Relative risk of developing asthma after prenatal antibiotic exposure: Protocol for a systematic review and meta-analysis

Alissa M. Cait, Alexander Wedel, Jeanne L. Arntz, Jacyra Duinkerken, Swarali Datye, Moumen M. Alhasan, Melanie L. Conrad

Title: Relative risk of developing asthma after prenatal antibiotic exposure: Protocol for a systematic review and meta-analysis

Authors: Alissa M Cait[a] Alexander Wedel[b,] Jeanne L. Arntz[c], Jacyra Duinkerken[c], Swarali Datye[c], Moumen M. Alhasan[c], Melanie L. Conrad[c]

[a]Malaghan Institute of Medical Research, Wellington, New Zealand; [b] Institute of Education, Department of Educational Psychology, Technische Universität Berlin, Berlin, Germany; [c] Institute of Microbiology, Infectious Diseases and Immunology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany.

Author contributions: The study was conceptualized by AMC and MLC. All authors contributed to the development of objectives and eligibility criteria. The search strategy was developed by AMC, SD, JLA and JD. MMA, SD, JD and JLA performed the screening and extracted the data. AW provided statistical expertise and performed the analysis. All authors will contribute to writing and preparing the manuscript. All authors will review and approve the final version of the manuscript.

Registration: This protocol was developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses - Protocol (PRISMA-P)[1]. This protocol will be registered in PROSPERO.

Amendments: Important protocol amendments post registration will be documented in the final systematic review and meta-analysis publication. In the event of a protocol amendment, the date of each amendment will be documented along with a description of the change and the rationale for the change.

Support: Charité Universitätsmedizin - Berlin and The Konrad-Adenauer Foundation.

INTRODUCTION

Rationale: Asthma is an increasingly prevalent disease characterized by chronic airway inflammation and hyperreactivity, which contributes to airway obstruction and subsequent wheeze, cough and shortness of breath. Though asthma has a poorly understood aetiology, strong evidence indicates that in addition to genetic factors, the environment contributes substantially to disease susceptibility, especially when these exposures occur prenatally or in early life[2]. In particular, environmental exposures such as air pollution[3], maternal stress[4,5,6] and antibiotic use during pregnancy[7], are associated with increased risk of childhood asthma.

Antibiotics account for 80% of medications prescribed during pregnancy, and it is estimated that around 20-25% of pregnant women receive at least one course of an antibiotic during this time period[8]. Antibiotics are most commonly prescribed for sexually transmitted diseases, urinary tract or upper respiratory tract infections[8], and although antibiotics are necessary in these situations[9], the association of these medications with adverse pregnancy outcomes must also be considered[10]. It is not yet understood how antibiotics taken during pregnancy affect asthma susceptibility in children. If prenatal antibiotic exposure has even a small effect on childhood disease susceptibility, this could substantially influence public health.

Several observational cohorts following mother-child dyads have examined whether prenatal antibiotic use leads to an increased risk of childhood asthma development. Though many studies have been performed, a mixture of conclusions has complicated arrival at a consensus. Several analyses found an association between prenatal antibiotic exposure and the occurrence of asthma or wheeze by the age of 10[11-16]. Mulder (2016), on the other hand, found that general antibiotic use did not increase the risk of childhood asthma[17]. Another study found that their statistically significant effect regarding antibiotic use during pregnancy and risk for childhood asthma was confounded by adjusting for siblings that had not been foetally exposed[18]. Due to this disagreement between studies, a meta-analysis is indeed called for to assess all the literature that is currently available.

A strong link has been observed between the intestinal microbiome, antibiotic use and asthma risk. The neonatal microbiome plays an important role in the development of the child's immune system, and it has been indicated that prenatal antibiotic treatment disrupts both the maternal and the neonatal microbiome, which in turn may disrupt the neonate's immune system development. Poor immune system development leads to lower immune tolerance, which is associated with an increased risk of asthma.[19-21]. This is an important finding, because it has been shown that even short-term antibiotic treatment can have a long-lasting impact on the human microbiome[22], meaning that prenatal, or even pre-conceptional antibiotic use might also impact childhood health. Studies have shown that intrapartum antibiotics as well as the method of birth may also have an impact on the gut microbiota during the first year of life[23].

