reported       | 7,085             | 6–7, 3,256/13–14,3829 | 45.70    | In the first 1 year of life | Asthma symptoms in the last 12 months, atopic dermatitis symptoms in the last 12 months, use of acetaminophen in the first year of life, use of acetaminophen in the last 12 months |
| Sultesz et al., 2020 [26] | Cross-sectional | Hungary      | Population         | Core questions of ISAAC Phase I | 3,836             | 6–12              | 48.40    | In the first 1 year of life | /                                                                                                                                                           |
| Sultész et al., 2010 [27] | Cross-sectional | Hungary      | Population         | Core questions of ISAAC Phase I | 3,933             | 6–12              | 50.20    | In the first 1 year of life | /                                                                                                                                                           |
| Tamay et al., 2007 [28] | Cross-sectional | Turkey       | Population         | ISAAC questionnaire | 2,387             | 6–12              | 49.64    | In the first 1 year of life | Family history of atopy, the presence of physician-diagnosed eczema or food allergy, frequent upper airway infections and sinusitis, history of adenoidectomy, antibiotic or paracetamol use in the first year of life, cat or dog ownership in the first year of life, home dampness, exposure to diesel trucks, perianal redness |
| Tong et al., 2020 [29] | Cross-sectional | China        | Population         | ISAAC, ECRHS, SFAR  | 5,550             | 6–12              | 53.90    | In the past 5 years Younger than 3 years | Gender, age, family history of allergy, air purifier Maternal history of allergy, maternal age at pregnancy, maternal smoking during pregnancy, mode of delivery, gestational age at delivery, daycare attendance, number of previous live births, bronchitis, and sex of the child |
| Yamamoto-Hanada et al., 2017 [22] | Prospective cohort | Japan        | Hospital           | Questionnaire       | 902               | 5                 | 51.00    | Younger than 3 years        | Maternal history of allergy, maternal age at pregnancy, maternal smoking during pregnancy, mode of delivery, gestational age at delivery, daycare attendance, number of previous live births, bronchitis, and sex of the child |
| Yang et al., 2014 [30] | Cross-sectional | Korea        | Population         | ISAAC questionnaire | 7,389             | 13.9              | 44.10    | Antibiotic use in infancy | Age, sex, BMI, parental history of allergic rhinitis, each school, and household income |
| Zou et al., 2020 [31] | Cross-sectional | China        | Population         | ISAAC               | 13,335            | 4–6               | 50.60    | In the first 1 year of life | Child's age, sex, district, family history of atopy, breastfeeding, early home decoration, first-year pet-keeping, first-year environmental tobacco smoke (ETS), and first-year home dampness-related exposures |

AR, allergic rhinitis; ISAAC, International Study of Asthma and Allergies in Childhood; ECRHS, European Community Respiratory Diseases Survey; BAMSE, Barn (Children) Allergy Milieu Stockholm Epidemiology; SFAR, the Score for Allergic Rhinitis.
3.4.2 Subgroup meta-analysis

Early-life antibiotics were associated with an increased incidence of allergic rhinitis in children in prospective cohort studies (ES = 2.98, 95% CI: 2.77–3.22; $I^2 = 17.8\%$, $P_{\text{heterogeneity}} = 0.298$) and cross-sectional studies (ES = 3.78, 95% CI: 3.52–4.05; $I^2 = 10.9\%$, $P_{\text{heterogeneity}} = 0.346$), but not in one retrospective cohort study (ES = 4.10, 95% CI: 0.66–25.53) (Figure 3). In Asia, the incidence of allergic rhinitis in the antibiotic group was higher than in the no medication group (ES = 3.68, 95% CI: 3.38–4.01; $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = 0.544$). In Europe and the USA, the incidence of allergic rhinitis in the antibiotic group was also higher than that in the no medication group (ES = 3.20, 95% CI: 3.00–3.42; $I^2 = 70.8\%$, $P_{\text{heterogeneity}} = 0.001$ and ES = 3.68, 95% CI: 2.74–4.95; $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = 0.907$) (Figure 4). Compared with the no medication group, children who received antibiotics in the first 1 week of life (ES = 5.75, 95% CI: 2.18–15.18), first 1 year of life (ES = 3.37, 95% CI: 3.20–3.55; $I^2 = 64.2\%$, $P_{\text{heterogeneity}} = 0.001$), or first 3 years of life (ES = 5.21, 95% CI: 2.42–11.19) had a higher incidence of allergic rhinitis (Figure 5).

3.5 Sensitivity analysis

As shown in Figure 6, no individual study influenced the results of the meta-analysis.

3.6 Publication bias

The funnel plot of the incidence of allergic rhinitis was drawn. All studies are included in the plot. The results showed that the funnel plot had a moderate symmetry and low publication bias (Figure 7).

4 Discussion

Previous studies reported conflicting results regarding the early-life use of antibiotics and allergic rhinitis [6,11]. This meta-analysis aimed to investigate the correlation between early-life antibiotic use and allergic rhinitis. The results strongly suggest that the use of antibiotics in early life was associated with allergic rhinitis.
Table 2: Quality evaluation using the NOS scale

| Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at the start of the study | Comparability of cohorts based on the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow-up of cohorts | Total quality scores |
|----------------------------------------|------------------------------------|---------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------|----------------------|---------------------------------|-----------------------------|------------------|
| Cohort studies                          |                                    |                           |                                                                                 |                                                        |                      |                                 |                             |                  |
| Ortqvist et al. [1]                     | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 9                |
| Aversa et al. [15]                      | *                                  | *                         | *                                                                                | **                                                     | *                    | /                               | /                           | 7                |
| Celedón et al. [16]                     | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 9                |
| Harris et al. [17]                      | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 9                |
| Mai et al. [18]                         | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 9                |
| Metzler et al. [19]                     | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 9                |
| Mitre et al. [20]                       | *                                  | *                         | *                                                                                | **                                                     | *                    | /                               | /                           | 7                |
| Ni et al. [21]                          | *                                  | *                         | *                                                                                | **                                                     | *                    | /                               | /                           | 7                |
| Yamamoto et al. [22]                    | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 8                |
| Cross-sectional studies                |                                    |                           |                                                                                 |                                                        |                      |                                 |                             |                  |
| Ho and Wu [23]                          | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 7                |
| Kim et al. [24]                         | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 7                |
| Penaranda et al. [25]                   | *                                  | /                         | **                                                                               | *                                                      | *                    | *                               | *                           | 6                |
| Sultesz et al. [26]                     | *                                  | *                         | *                                                                                | *                                                      | *                    | *                               | *                           | 6                |
| Sultesz et al. [27]                     | *                                  | *                         | *                                                                                | *                                                      | *                    | *                               | *                           | 6                |
| Tamay et al. [28]                       | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 7                |
| Tong et al. [29]                        | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 7                |
| Yang et al. [30]                        | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 7                |
| Zou et al. [31]                         | *                                  | *                         | *                                                                                | **                                                     | *                    | *                               | *                           | 7                |
Figure 3: Forest plot for the subgroup analysis by study design in the antibiotic and no medication groups.

Figure 4: Forest plot for the subgroup analysis by area in the antibiotic and no medication groups.
Figure 5: Forest plot for the subgroup analysis by the timing of antibiotic exposure in the antibiotic and no medication groups.

Figure 6: Forest plot for the sensitivity analysis in the incidence of allergic rhinitis in the antibiotic and no medication groups.
Some antibiotics, especially macrolides, have been found to play an anti-inflammatory role not only by inducing the apoptosis of inflammatory cells but also by regulating the production of pro-inflammatory mediators [18,32,33]. The common side effect of antibiotics is to cause intestinal flora imbalance. The intestinal microbiome has become a research hotspot in the medical field [32]. The formation and changes in the intestinal microbiome exert a direct impact on the growth and development of the fetus from pregnancy to fetal delivery to the early stage of feeding. Allergic rhinitis is one of these allergic diseases. A meta-analysis also revealed an increased incidence of hay fever, eczema, and food allergy in children with early-life antibiotics [34].

In recent years, the incidence of allergic rhinitis has increased significantly in most countries and regions, and the increasing burden of disease has become a global health concern [18,33,35]. More than 500 million people are estimated to suffer from allergic rhinitis worldwide, and the prevalence rate in the USA is 15–30%. In this study, a significant difference was noted in the incidence of allergic rhinitis in the antibiotic and no medication groups. Hence, the incidence of allergic rhinitis in children with early-life antibiotics was higher than in the no medication group. This finding was in agreement with the study observations made by Wilson [36] and Celedon et al. [11] that antibiotics were associated with allergic rhinitis. A Swedish study of 722,767 children also reported similar results [37]. Still, Fsdini et al. [6] reported a limited association between antibiotics and allergic rhinitis in early life. Such discrepancies might be due to the populations being studied, age at exposure, types of antibiotics, dosage, indications, etc. Indeed, Kim et al. [24] showed that the incidence of allergic rhinitis increased with the annual average number of antibiotic prescription days, reaching an OR of 13.4 for >90 days. Tong et al. [29] examined the number of treatments per year and also observed an increased incidence of allergic rhinitis with an increasing number of treatments per year, with an OR of 4.0 for >7 treatments/year. Generally, it appears that penicillin does not increase the incidence of allergic rhinitis, while antibiotics like cepham, macrolides, cephalosporins, and sulfonamides increase the incidence [15,22]. Hence, future studies should be carefully designed to control the effect of such confounders on the incidence of allergic rhinitis in later life.