Since asthma prevalence is increasing globally, it is important reach a statistically sound conclusion regarding the possible causes, in order to provide healthcare professionals with the data they need to inform their patients. Therefore, we aim to conduct a robust systematic review and meta-analysis of all available evidence to determine the relationship between prenatal antibiotic exposure and the subsequent risk of childhood asthma.

Objectives: The objective of this protocol is to define the methods for a systematic review to assess the impact of prenatal antibiotic exposure on relative risk of developing childhood asthma. The specific review question to be addressed in this protocol and the following systematic review is as follows:

Do children who were exposed to antibiotics prenatally have an increased risk of developing asthma?

Population: All pregnant women who used antibiotics during their pregnancy.
Exposure: Antibiotics used during pregnancy.
Comparator: Antibiotic-free pregnancy.
Outcomes: Childhood asthma and other childhood atopic diseases (continued below).

METHODS.

Eligibility criteria:
Participants: We will include studies following mothers of any age and their delivered babies.

Intervention: Of interest is the use of any antibiotic (prescription or self-prescription), or antibiotics at any time point during pregnancy, with no limit to the number of antibiotic courses taken by the mother. We will exclude any studies that have shared antibiotic and antifungal or antiviral drug administration.

Comparators: The main control group will include children from healthy mothers -not asthmatic or genetically predisposed to asthma- with no familial relation to the study group (i.e. no sibling comparison) who did not take antibiotics during pregnancy. If data are reported separately, we will include studies examining children from the same parents as the study case, but who were not exposed to prenatal antibiotics.

Outcome: The primary outcome of the included studies will be asthma in children from birth to 5 years of age. Secondary outcomes will be other allergic diseases: atopic dermatitis, allergic rhinitis, IgE mediated immediate type allergy and food allergy in children from birth to 5 years of age. We will extract outcomes in all data forms (e.g. dichotomous, continuous) as reported in the studies.

Study designs: All observational studies - analytical studies such as pro- and retrospective cohort studies and follow-up studies will be included. Narrative reviews will be excluded, as well as descriptive studies such as population studies.

Time frame: We will include studies wherein the intervention has been administered at any trimester in pregnancy and where the follow up of the children was recorded for at least 5 years. Studies from the 1946 until the present day will be included.

Setting: There will be no restrictions by type of setting. i.e. geographical location or socioeconomic status of the mothers.

Information sources. Search strategies were developed using a combination of medical subject headings (MeSH) and keywords related to our population (pregnant women), exposure (antibiotics), and outcome (asthma and other atopic diseases) topics with Boolean operators. The search strategy was designed in MEDLINE (Ovid) and then adapted to other databases. The search strategy uses terms derived from initial scoping searches and expertise in the subject area.

We will use the following databases:

Table 2. Databases and information sources to be searched.

Database/Information Source	**Interface/URL**
MEDLINE	Ovid
EMBASE	Ovid
Proquest Disertations and Theses A&I (grey literature)	Proquest
Cochrane central register of controlled trials	Central

Search strategy

No limits on study design, date or language will be imposed on the search beyond that of the databases themselves. Studies in English, German, French, Dutch, or Arabic will be included in the review. Only quantitative studies will be sought, descriptive papers such as narrative reviews will be excluded.

The search strategy for MEDLINE using the Ovid interface is presented in table 2.

Table 2: Search strategy for MEDLINE (Ovid). ti = title, kw= author keywords, ab= abstract, exp = explode

Maternal Exposure/ or Pregnancy/ or Prenatal Exposure Delayed Effects/ or Prenatal Care/
(maternal or prenatal or gestatio* or pregnan* or perinatal or antenatal).ti,kw,ab.
1 or 2
exp Anti-Bacterial Agents/
(anitbact* or anti$infecti or anti$micro or bacteriostat* or bactericid*).ti,kw,ab.
4 or 5
exp Asthma/ or exp Hypersensitivity/
(asthma* or allerg* or respiratory hypersensitivity or hypersensitivity or wheez* or AHR or atopy or atopic dermatitis or eczema or allergic rhinitis or IgE).ti,kw,ab.
7 or 8
3 and 6 and 9

STUDY RECORDS.

Data management: Literature references will be managed via Endnote; the preferred software for managing systematic review bibliographies and de-duplicated using EndNote's algorithms. Additionally, literature search results will be uploaded to Distiller Systematic Review (DSR) Software (Evidence Based Partners, Ottawa, Canada), a programme that facilitates coordinated paper screening and data extraction.

Selection process: Two independent reviewers will examine the title and abstract of the studies found in the search results, and will remove irrelevant studies. Next, a second selection will be performed by examining the full text of the articles and carefully applying the eligibility criteria to determine inclusion. In case of exclusion, the reason will be recorded. In the case that a conflict arises, the paper in question will be discussed with a third reviewer.

Data collection process: For each eligible study, two researchers will extract the data independently and in duplicate using carefully constructed forms in DistillerSR. Additionally, to avoid any inconsistency between the reviewers a collaboration exercise will be conducted before the extraction of data.

The abstract of the data will contain the intervention type and all of the desired outcomes. Any disagreement will be resolved through discussion or through one of our two arbitrators. In case of any uncertainty, we will contact the study authors.

Data items. The following data will be extracted and summarized:

i. *Study ID:* authors, title, year and journal
ii. *Study design characteristics:* sample size for control and treated groups

iii. *Detailed description of exposure:* antibiotics used, their dosage and dosage form, duration of the treatment and the cause of prescription, duration of the follow up, and which other types of drugs were used during pregnancy.
iv. *Disease characteristics in offspring:* type of diagnosis, method of diagnosis, age of diagnosis
v. *Outcome measures:* Type of effect size e.g. RR/OR/SMD/r etc, 95% CI, p-value, r, confounding factors

Information will be extracted from all articles determined to be relevant by the screening process. If necessary data is missing, we will contact the authors for additional data.

Outcomes and prioritization. The main outcome will be childhood asthma in a child aged 0-5, defined as either 1) an asthma diagnosis by a doctor; 2) a report of two or more of the following symptoms:

- Wheeze
- Shortness of breath or heavy breathing
- Cough
- Chest tightness, especially for >10 days during Upper Respiratory Tract Infection (URTI) with
    - > 3 episodes per year or
    - severe episodes or night worsening,

  without showing one of the following:
    - Isolated cough with no other respiratory symptoms
    - Chronic production of sputum
    - Shortness of breath associated with dizziness, light-headedness or peripheral tingling (paraesthesia)
    - Chest pain
    - Exercise-induced dyspnoea with noisy inspiration

or 3) a confirmed or documented variable expiratory airflow limitation.
'Variable' refers to improvement and/or deterioration in symptoms and lung function. Excessive variability may be identified over the course of one day, from day to day, from visit to visit, or seasonally, or from a reversibility test.

Subgroup analysis. Subgroup analysis will be performed to assess potential sources of data heterogeneity based on the following:

1. Impact of prenatal antibiotic exposure on secondary outcomes, i.e. other atopic diseases
    i. atopic dermatitis
    ii. allergic rhinitis
    iii. IgE mediated immediate type allergy
    iv. food allergy
2. Is antibiotic administration during a specific trimester associated with a higher likelihood of developing asthma during childhood?
3. Are specific antibiotic types (i.e. gram-positive spectrum, gram-negative spectrum and anaerobic spectrum antibiotics) associated with a higher likelihood of developing asthma during childhood?
4. Is the impact of antibiotics on the risk of developing childhood asthma dose dependent?
5. Does the route of administration have an impact on the effects of the antibiotic?
6. Is the type of infection in the mother related to the severity of asthma in offspring?
7. Is the severity of asthma in the offspring dependent on the sex of the child?

8. What is the impact of time (year of study) on the association between antibiotics and childhood asthma?

Risk of bias in individual studies: The potential studies to be included in the meta-analysis will be evaluated for the risk of bias, using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies. Each study will be assessed by two independent reviewers, for criteria including the selection of the study populations, the comparability between the cohorts and the outcome of interest. The studies will be awarded a maximum of 9 points each, depending upon the fulfilment of the specific criteria. Studies will be eligible for inclusion in the meta-analysis if they are scored at least 6 points or more. If any disagreements between the reviewers arise, they will be resolved using a third reviewer as an arbitrator.

DATA SYNTHESIS.

Study criteria for quantitative synthesis: The quantitative synthesis will include all studies that report at least one measurement of one predictor and one outcome variable. Additionally, data will only be integrated when it was collected under ethically sound conditions, and when sufficient and reliable information for the measurement instrument and protocol was provided in the study.