In the subgroup analyses based on study design, continents, and age at exposure, all subgroups showed a higher incidence in the antibiotic group compared with the no medication group, except for the retrospective cohort study, but there was only one study in that subgroup. These results were consistent with the results by Spector et al. [38].

Nevertheless, the present study has some limitations. First, the quality of a meta-analysis is only as high as the quality of the included studies. Although most studies were of high quality according to the NOS, some lower-quality studies had to be included. In addition, many of the included studies examined antibiotics as the exposure, without considering the different types of antibiotics and their dosages. Therefore, subgroup analyses based on the antibiotics could not be performed here. Second, heterogeneity was high for some analyses, indicating important differences in study populations and treatments. Third, limited publication bias was observed.

In conclusion, this meta-analysis suggests that antibiotics in early life might be associated with allergic rhinitis. Even though antibiotics can be necessary for early life, these results highlight that the use of antibiotics in infants should be carefully weighed to avoid the inappropriate use of antibiotics and cause health issues in later life.

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Yangyan Yan, Jing Bi, and Jia Liu worked on investigation and data collection. Yong Fu conducted the critical revision of the manuscript. All authors read and approved the final manuscript.

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## Appendix

### Table A1: Search strategies

| PubMed | Search strategy                                                                 | Numbers   |
|--------|----------------------------------------------------------------------------------|-----------|
| P      | #1 'Anti-Bacterial Agents'[Mesh]                                                  | 413,196   |
|        | #2 (Agents, Anti-Bacterial) OR (Anti Bacterial Agents) OR (Antibacterial Agents) OR (Agents, Antibacterial) OR (Anti Bacterial Agent) OR (Agent, Antibacterial) OR (Anti-Bacterial Compounds) OR (Compounds, Anti-Bacterial) OR (Anti-Bacterial Agent) OR (Agent, Anti-Bacterial) OR (Anti Bacterial Agent) OR (Anti-Bacterial Compound) OR (Antibacterial Compounds) OR (Compound, Anti-Bacterial) OR (Bacteriocidal Agents) OR (Agents, Bacteriocidal) OR (Bacteriocidal Agent) OR (Agent, Bacteriocidal) OR (Bacteriocide) OR (Bacteriocides) OR (Antimycobacterial Agents) OR (Agents, Anti-Mycobacterial) OR (Anti Mycobacterial Agents) OR (Anti Mycobacterial Agent) OR (Agent, Anti-Mycobacterial) OR (Anti Mycobacterial Agent) OR (Antimycobacterial Agent) OR (Agent, Antimycobacterial) OR (Antimycobacterial Agents) OR (Agents, Antimycobacterial) OR (Antibiotics) OR (Antibiotic) | 1,011,721 |
|        | #3 #1 OR #2                                                                        | 1,011,721 |
| Intervention | #4 'Rhinitis, Allergic'[Mesh]                                                     | 22,630    |
|        | #5 (Allergic Rhinitides) OR (Rhinitides, Allergic) OR (Allergic Rhinitis)         | 33,406    |
|        | #6 #4 OR #5                                                                        | 33,406    |
|        | #7 #3 AND #6                                                                        | 580       |
| Study type | #8 ('Cohort Studies'[Mesh]) OR ((Cohort Study) OR (Studies, Cohort) OR (Study, Cohort) OR (Concurrent Studies) OR (Studies, Concurrent) OR (Concurrent Study) OR (Study, Concurrent) OR (Closed Cohort Studies) OR (Cohort Studies, Closed) OR (Closed Cohort Study) OR (Cohort Study, Closed) OR (Study, Closed Cohort) OR (Studies, Closed Cohort) OR (Birth Cohort Studies) OR (Birth Cohort Study) OR (Cohort Studies, Birth) OR (Cohort Study, Birth) OR (Studies, Birth Cohort) OR (Study, Birth Cohort) OR (Analysis, Cohort) OR (Analyses, Cohort) OR (Cohort Analyses) OR (Cohort Analysis) OR (Historical Cohort Studies) OR (Cohort Studies, Historical) OR (Cohort Study, Historical) OR (Historical Cohort Study) OR (Study, Historical Cohort) OR (Studies, Historical Cohort) OR (Incidence Studies) OR (Incidence Study) OR (Studies, Incidence) OR (Study, Incidence)) | 2,935,745 |
|        | #9 #7 AND #8                                                                        | 164       |
|        | #10 #7 AND #8                                                                       |           |