Data handling and combining: Since simply averaging effect sizes or pooling data can result in incorrect estimations of standard errors and false test statistics[24], we will apply a meta-analytic model to the data. A first choice for a meta-analytic summary is the aggregate level on which to conduct the analysis. Models with individual participant data can either be calculated from all participant data of all studies in one step (one-stage), or with data aggregates from each study (two-stage). Except for uncommon cases or very large datasets, both designs produce comparable results and can be specified to result in quasi-identical values[25,26]. We expect differences in the collected studies, and plan to conduct the meta-analysis on aggregated data from each study.

On the aggregate level, effect sizes of outcomes will likely be reported as log OR (Odds Ratio) or log HR (Hazard Ratio) with the corresponding variance. Since these outcome types are not interchangeable, the aggregation will possibly include calculating the respective outcome types from within-study data. If individual data was not reported, we will transform HR into OR (or OR into HR) according to Shor et al. (2017)[27], Zhang and Yu (1998)[28] and Van der Weele, (2019)[29]. If the predominant outcome type is HR, a back-transformation is necessary before entering the data into the meta-analytic model to account for typical skewness and asymmetry of the HR.

The aggregated data will then be entered into a multivariate meta-analytic regression model, which controls for correlation between predictors. Both random- and fixed-effects models will be estimated with REML in the metafor package for r[30]. This package provides different estimation techniques, such as Peto's one-step method, the conditional logistic model and the Mantel-Haenszel method according to Rothman et al. (2008)[31]. Here, the choice depends much on the empirical data. Additional subgroup analysis will be conducted to check for moderation effects (e.g. trimester, type of antibiotic).

To address variance between studies, heterogeneity will be calculated with the Q- and I^2-statistic[32]. In combination with a power-analysis approach as described by Valentine, Pigott and Rothstein (2010)[33], this allows for precise interpretation.

Proposed additional analyses: In addition to the meta-analytic model described above, sensitivity analysis will be carried out. To check for publication bias, a contoured funnel-plot will be constructed. Further outlier analysis will firstly be based on effect sizes and variances and secondly consist of Viechtbauer and Cheung's outlier battery, which is implemented in the metafor package for r.

If meta-analytic models cannot be estimated, a descriptive table with all study results will be provided.

Confidence in cumulative evidence: The strength of evidence for all outcomes will be judged using the Tool to Assess Risk of Bias in Cohort Studies, contributed by the CLARITY Group at McMaster University. The quality of the evidence will be assessed across seven domains: selection of exposed and non-exposed cohorts; assessment of exposure; outcome of interest; prognostic factors; assessment of outcome; follow up; co-interventions. Each study will receive a score of 1-4, where 1 corresponds with low risk of bias and 4 corresponds with high risk of bias.[34]

DISCUSSION.

This systematic review and metanalysis will synthesize current evidence surrounding the impact of gestational antibiotic exposure on childhood atopic disease. The results of this review will aid in understanding the risks associated with antibiotics prescribed during pregnancy and allow for informed decision making by physicians.

REFERENCES.

1. Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., … Stewart, L. A. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*, *4*(1), 1. https://doi.org/10.1186/2046-4053-4-1
2. Stein, M. M., Hrusch, C. L., Gozdz, J., Igartua, C., Pivniouk, V., Murray, S. E., Ledford, J. G., Dos Santos, M. M., Anderson, R. L., Metwali, N., Neilson, J. W., Maier, R. M., Gilbert, J. A., Holbreich, M., Thorne, P. S., Martinez, F. D., Von Mutius, E., Vercelli, D., Ober, C., & Sperling, A. I. (2016). Innate immunity and asthma risk in amish and hutterite farm children. *New England Journal of Medicine*, *375*(5), 411-421. https://doi.org/10.1056/NEJMoa1508749
3. Deng, Q., Lu, C., Li, Y., Sundell, J., & Norbäck, D. (2016). Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema. *Environmental Research*, *150*, 119–127. https://doi.org/10.1016/j.envres.2016.05.050
4. Rosa, M. J., Lee, A. G., & Wright, R. J. (2018). Evidence establishing a link between prenatal and early-life stress and asthma development. *Current Opinion in Allergy and Clinical Immunology*, *18*(2), 148–158. https://doi.org/10.1097/aci.0000000000000421
5. Rosa, M. J., Just, A. C., Kloog, I., Pantic, I., Schnaas, L., Lee, A., … Wright, R. J. (2017). Prenatal particulate matter exposure and wheeze in Mexican children. *Annals of Allergy, Asthma & Immunology*, *119*(3), 232-237.e1. https://doi.org/10.1016/j.anai.2017.06.016
6. Trump, S., Bieg, M., Gu, Z., Thürmann, L., Bauer, T., Bauer, M., … Eils, R. (2016). Prenatal maternal stress and wheeze in children: novel insights into epigenetic regulation. *Scientific Reports*, *6*(1), 1. https://doi.org/10.1038/srep28616
7. Metzler, S., Frei, R., Schmaußer-Hechfellner, E., von Mutius, E., Pekkanen, J., Karvonen, A. M., … Doekes, G. (2019). Association between antibiotic treatment during pregnancy and

infancy and the development of allergic diseases. *Pediatric Allergy and Immunology*, *30*(4), 423–433. https://doi.org/10.1111/pai.13039
8. Källén, B., Finnström, O., Nygren, K.-G., & Otterblad Olausson, P. (2013). Maternal drug use during pregnancy and asthma risk among children. *Pediatric Allergy and Immunology*, *24*(1), 28–32. https://doi.org/10.1111/pai.12034
9. Bookstaver, P. B., Bland, C. M., Griffin, B., Stover, K. R., Eiland, L. S., & McLaughlin, M. (2015). A Review of Antibiotic Use in Pregnancy. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *35*(11), 1052–1062. https://doi.org/10.1002/phar.1649
10. Harbison, A. F., Polly, D. M., & Musselman, M. E. (2015). Antiinfective therapy for pregnant or lactating patients in the emergency department. *American Journal of Health-System Pharmacy*, *72*(3), 189–197. https://doi.org/10.2146/ajhp130797
11. Lapin, B., Piorkowski, J., Ownby, D., Freels, S., Chavez, N., Hernandez, E., … Persky, V. (2015). Relationship between prenatal antibiotic use and asthma in at-risk children. *Annals of Allergy, Asthma & Immunology*, *114*(3), 203–207. ttps://doi.org/10.1016/j.anai.2014.11.014
12. McKeever, T. M., Lewis, S. A., Smith, C., & Hubbard, R. (2002). The Importance of Prenatal Exposures on the Development of Allergic Disease. *American Journal of Respiratory and Critical Care Medicine*, *166*(6), 827–832. https://doi.org/10.1164/rccm.200202-158oc
13. Metsälä, J., Lundqvist, A., Virta, L. J., Kaila, M., Gissler, M., & Virtanen, S. M. (2014). Prenatal and post-natal exposure to antibiotics and risk of asthma in childhood. *Clinical & Experimental Allergy*, *45*(1), 137–145. https://doi.org/10.1111/cea.12356
14. Chu, S., Yu, H., Chen, Y., Chen, Q., Wang, B., & Zhang, J. (2015). Periconceptional and Gestational Exposure to Antibiotics and Childhood Asthma. *PLOS ONE*, *10*(10), e0140443. https://doi.org/10.1371/journal.pone.0140443
15. Kashanian, M., Mohtashami, S. S., Bemanian, M. H., Moosavi, S. A. J., & Moradi Lakeh, M. (2017). Evaluation of the associations between childhood asthma and prenatal and perinatal factors. *International Journal of Gynecology & Obstetrics*, *137*(3), 290–294. https://doi.org/10.1002/ijgo.12141
16. Stokholm, J., Sevelsted, A., Bønnelykke, K., & Bisgaard, H. (2014). Maternal propensity for infections and risk of childhood asthma: a registry-based cohort study. *The Lancet Respiratory Medicine*, *2*(8), 631–637. https://doi.org/10.1016/s2213-2600(14)70152-3
17. Mulder, B., Pouwels, K. B., Schuiling-Veninga, C. C. M., Bos, H. J., de Vries, T. W., Jick, S. S., & Hak, E. (2016). Antibiotic use during pregnancy and asthma in preschool children: the influence of confounding. *Clinical & Experimental Allergy*, *46*(9), 1214–1226. https://doi.org/10.1111/cea.12756
18. Yoshida, S., Ide, K., Takeuchi, M., & Kawakami, K. (2018). Prenatal and early-life antibiotic use and risk of childhood asthma: A retrospective cohort study. *Pediatric Allergy and Immunology*, *29*(5), 490–495. https://doi.org/10.1111/pai.12902
19. Fujimura, K. E., Sitarik, A. R., Havstad, S., Lin, D. L., Levan, S., Fadrosh, D., … Lynch, S. V. (2016). Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nature Medicine*, *22*(10), 1187–1191. https://doi.org/10.1038/nm.4176
20. Sjögren, Y. M., Tomicic, S., Lundberg, A., Böttcher, M. F., Björkstén, B., Sverremark-Ekström, E., & Jenmalm, M. C. (2009). Influence of early gut microbiota on the maturation of childhood mucosal and systemic immune responses. *Clinical & Experimental Allergy*, *39*(12), 1842–1851. https://doi.org/10.1111/j.1365-2222.2009.03326.x
21. Arrieta, M.-C., Stiemsma, L. T., Dimitriu, P. A., Thorson, L., Russell, S., Yurist-Doutsch, S., … Brett Finlay, B. (2015). Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Science Translational Medicine*, *7*(307), 307ra152. https://doi.org/10.1126/scitranslmed.aab2271
22. Jakobsson, H. E., Jernberg, C., Andersson, A. F., Sjölund-Karlsson, M., Jansson, J. K., & Engstrand, L. (2010). Short-Term Antibiotic Treatment Has Differing Long-Term Impacts on the Human Throat and Gut Microbiome. *PLoS ONE*, *5*(3), e9836. https://doi.org/10.1371/journal.pone.0009836

23. Azad, M., Konya, T., Persaud, R., Guttman, D., Chari, R., Field, C., … Kozyrskyj, A. (2015). Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology*, *123*(6), 983–993. https://doi.org/10.1111/1471-0528.13601
24. Moeyaert, M., Ugille, M., Ferron, J. M., Onghena, P., Heyvaert, M., Beretvas, S. N., & Van den Noortgate, W. (2015). Estimating intervention effects across different types of single-subject experimental designs: Empirical illustration. *School Psychology Quarterly*, *30*(1), 50–63. https://doi.org/10.1037/spq0000068
25. Burke, D. L., Ensor, J., & Riley, R. D. (2016). Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Statistics in Medicine*, *36*(5), 855–875. https://doi.org/10.1002/sim.7141
26. Kontopantelis, E. (2018). A comparison of one-stage vs two-stage individual patient data meta-analysis methods: A simulation study. *Research Synthesis Methods*, 1. https://doi.org/10.1002/jrsm.1303
27. Shor, E., Roelfs, D., & Vang, Z. M. (2017). The "Hispanic mortality paradox" revisited: Meta-analysis and meta-regression of life-course differentials in Latin American and Caribbean immigrants' mortality. *Social Science & Medicine*, *186*, 20–33. https://doi.org/10.1016/j.socscimed.2017.05.049
28. Zhang, J., & Yu, K. F. (1998). What's the Relative Risk? *JAMA*, *280*(19), 1690. https://doi.org/10.1001/jama.280.19.1690
29. Van der Weele, T. J. (2020). Optimal approximate conversions of odds ratios and hazard ratios to risk ratios. *Biometrics*, 1. https://doi.org/10.1111/biom.13197
30. Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of statistical software*, *36*(3), 1-48. https://doi.org/10.18637/jss.v036.i03
31. Rothman, K. J., Greenland, S., & Lash, T. L. (2008). *Modern epidemiology* (3rd ed.). Philadelphia: Lippincott Williams & Wilkins
32. Borenstein, M., Higgins, J. P., Hedges, L. V., & Rothstein, H. R. (2017). Basics of meta-analysis: I2 is not an absolute measure of heterogeneity. *Research synthesis methods*, *8*(1), 5-18. https://doi.org/10.1002/jrsm.1230
33. Valentine, J. C., Pigott, T. D., & Rothstein, H. R. (2010). How Many Studies Do You Need? *Journal of Educational and Behavioral Statistics*, *35*(2), 215–247. https://doi.org/10.3102/1076998609346961
34. Tool to Assess Risk of Bias in Cohort Studies. Retrieved May 21, 2020, from https://www.evidencepartners.com/resources/methodological-resources/